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World Journal of Orthopedics (World J Orthop, WJO, online ISSN 2218-5836, DOI: 10.5312) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Glucosamine and chondroitin for the treatment of osteoarthritis

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options. However, they act as symptomatic treatments, not offering a cure of OA and they are accused for an increased risk of adverse events. Glucosamine (GL) and chondroitin (CH) are nutritional supplements that have recently gained widespread use as treatment options for OA. They potentially or theoretically act as chondroprotectors or/and as "disease-modifying OA drugs" offering not only symptomatic relief but also alteration of the natural history of OA. However, although many studies have showed a significant treatment effect, accompanied with remarkable safety, there is still controversy regarding their relative effectiveness compared with placebo or other treatments. The scope of this review is to present and critically evaluate the current evidence-based information regarding the administration of GL and CH for the treatment of knee or hip OA. Our focus is to investigate the clinical efficacy and safety after the use of these supplements. An effect of GL and CH on both clinical and radiological findings has been shown. However, only a few high-quality level I trials exist in the literature, especially on the assessment of radiological progression of OA. The effect sizes are generally small and probably not clinically relevant. Even the validity of these results is limited by the high risk of bias introduced in the studies. Both GL and CH seem to be safe with no serious adverse events reported. There is currently no convincing information for the efficacy of GL and CH on OA.

Key words: Glucosamine; Chondroitin; Osteoarthritis; Knee; Cartilage

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Abstract

The prevalence of primary or idiopathic osteoarthritis (OA) of knee and hip joints has substantially increased in general population during the last decades. Analgesics and non-steroidal anti-inflammatory drugs are currently extensively used as non-surgical treatment

Core tip: In this review we present and critically evaluate the current information regarding the administration of glucosamine (GL) and chondroitin (CH) for the treatment of knee or hip osteoarthritis. A clinical and radiological effect of GL and CH has been shown. However, only a few high quality trials exist. The effect

sizes are small and probably not clinically relevant. The validity of these results is limited by high risk of bias introduced in the studies. Both GL and CH seem to be safe with no serious adverse events but there is currently no convincing information for their efficacy as treatment options in osteoarthritis.

Vasiliadis HS, Tsikopoulos K. Glucosamine and chondroitin for the treatment of osteoarthritis. *World J Orthop* 2017; 8(1): 1-11 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/1.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.1>

INTRODUCTION

The prevalence of primary or idiopathic osteoarthritis (OA) of knee and hip joints has substantially increased in general population during the last decades. The aging of the population and the increment of life expectancy are contributing factors; however, there is also a high incidence of OA in younger ages^[1,2]. Approximately 5% of the population aged between 35 and 54 years has radiographic signs of knee osteoarthritis, which reaches 30% for ages between 45 and 65^[3]. Except from post-traumatic OA, a reason for younger patients may be the wide participation in high competitive sports and the increment of recreational athletes even in not regularly and inadequately trained population. This subjects their joints to distracting repetitive forces that may lead to progressive cartilage damage and subsequently to secondary or posttraumatic OA.

Focal cartilage lesions usually occur at a first stage, often remaining asymptomatic. Untreated or under-treated lesions may lead to OA. The treatment of OA in elder patients is well clarified and accepted to be joint reconstruction *via* an arthroplasty (either hip or knee). However, arthroplasty may be considered a salvage procedure requiring a modification of daily life postoperatively, not participation in contact sports or high impact sports and is subject to revision surgery after a certain period of time. Therefore this treatment option does not apply to the more active and/or younger patients, even those with severe OA.

Therefore, there is increasing need for treating OA with less invasive interventions, with pharmaceutical agents being the most favourite especially for younger age groups. Analgesics and non-steroidal anti-inflammatory drugs are currently extensively used^[4-6]. However, they frequently cause serious adverse events, including the gastrointestinal or cardiovascular system. Given also that they rather act as symptomatic treatment, not offering a cure of OA, a long-term use is usually required, increasing the risk of such events^[4,5].

An ideal treatment would not only reduce the symptoms but additionally modify the natural history of OA, slowing or even altering the inflammation and destructive effect on the articular cartilage and joint tissues. Such substances that protect the articular

cartilage during the course of OA have been termed as "chondroprotective agents" or "chondroprotectors". When these agents appear to alter the course of the disease (e.g., by modifying the biochemical cascades that contribute to the OA), they are termed "disease-modifying OA drugs" (DMOADs). Such agents aim to protect the joint cartilage along with the subchondral bone and synovial membrane, which are the main structures of the joint^[7-9].

Glucosamine (GL) and chondroitin (CH) are nutritional supplements that have gained widespread use. They are two main categories of agents potentially or theoretically acting as chondroprotectors and/or as DMOADs. Although many studies have been published showing a significant treatment effect, accompanied with remarkable safety, there is still controversy regarding their relative effectiveness compared with placebo or other treatments, their cost-effectiveness and the need for insurance coverage of the therapy cost^[10-12]. Due to methodological and bias concerns, these studies have failed to persuade most of the big national insurance committees (like FDA or NICE) or the biggest scientific societies (like EULAR, ACG EULAR or OARSI) to include GL and CH as first line treatment options in their guidelines^[13-19]. However despite this, global sales of GL supplements reached almost \$2bn in 2008 in United States, after an increase of about 60% compared with 2003, with a forecasted continued growth that would reach \$2.3bn in 2013^[20].

The scope of this review is to present and critically evaluate the current evidence-based information regarding the administration of GL and CH for the treatment of knee or hip OA. Our focus is to investigate the clinical efficacy and safety after the use of these supplements. Initially we will present the theoretical mechanism of action of these agents, through which they may affect the progress of OA. Next, we will present the clinical evidence, mainly based on the level I information from systematic reviews (SRs) of randomised control trials (RCTs). Finally, we will discuss the information along with probable factors that may contribute to a safe conclusion regarding the efficacy and safety of the use of GL and CH for the treatment of osteoarthritis.

BACKGROUND

Molecular structure of articular cartilage and mechanism of primary OA

Articular cartilage has a vast preponderance of extracellular matrix (composed of collagen and proteoglycans), in which cells (chondrocytes) are distributed sparsely. Collagen fibrils (mainly of type II collagen) form the framework of articular cartilage^[21]. The proteoglycan aggregate is an aggregation of proteoglycan monomers attaching to the filamentous hyaluronan backbone and fills the space of the collagen network^[22]. The proteoglycan molecules (also called aggrecans) consist of numerous long-chain glycosaminoglycans (GAGs)

linked to a core protein. Such GAGs (CH sulfate and keratan sulphate) are linear polymers composed of sugar residues^[23]. They are composed of repeating units of N-acetylgalactosamine and glucuronic acid (in CH sulphate) and N-acetylglucosamine and galactose (in keratan sulphate). GAGs are negatively charged, so they attract a large quantity of water molecules. More than 70% of the net weight of cartilage consists of water. Synovial fluid produced from synovial cells, lubricates the joint surfaces and also provides cartilage with oxygen and nutrition.

In OA, matrix metalloproteinases (MMPs) and aggrecanases produced by inflamed synovial cells and the diseased chondrocytes result in a gradual degradation of collagen and proteoglycan molecules. Lytic enzymes released as a result of this degradation also enhance synovial inflammation and induce chondrocytes' apoptosis. The inflammation leads to progressive cartilage degradation. The network described above is gradually destructed. Loss of aggrecans from the extracellular matrix leads to a change in the biomechanical properties of the cartilage tissue. This adds to an increased mechanical wear and would result in an accelerated damage of articular cartilage and eventually to OA. This mechanism of OA may be triggered by traumatic lesions and degradation of focal lesions of cartilage, chondrocyte apoptosis and consequent release of lytic enzymes entering the above described cascade of events.

Prostaglandins released by synoviocytes and chondrocytes during this inflammatory cyclic reaction of cartilage degradation are also known to enhance pain and inflammation.

The above suggested mechanism is primarily apparent in primary osteoarthritis, which is characterised by a generalized cellular dysfunction starting with focal degradation in the most loaded areas of the joint articular surface. In secondary cases of osteoarthritis, other factors also contribute to the joint damage. For example in posttraumatic OA a traumatic focal cartilage lesion may trigger this cascade of degradation. In this case the combination of the mechanic break down in the lesion area and the enzymatic degradation of the damaged cartilage finally lead to OA.

In vitro and animal studies

GL: GL is a water-soluble amino monosaccharide and one of the most abundant monosaccharides in the human body. It is present in high quantities in articular cartilage, being a normal constituent of GAGs in cartilage matrix and also in the synovial fluid. It is a constituent of keratan sulphate. There are two forms: Glucosamine sulphate (GS) and glucosamine hydrochloride (GH).

The way that exogenous administration of GL may work in OA is not yet fully defined. It is believed that GL may have an important role in regulating the anabolic processes of cartilage and also in the

synthesis of synovial fluid. Additionally it may inhibit the degenerative and catabolic process of OA with its anti-inflammatory and even antioxidant properties.

It is reported that GL may affect the cytokine-mediated pathways regulating inflammation, cartilage degradation, and immune responses^[24,25]. It appears to have immune-modulatory activity inhibiting the expression and/or activity of catabolic enzymes such as phospholipase A2, MMPs or aggrecanases^[24-27]. GL reduces or regulates interleukin-1 (IL-1) levels in synovial fluid and inhibits the actions of catabolic enzymes in the joint^[28-30]. This reduces inflammation and cartilage degradation potentially altering the progression of OA. Except from its anti-catabolic action, it has been suggested that GL sulphate has an anabolic effect by stimulating cultured human chondrocytes to synthesize proteoglycans and has been reported to be a substrate for new CH sulphate synthesis^[24,31]. It has also found to inhibit gene expression of OA cartilage *in vitro*^[31]. Finally, GL may act by inducing the production of hyaluronic acid by the synovial membrane^[31]. Along with its indirect effect on the cartilage metabolism, being a precursor of GAGs, it is also possible that supplementation with GL may help promote GAG synthesis or reduce its degradation.

Animal studies have also supported the anabolic and/or anti-catabolic effect of GL on cartilage. A GL analogue has demonstrated both anti-arthritis and anti-inflammatory properties in rats^[32]. Another study reports a positive effect on cartilage, enhancing the rate of new proteoglycan synthesis^[33] and others have confirmed the effectiveness of GL in delaying the cartilage degradation and the progression and severity of OA^[34]. Long-term oral administration of GL sulphate also reduced the destruction of cartilage and upregulation of MMP-3 mRNA in a model of spontaneous osteoarthritis in Harley guinea pigs^[30,35]. However, the preparation used in many of *in vitro* and *in vivo* studies was not a GL sulphate ester but a preparation in which GL and sulphate occurred as two single molecules in crystalline form^[36].

CH: CH sulfate is a sulfated GAG being also a major component of the extracellular matrix of articular cartilage. It is found attached to proteins as part of the aggrecan of the cartilage. It plays a major role in creating considerable osmotic pressure that expands the matrix and places the collagen network under tension^[37]. It provides cartilage with resistance and elasticity allowing it to resist tensile stresses during various loading conditions^[38].

Similarly to GS, the exogenous administration of chondroitin sulphate (CS) has been suggested to act against OA by three main mechanisms; anabolic effect by stimulating the production of extracellular matrix of cartilage, suppression of inflammatory mediators and inhibition of cartilage degeneration^[21]. Studies have demonstrated that CS counteracts the action of IL-1b (a factor that induces articular inflammation and

cartilage degeneration), thus playing a chondroprotective role^[39,40]. Additionally an effect on subchondral bone had been suggested by reducing the resorptive activity in subchondral bone^[41,42].

Proteoglycan content in cartilage was also significantly higher in animals treated with oral or intramuscular administration of CS than that in control animals^[43]. It has been shown that CS significantly decreases collagenolytic activity^[44]. Other studies suggested that the benefits of CS on degenerative osteoarthritic chondrocytes are larger than those on normal chondrocytes^[39,45].

Bioavailability

As described above, both GL and CH are components of the extracellular matrix of articular cartilage. Experimental studies have also suggested an additional action in inflammatory pathways that contribute to OA. Provided this, their external administration has been widely considered as a treatment option for OA.

GL and CH have been used for medicinal purposes for nearly 40 years^[46]. However, their bioavailability after oral administration in humans is a subject still under debate. A key issue would be the absorption of these agents through their passing from the gastrointestinal system.

In mammals, the major site of their metabolism and degradation is the liver, but the exact mechanism is unclear^[21]. Published information is rather controversial. Early pharmacodynamic studies inferred absorption only indirectly. Laboratory work has suggested that GL is substantially degraded in the gastrointestinal tract^[47]. Other studies show that despite its large molecular size, ingested CH is partially absorbed in the intestine and some of it may reach joints^[10,48]. A pharmacokinetic study in dogs, showed that GL (hydrochloride) is absorbed with a bioavailability of about 10%-12% from single or multiple doses^[49]. In humans, serum GL levels following an oral dose of 1.5 g GL sulfate do not appear to exceed 12 mmol/L. Animal studies have also shown that after oral administration of GL hydrochloride, synovial GL concentrations are higher in joints with synovial inflammation compared to levels attained in healthy joints^[50].

Regarding CS, different bioavailability and pharmacokinetic variables have been reported, usually depending on the study methodology or the CS characteristics^[51]. A bioavailability of 10%-20% has been reported in earlier studies^[52-54]. Study in humans has shown a significant increase in plasma levels (more than 200% compared with pre-dose levels) over a 24-h period^[48]. Use of labelled CS has shown a high level of CS, observed in the human synovial fluid and articular cartilage after oral administration^[53]. A limitation to the studies provided above is that both GL and CS are drugs of biological origin. Thus, their measurement in biological fluids does not discriminate the drug from endogenous molecules.

CLINICAL EVIDENCE

Based on laboratory and animal studies, it has been suggested that GL and CH may be effective on preserving cartilage in early OA, and hence might slow down its progression. This would result in a relief from symptoms including pain and stiffness. This claim was also based on clinical studies that reported a clinical benefit after oral administration. However, recent SRs have cast doubt on this.

Quite early, in 2000, a large SR of RCTs assessed the efficacy and safety of GL (GS or GH) and CH^[55]. Assessing 15 RCTs, the authors found moderate effect sizes for GL (0.44, 95%CI: 0.24-0.64) and large effects for CH (0.96, 95%CI: 0.63-1.3). They also extensively investigated the quality of information provided by these studies. A high risk of bias was reported, with poor methodology and poor reporting among the included trials. In all but two trials there was some level of manufacturer sponsorship, while none of the studies reported independent funding from a governmental or non-for-profit organization. They also found that pooled effect sizes were substantially higher compared to those of lower quality or smaller trials, which seem to exaggerate the efficacy of both GL and CH. A high risk of publication bias was also shown on funnel plots, suggesting a high probability of not reporting of small trials or of those with small or null treatment effect.

Richy *et al.*^[56] assessed also 15 RCTs, concluding to a superiority of GL and CH in clinical and radiological findings. Although the authors assessed the quality of the included trials, no further analysis was performed to detect any association with the effect sizes.

Wandel *et al.*^[11] assessed RCTs that compared CS, GS, GH, or the combination of any two with placebo or head to head. Small trials and ones using sub-therapeutic doses were excluded. A network meta-analysis of 10 trials was conducted. In 5 trials, GS was compared with placebo, in 3 CS with placebo, and one compared GH, CS and their combination with placebo. In another placebo controlled trial GS was used; however, after 80% of the patients had been treated, the investigators were forced to change into GH because the manufacturer of GS declined to supply matching placebos^[57]. Seven of the trials were funded by manufacturers. Joint pain was extracted in nine time-windows starting from "up to 3 mo", up to "22 mo or more". Effect sizes for joint pain were -0.17 (95%CI: -0.28 to -0.05) for GL, -0.13 (95%CI: -0.27 to 0.00) for CH, and -0.19 (95%CI: -0.37 to 0.00) for the combination suggesting a close to null effectiveness of the interventions. Stratified analysis revealed that the estimated differences between supplements and placebo were significantly more pronounced in industry funded trials [by on average, 0.5 cm (0.1 to 0.9 cm) in a 10-cm VAS scale, $P = 0.02$]. The analysis of 6 trials providing outcome on radiological joint space, showed no clinically relevant effect on joint space narrowing for

any of the interventions. No differences were found in adverse events, and withdrawals or drop-outs because of adverse events. The authors concluded that CH, GL, and their combination do not have a clinically relevant effect on perceived joint pain or on joint space narrowing. They suggested that health authorities and health insurers should not cover the costs of these preparations, and new prescriptions to patients who have not received other treatments should be discouraged.

Vlad *et al.*^[58] analysed 15 RCTs comparing GL (12 GS and 3 GH) with placebo. Industry funding was reported for 11 trials, while 13 studies used an industry-supplied drug. Rottapharm provided GS in 8 trials and contributed to a ninth trial. The authors reported a marked heterogeneity among trials. They found marked differences between subgroups of trials when grouped by various trial characteristics. Overall, they found a pooled effect size of 0.35 (95%CI: 0.56 to 0.14) in favour of GL. However, there was substantial heterogeneity among trials, questioning the reliability of this finding. This heterogeneity remained high in the industry-funded trials but not in the independent trials. The 11 industry-funded trials had a pooled effect size of 0.47 (95%CI: 0.24-0.70) favouring GL; however a null effect size was found when only the 4 non-industry-funded trials were analysed 0.05 (95%CI: -0.32 to 0.41). Trials with Rottapharm products (a GS product) showed an increased effect size compared with trials with other products ($P = 0.01$.) In general, heterogeneity was absent and effect sizes were smaller in high quality, more recently published and not funded trials, suggesting a high risk of bias for the overall quality of provided information in the related literature. Trials using GS had an effect size favouring the intervention (0.44, 95%CI: 0.18 to 0.70) although GH did not show superiority over placebo. High heterogeneity was found in both cases. The authors concluded that there is sufficient information to conclude that GH lacks efficacy for pain in OA. Among GS trials, marked heterogeneity existed; therefore no definitive conclusion about efficacy is possible.

Reichenbach *et al.*^[10] assessed 22 RCTs or quasi-RCT trials that compared CH with placebo or no intervention. The authors also reported a low quality of evidence as only a few trials had an adequate generation of allocation sequence (1 study) or adequate concealment (2 studies) or followed an intention to treat analysis (3 studies). The meta-analysis of 20 trials providing pain outcomes suggested a pooled large effect size that favours CH sulphate -0.75 (-0.99 to -0.50), corresponding to a difference of 1.6 cm on a 10 cm VAS. However, the heterogeneity was large ($I^2 = 92\%$) and the funnel plot was asymmetrical suggesting high publication bias. More recent trials tended to be larger and of higher quality and included patients with lower-grade of osteoarthritis than did earlier trials. Stratified analysis found that when the analysis was restricted to methodologically sound trials of adequate sample size,

there was a null effect size with low heterogeneity. From 5 trials assessing the difference of mean joint space width, the authors found a mean effect size of 0.18 SD units favouring CH, an effect size that was not clearly clinically significant. The authors finally discouraged the use of CH. In this trial only one time point was assessed per trial, which was criticised.

Another SR assessed the short-term efficacy of several pharmacotherapeutic interventions in osteoarthritic knee pain^[59]. Among 63 RCTs assessing different interventions, 7 assessed GS and 6 CS, with minimal daily administered doses of 1500 mg and 800 mg, respectively. Mean pain relief values for GS or CS had no clinical relevance within 4, 6, 8 or 12 wk. Only for CH sulphate, there was a slight increase in efficacy equivalent to a categorical shift from none to perceptible improvement up to 12 wk.

A SR conducted by Lee *et al.*^[60] included six trials evaluating the effects of CH (4 studies) or GL (2 studies) on narrowing of joint space. They found significant small to moderate protective effects on minimum joint space narrowing, after 3 years of treatment with GS (SMD 0.43, 95%CI: 0.24-0.63, $P < 0.001$). The same was observed for CH sulphate, which had a small but significant protective effect on minimum joint space narrowing after 2 years (SMD 0.26, 95%CI: 0.13-0.39). This SR concluded that GL and CS may delay radiological progression of OA of the knee after daily administration for over 2 or 3 years. However, the number of RCTs assessed was low and important big studies were missing from the evaluation^[61,62]. No clinical assessment was included in the outcomes and no methodological assessment of the included trials was performed. Two of the publications assessing CH where part of the same study, which was not taken into account in the meta-analysis^[63,64].

A comprehensive Cochrane SR assessed RCTs of GL^[12]. After the update in 2009, 25 RCTs were included (with 4963 patients). The analysis of the literature in this SR showed controversial results. There was evidence to show that GL is more effective in treating pain when compared with placebo showing an estimated relative per cent change from baseline of 22%. There was also superiority in Lequensne Index score (11% relative change from baseline), WOMAC total score and physician global assessment but not in other outcomes like WOMAC pain, stiffness and function subscales, minimum joint space width, patient global assessment. The majority of studies included had some form of relationship with a specific pharmaceutical manufacturer (Rottapharm). Interestingly, the authors found significant differences between the studies related with this manufacturer and the rest of the studies. Thus, studies in which this company's product was compared with placebo showed superiority of GL, even in radiological progression. However, pooled results from studies not using this product or from higher quality studies (with adequate allocation concealment) failed to show any benefit. It was clear though that GL had an

excellent safety profile, with complication rate equal to placebo and significantly less than NSAIDs.

Similarly, a recent SR from Singh *et al.*^[65], in the Cochrane library, included 42 RCTs that assessed the effectiveness of CH compared with placebo or control treatments. The authors concluded that there was a superiority of CH (alone or in combination with GL) over placebo, in terms of pain relief, in short-term studies. Moreover, CH had a lower risk of adverse events compared with control treatments. A limitation was the generally poor quality of studies available.

Regarding safety, all the SRs confirmed the safe profile of both GL and CH. In the total number of adverse events, withdrawals, or serious adverse events, no difference was found comparing with placebo^[10,11,56]. Between trial heterogeneity, when reported for adverse events, was low in all cases^[10,11].

DISCUSSION

There are several publications, from case series to RCTs, assessing the effectiveness and safety of GL and CH for the treatment of OA. However, there is criticism regarding the quality and validity of the majority of these studies. Even higher quality level I trials have been criticized for their non-transparent and low quality design. The vast majority have also been conducted by the manufacturing companies, increasing the risk of sponsorship bias. The low number of participants, non-defined source and preparation of the supplements used, short-term of follow up and outcome retrieval, non-defined dosing have also been discussed as sources of bias. Besides, there is increased heterogeneity among trials, mainly due to different dosing, different duration of application, different follow-up times, use of various escape or concomitant treatments (*e.g.*, pain killers, NSAIDs, physiotherapy).

Meta-analysis is the best tool available to collect and summarize all this spare and controversial information and to synthesise it, providing a more secure conclusion on the efficacy and safety of these interventions. The stratified analysis and subgroup analysis give the possibility to detect the effect of factors that are considered to potentially introduce heterogeneity or bias, like sponsorship of the study, inadequate treatment concealment, not binding of the outcome assessors, *etc.*

There are several level I SRs assessing GL and CH. Each of these has different inclusion or exclusion criteria resulting in a variety of number of studies included. The outcomes that are extracted from primary studies and analysed in the meta-analysis also differ in their nature and also in the time points assessed.

Despite the different methodology of these SRs, it seems that almost all conclude to a similar result; CH and GL have an effect size slight better when compared with placebo. However, when only the information from best quality trials are considered, then none of these supplements seem to demonstrate any superiority. Therefore, almost all of these level I reviews conclude to

a lack of established efficacy, eventually suggesting that CH or GL should not be used in new patients.

Most of these SRs confirmed that the heterogeneity among trials could not be expected by chance alone. Bigger, methodologically sound independent trials did not show heterogeneity and did also not show relative efficacy of the intervention (either GL or CH)^[10]. Cumulative analysis has also shown that newer publications showed smaller effects than did older publications^[10,19].

According to the outcome of most of the SRs, there is a substantially increased risk of sponsorship bias in the available RCTs and this bias contributes to increased heterogeneity. It seems that the majority of the studies is financially supported in any form; either the manufacturer conducted the study, or provided with the drug or authors were supported. Sponsored trials showed more favourable results for the interventions although the rest of the studies did show null efficacy. It was also shown from some SRs that when a specific company was involved, the results were more favourable for the intervention. However, we should not exclude the possibility that some of this heterogeneity could be due to the use of different supplement formulations or to different dosing protocols. Such information was not regularly provided so to systematically detect this possibility.

Assumptions about reasons for failure

Animal studies have shown very good results favouring these supplements. However, it seems that these findings do not correlate with clinical level I studies. There are two possible explanations for this inconsistency. One might be the publication bias. It has been shown that studies with negative results are more likely not to be published^[66,67]. This may be even more exacerbated in experimental animal studies, as usually protocols are not preregistered and therefore there is usually no obligation to publish any of the results. Another important reason is potentially the concentrations of supplements experimentally used in animals. The plasma concentrations achieved in animal studies can be hundreds times higher than the maximal concentration that can realistically be achieved after oral administration of 1500 mg of GL sulphate in human subjects^[68]. Therefore, although a positive effect is noticed even in histological examination of cartilage, such a result cannot realistically be expected for humans^[69]. It has been suggested that the therapeutic doses used in humans do not even allow the identification of proteoglycan synthesis as a mechanism of action of GL^[69-71]. Therefore, extrapolation of the *in vitro* data directly to the *in vivo* situation should be done with great caution^[69].

Pharmacokinetic and bioavailability of these supplements in the human joints after oral administration is certainly an issue that has to be further investigated^[72]. There is evidence supporting that both GL and CH reach and retain a certain concentration in plasma

and also in joint fluid and cartilage, after normal doses administered *per os*^[50,68,73-75]. However, as previously mentioned, there is no solid evidence to directly prove cartilage synthesis or regeneration in humans, as a result of this concentration.

Regarding dosing, little research has been published, thus no dietary reference intake currently exists for either GL or CH. There is an accepted daily dosage of 1500 mg for GL and 1200 mg for CH, rather empirically adopted, although different dosage schemes have been suggested in the literature^[61,76]. This lack of consensus regarding the total daily dose or the dosing scheme may be an additional reason for the controversial and heterogeneous outcomes of related studies. However, the results and conclusions for the effectiveness or safety of GL and CH remain the same, even in SRs that excluded the subtherapeutic doses of GL and CH, which probably rejects this assumption^[11,59].

A very important factor in the use of GL or CH is the length of therapy^[46]. There are preliminary studies that showed clinical efficacy even at 4-12 wk of treatment^[77,78]. However, these studies were of poor quality and high risk of bias and usually involved a rescue treatment with pain killers^[46]. In more recent and higher quality trials, effects are not seen before 3 to 6 mo. Nevertheless, in most of the recent studies, the duration has been extended at least to 6 mo.

The selection of the patients and the use of treatment algorithms are probably mandatory. Even in single trials, there is usually not a limitation in specific age groups or OA grading. In 2 years follow up of GAIT trial, patients with more primary OA (Kellgren/Lawrence grade 2), seemed to have the higher potential for disease modification when compared with grade 3 cases, after combined GL and CH administration^[62]. However, there is little known for the relative efficacy of any of these supplements in different age groups or different OA grades. Summarizing the outcomes of all these groups includes the assumption of equal action and effectiveness, which is yet not shown.

Felson *et al*^[79] highlighted the role of the mechanical environment of an osteoarthritic joint for the success of any pharmacological treatment. Mechanical abnormalities, including joint malalignment, bony remodelling or instability, contributing to or being caused by the OA, may need to be addressed and corrected if possible, before any pharmacological treatment. None of the currently available drugs or supplements could probably have a reversible effect on the joint as a whole. Tissue-level dynamic stresses on cartilage in OA joints may also exceed thresholds that could be reversed by any effective pharmacologic agent. The mechanical factor has not been widely considered in the trials that assess the treatment role of either GL or CH, and this is potentially a reason for the lack of efficacy as it is shown in these trials.

Joint space narrowing has been used as an indicator for the alteration of the OA progression in the knee joint after the use of GL or CH^[63,64,80-82]. Meta-analysis

of this data has concluded that GL and CH may reduce the joint space narrowing after 2-3 years of continuous administration^[60]. The SR of Wandel *et al*^[11] additionally analysed 3 more recent RCTs concluding to a null effect size^[11,62,83,84]. However, the measurement of joint space was performed by X-rays, which is criticised as a not accurate and reliable tool. In none of these studies the cartilage width was assessed.

Limitations of evidence

The quality and validity of the information provided above, regarding the efficacy and safety of GL or CH, is limited by the quality of the studies available. The low quality of published studies and the high risk of bias which is introduced by several factors (*e.g.*, poor methodology, poor reporting) limit the value of any suggestion or guidelines. The high interest of industry may have potentially impacted the currently available information.

There is evidence from funnel plots suggesting an absence of trials with both small numbers of participants and small or null treatment effects. This may be the result of selective publication of "positive" trials (that favours the new intervention) or of premature termination of trials with negative or null results. The high rate of sponsorship among the RCTs of GL or CH strengthens the possibility of high publication bias. However, this is just an assumption and in any case cannot be considered as evidence.

The pooling of different preparations of these supplements or products with different administration paths may increase the heterogeneity and decrease the validity of the outcomes in any meta-analysis. In many published trials the specific preparation of the supplements is not reported.

In many published meta-analyses, although the overall summary suggested a superiority of the intervention, the subgrouping of higher quality studies revealed a null effect size. In almost all cases only a few studies were of high quality. Therefore, one should argue that the limited number of studies decrease the power of the meta-analysis. This might provide a potential explanation for the trend for null effect sizes in such assessments.

Implications for research

Despite the large number of the available RCTs, there are still several questions not yet answered, first being the efficacy of GL and CH.

There is need for higher quality of information, either from RCTs or SRs. Therefore, more independent (not sponsored) high-quality randomized trials should be conducted. Trials should adhere to methodological standards that aim to reduce the risk of bias introduced (*e.g.*, CONSORT)^[85]. SRs play also a mandatory role in evidence based information and should also follow similar standards (*e.g.*, MECIR)^[86].

The best dosage scheme is still not yet defined by evidence. The duration of treatment that might provide

(if any) symptoms' relief or cartilage restoration is also still unknown. More advanced tools (*e.g.*, MRI) should be used to assess the joint and to detect for any restoration or regeneration of cartilage. The quality and quantity of cartilage should also be more accurately defined (*e.g.*, with DGEMRIC)^[87].

It is still unclear which patients groups (if any) may profit from the use of such supplements. For this reason research, should be focused on assessing specific age groups, with specific OA grading. Inclusion criteria should be carefully and strictly defined. Idiopathic OA patients should be examined separately from secondary cases. By adding confounding factors like different stages of OA or different age groups the heterogeneity is increased, thus limiting the validity of outcomes. A more specific determination of supplements' characteristics and preparations is also mandatory to decrease this heterogeneity.

Implications for practice

There is currently no convincing information on the efficacy of GL or CH as treatment options in OA.

A positive effect of GL and CH on both clinical and radiological findings has been shown. However, only a few high-quality level I trials exist, especially for the assessment of radiological progression of OA. The effect sizes are small and probably not clinically relevant. However, even the validity of these results is limited by the high risk of bias introduced in the studies. Both GL and CH seem to be safe with no serious adverse events reported.

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Current management of talar osteochondral lesions

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Abstract

Osteochondral lesions of the talus (OLT) occur in up to 70% of acute ankle sprains and fractures. OLT have become increasingly recognized with the advancements in cartilage-sensitive diagnostic imaging modalities. Although OLT may be treated nonoperatively, a number of surgical techniques have been described for patients whom surgery is indicated. Traditionally, treatment of symptomatic OLT have included either reparative procedures, such as bone marrow stimulation (BMS), or replacement procedures, such as autologous osteochondral transplantation (AOT). Reparative procedures are generally indicated for OLT < 150 mm² in area. Replacement strategies are used for large lesions or after failed primary repair procedures. Although short- and medium-term results have been reported, long-term studies on OLT treatment strategies are lacking. Biological augmentation including platelet-rich plasma and concentrated bone marrow aspirate is becoming increasingly popular for the treatment of OLT to enhance the biological environment during healing. In this review, we describe the most up-to-date clinical evidence of surgical outcomes, as well as both the mechanical and biological concerns associated with BMS and AOT. In addition, we will review the recent evidence for biological adjunct therapies that aim to improve outcomes and longevity of both BMS and AOT procedures.

Key words: Osteochondral lesions of talus; Comprehensive review; Diagnosis; Bone marrow stimulation; Autologous autograft transfer; Biologics

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Core tip: Osteochondral lesions of the talus are often missed after acute ankle sprains and fractures. Magnetic resonance imaging is most sensitive in diagnosing these injuries. Bone marrow stimulation (BMS) is effective for lesions < 150 mm² in area, but replacement procedures such as autologous osteochondral transplantation or allografts may be required for larger lesions or if BMS fails. Long term studies should attempt to determine the most effective treatment strategy and the critical defect strategy beyond which BMS will not work.

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INTRODUCTION

Osteochondral lesions of the talus (OLT) can occur in up to 70% of acute ankle sprains and fractures^[1]. OLT have become increasingly recognized with the advancements in cartilage-sensitive diagnostic imaging modalities such as magnetic resonance imaging (MRI). These lesions typically involve a component of the articular surface and/or subchondral bone (SCB)^[2]. Although trauma is the primary etiology, non-traumatic causes have been reported including congenital factors, ligamentous laxity, spontaneous necrosis, steroid treatment, embolic disease, and endocrine abnormalities^[2,3].

A systematic review by Zengerink *et al*^[4] demonstrated that up to 50% of patients failed to resolve their symptoms by conservative treatment. Traditionally, treatment of symptomatic OLT have included either reparative or replacement surgical procedures. Typically, the decision to repair or replace is based primarily on lesion size. Reparative procedures, including bone marrow stimulation (BMS), are generally indicated for OLT < 15 mm in a diameter or 150 mm² in area^[5]. Replacement strategies, such as osteochondral autologous transplantation (AOT), are used for large lesions or failed primary repair procedures^[6]. Although previous clinical literature has demonstrated good to excellent short- and mid-term clinical outcomes, there has been an increase in the concerns regarding the methodological quality of previous clinical studies and deterioration of the ankle joint following surgical interventions.

In this review, we describe the most up-to-date clinical evidence of surgical outcomes, as well as increasing concerns associated with BMS and AOT. In addition, we will review the recent evidence for biological adjunct therapies that have been used to improve outcomes and longevity of both BMS and AOT.

CLINICAL PRESENTATION AND DIAGNOSIS

Most OLT are a sequelae of ankle injuries. Unfortunately, there are no specific physical examination findings that can accurately assess and diagnose OLT, and up to 50% of patients have missed OLT on plain radiographs^[7]. It is therefore important to have a high level of suspicion of OLT in patients who have persistent ankle joint pain and a history of ankle injuries.

Patients with OLT frequently present with non-specific chronic ankle pain. Associated symptoms may also include generalized ankle swelling, stiffness, and weakness, which is often exacerbated by prolonged weight-bearing or high impact activities^[2]. In the physical examination, a patient's complaint of tenderness or pain may be poorly localized and may not correspond with the location of the OLT^[8]. Examiners should perform both anterior drawer and standard inversion maneuvers to detect concomitant lateral ankle instability, and they should also assess hindfoot malalignment, joint flexibility, and joint laxity.

Anteroposterior, mortise, and lateral ankle weight-bearing radiographs are useful when assessing joint alignment and other coexisting abnormalities such as osteophytes and loose bodies. However, more advanced imaging is often recommended, since plain radiographs have been shown to miss up to 50% of OLT^[9]. Computed tomography (CT) has excellent ability to detect OLT, accounting for 0.81 sensitivity and 0.99 specificity^[7]. Although CT is useful in obtaining detail about bony injury including the condition of SCB, concomitant osteophytes, and loose bodies, it lacks the ability to assess the cartilage compartment of OLT. MRI is the recommended imaging diagnostic modality, with 0.96 sensitivity and 0.96 specificity^[7]. MRI is advantageous in that it can show both osseous and soft tissue pathologies that are frequently associated in OLT. Although several scoring systems based on the MRI have been developed for grading of OLT^[10-15], it is unclear whether any classification can direct clinical decision making. Research by Ferkel *et al*^[11] showed little correlation between MRI grading and clinical outcomes. In a prospective study of 120 ankles, Choi *et al*^[12] also found no correlation between any radiological grading and clinical outcome.

TREATMENT

Conservative treatment

Non-operative treatment strategies in asymptomatic patients can include rest and/or restriction of activities along with the use of a non-steroidal anti-inflammatory drug^[4]. A systematic review by Zengerink *et al*^[4] reported that 45% of patients reported successful outcomes when treated with conservative treatment consisting of weight-bearing as tolerated. The authors also demonstrated that 53% of patients who underwent

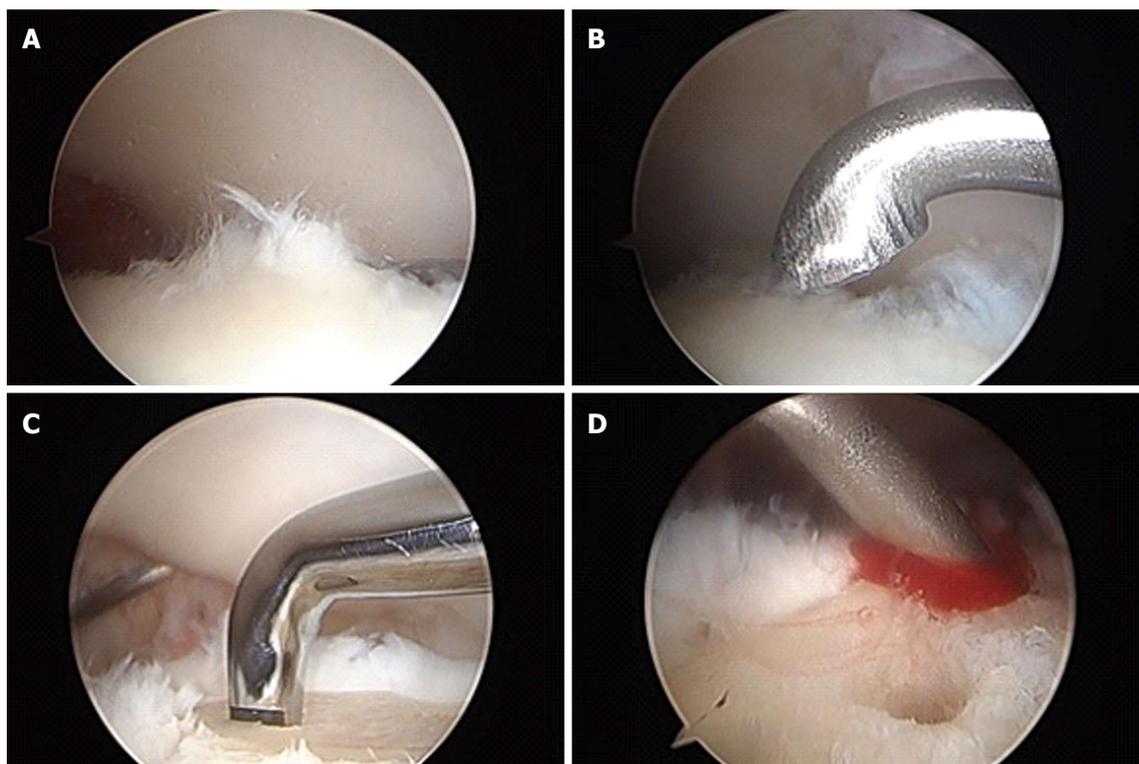


Figure 1 Arthroscopic images of osteochondral lesions of the talus. A: Osteochondral lesion of the talus identified arthroscopically; B: Frayed or fibrillated cartilage is curetted out; C: Subchondral plate is violated with microfracture pick; D: After the subchondral bone plate is violated, bleeding occurs beginning the healing response.

cast immobilization for at least 3 wk up to 4 mo reported successful clinical outcomes. However, success was determined based on symptomatic complaint rather than on the physiological healing of the OLT. In addition, the long-term outcome of these treatment strategies has yet to be established. Recent clinical studies have revealed that OLT of the ankle joint have higher levels of intra-articular inflammatory cytokines than normal ankle joint which may lead to progressive deterioration of global, as well as focal lesions over time^[16].

Operative treatment

There are two basic techniques for operative treatment for OLT: Reparative including BMS and replacement procedures including AOT. The decision to either proceed with BMS or AOT is primarily determined by lesion size. Traditionally, lesions of smaller sizes (< 15 mm in diameter or < 150 mm² in area) are treated with BMS, while larger lesions are treated with AOT^[6]. In addition, there has been recent evidence recommending AOT for patients who previously failed BMS^[17].

BMS

BMS is a reparative procedure that aims to stimulate the release of mesenchymal stem cells (MSCs) from the SCB marrow to infill fibrocartilage in the defect. In BMS, unstable cartilage, the calcified layer, and necrotic bone are debrided arthroscopically. A microfracture pick or small diameter drill is then used to penetrate the SCB plate (Figure 1).

While lesion size has been identified as the primary prognostic indicator affecting outcomes after BMS, several other prognostic factors have also been identified. Chuckpaiwong *et al*^[5] reported that almost all patients in their series with OLT greater than 15 mm in diameter failed BMS (96.7%; 31/32) while the other patients with lesions less than 15 mm in diameter had 100% success. Choi *et al*^[12] demonstrated a risk of failure with lesions greater than 150 mm² on MRI. Another important prognostic factor is containment (shoulder vs non-shoulder type) of OLT. Choi *et al*^[18] demonstrated that patients with shoulder-type OLT were more likely to have a worse clinical outcome than non-shoulder lesions. Because of the nature of BMS, subchondral bone cyst may affect the outcomes. To address this, Lee *et al*^[19] performed a randomized control study and found that there were no significant differences in clinical outcomes between patients in the subchondral cyst group and those patients treated with no subchondral cyst component. However, the longevity of these outcomes is of concern due to the lack of mechanical and biological function of SCB required for robust cartilage repair^[20].

Several clinical studies have demonstrated that nearly 85% of patients undergoing BMS report good to excellent clinical short- and mid-term outcomes^[4,21]. van Bergen *et al*^[22] evaluated long term clinical outcomes in 50 patients with at a mean follow-up of 141 mo and reported a mean American Orthopaedic Foot and Ankle Society (AOFAS) score of 88 out of 100 possible points.

Polat *et al.*^[23] demonstrated that out of 82 patients treated with BMS, 42.6% of patients had no symptoms and 23.1% of patients had pain after walking more than 2 h or after competitive sports activities at a mean follow-up of 121.3 mo.

Despite successful outcomes following BMS for OLT, there have been numerous studies demonstrating cause for concerns including the quality of the studies reporting positive outcomes, mechanical concerns regarding the fibrocartilage repair tissue, and long-term deteriorating clinical outcomes^[21]. A systematic review by Hannon *et al.*^[24] found gross inconsistencies and an underreporting of data in the included 24 clinical studies that report clinical outcomes after BMS for OLT. The authors found that only 46% of clinical studies reported the lesion size and only 25% performed postoperative radiological evaluation. Therefore, the authors concluded that there is not enough data in the current literature to accurately assess the outcome of BMS^[24].

Deterioration of reparative fibrocartilage quality has been reported in up to 35% of patients within the first five years of BMS, and only 30% of patients who received BMS have integration of the repair tissue with the surrounding native cartilage at second look arthroscopy 12 mo postoperatively^[11,14]. Becher *et al.*^[25] also demonstrated that although tissue regenerated at the site of microfracture, it was neither intact nor homogeneous. In a series of 120 ankles, Choi *et al.*^[12] has shown deterioration of clinical success rate over time following BMS.

There are numerous factors that may play a role in affecting the durability of the repair tissue following BMS. There is an increased awareness that impairment of SCB following BMS may be a cause of deterioration. Anatomically, the SCB is located under the articular cartilage offering biomechanical and biological support for overlying articular cartilage^[26,27]. During BMS, there is gross destruction of cross-talk between the SCB plate and the articular cartilage. This destruction is a result of the surgical trauma and compaction of the SCB plate that occurs with penetration of either a microfracture pic or drilling^[27]. In the sheep osteochondral lesion model, Orth *et al.*^[28] revealed that the SCB plate was not restored at 6 mo after BMS. This finding was supported in the human ankle by Reilingh *et al.*^[29] which revealed that the SCB were not filled completely in 78.6% (44 of 58) OLT at 1 year after BMS. This inevitable trauma to the SCB may be limited by using a small diameter microfracture pic rather than drilling or using larger diameter conventional microfracture pics^[27].

Mechanical and biological insufficiency may be part of the reasons for deterioration of fibrocartilage. Marrow stimulating techniques attempt to fill talar lesions with precursor cells and cytokines, resulting in a fibrin clot that will ultimately lead to fibrocartilaginous type-1 collagen formation^[10,24]. This cartilage consists of collagen that has different biomechanical properties than the native hyaline cartilage containing type-II collagen. It has been demonstrated that fibrocartilage has inferior

stiffness, resilience, and wear properties and therefore is at risk of degeneration^[30,31].

AOT

AOT replaces cartilage by transplanting a cylindrical osteochondral graft from a non weightbearing portion of the knee into a defect site on the talus (Figure 2). AOT is indicated in patients with lesion sizes greater than 15 mm in diameter or 150 mm², or in cases of failed previous BMS^[4,6]. Kim *et al.*^[32] reported prognostic factors affecting outcomes of AOT and found that patient age, sex, body mass index, duration of symptoms, location of OLT, and the existence of a subchondral cyst did not significantly influence clinical outcomes of AOT. By Haleem *et al.*^[33] reported that the size of the OLT is also not a significant predictor of outcomes and multiple grafts may be used without adversely affecting the outcome.

Several studies have reported good clinical outcomes following AOT at both short- and mid-term follow-up. A case series on 85 patients who underwent AOT found improved Foot and Ankle Outcome Score (FAOS) at 47.2 mo follow-up and improved Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores post-operatively at 24.8 mo follow-up^[34]. One study by Haleem *et al.*^[33] compared clinical and radiological MRI outcomes of OLT treated by single-plug vs double-plug AOT at 5-year follow-up. They found treatment with double-plug AOT did not show inferior clinical or radiological outcomes when compared to single-plug AOT in the intermediate term. Good outcomes are not limited to the general population only, and excellent outcomes have been reported in the athletic population at midterm follow-up. Fraser *et al.*^[35] reported improved AOFAS scores and found at final follow up of 24 mo, 90% of professional athletes and 87% of recreational athletes were able to return to pre-injury activity levels. Despite its apparent success and favorable short- and medium-term outcome profile, there has been no study to our knowledge that has described long-term (10+ years) outcomes after AOT.

AOT outcome studies however should be evaluated carefully. Hannon *et al.*^[24] showed that outcomes and clinical variables were reported in less than 73% and 67% of studies respectively. Therefore, the data between studies reported have been incongruent and limit cross sectional comparison

AOT has good clinical outcomes, but there are some mechanical concerns with the procedure such as formation of post-operative cysts, morbidity associated with accessing the ankle joint through osteotomies, and pressures on the graft due to malalignment. It has been suggested that biomechanical success may be limited by the alignment of the graft. Fansa *et al.*^[36] demonstrated increased contact pressure on the graft surface by 7-fold with a 1.0 mm of graft protrusion above the level of the native cartilage. Other mechanical considerations have also been an area of concern with AOT. The use of a medial malleolar osteotomy has raised concerns for

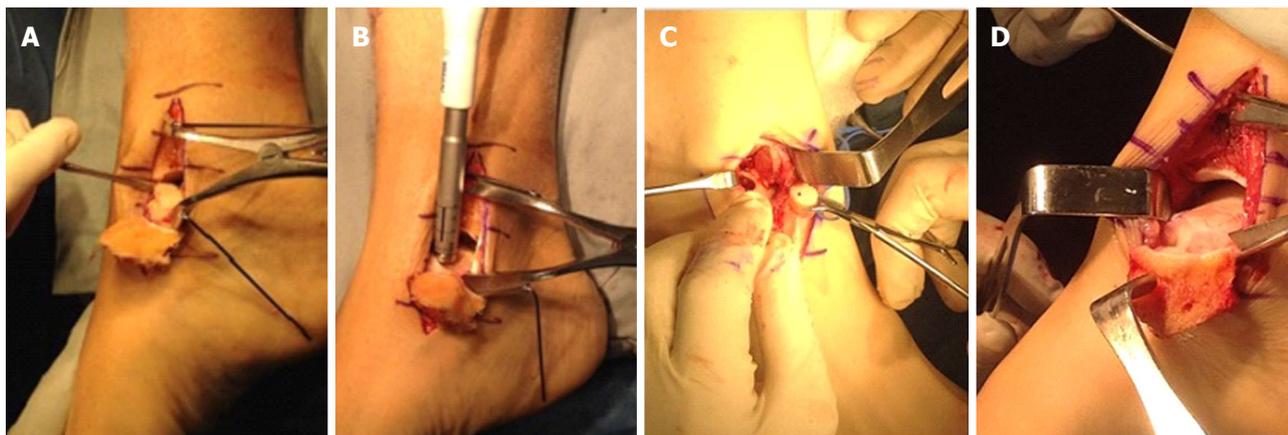


Figure 2 Autologous osteochondral transplantation procedure. A: Medial exposure of the talus; B: Preparation of the defect site; C: Insertion of cylindrical osteochondral plug into the prepared osteochondral lesions of the talus defect site; D: Exposure of the medial talus via the chevron-type medial malleolar osteotomy.

increasing the risk of mal/non-union. However, current evidence suggests adequate osteotomy, both medially and laterally, as well as cartilaginous healing in the short- to mid-term follow-up. Lamb *et al*^[37] demonstrated that a Chevron-type medial malleolar osteotomy had overall improved healing and fixation, with evidence of fibrocartilaginous tissue present at the superficial osteotomy interface. In addition, at a mean follow-up of 64 mo, a retrospective case series by Gianakos *et al*^[38] demonstrated that an anterolateral tibial osteotomy resulted in T2 mapping relaxation times similar to both superficial and deep interfaces of the native cartilage and had overall improved FAOS and MOCART scores and. However, it is known that ankle fractures may cause activation of intra-articular inflammatory cytokines, which may lead to progressive deterioration of OLT over time, and this may theoretically occur with malleolar osteotomy^[16]. There have been reports demonstrating the potential of poor integration of the AOT surface with the native tissue, cyst formation around the graft site, and deterioration of the graft cartilage as potential consequences following AOT procedure. However, a case series by Savage-Elliott *et al*^[39] demonstrated that although increasing age was related to increased cyst prevalence, the clinical impact of cyst formation was not found to be significant at a mean short-term follow up of 15 mo after surgery.

Lastly, concerns over donor site morbidity have gained increasing attention. Valderrabano *et al*^[40] reported on the outcomes of 12 patients undergoing AOT, of whom 50% experienced donor site morbidity with all patients showing MRI signs of cartilage change, joint space narrowing, or cystic changes in untreated donor sites. These results have been challenged by similar reports. Yoon *et al*^[17] found in 22 patients a 9% early donor site morbidity with 100% resolution at 48 mo follow-up. Fraser *et al*^[41] performed a retrospective analysis on 39 patients who underwent AOT and reported that at 24 mo follow-up, donor site morbidity was present in only 5% of patients and that Lysholm

scores were at 99.4 for the entire cohort. Therefore, OLT treated with AOT can have a low incidence of donor site morbidity with good functional outcomes.

Although the overall success of AOT for OLT may be limited by a combination of factors, evidence in the literature suggests that AOT is effective short- and mid-term follow-up, particularly for large lesions that may not be managed by other forms of treatment.

Osteochondral allograft transplantation

Osteochondral allograft transplantation is a technique that has been employed for the treatment of OLT and involves replacing defects in bone and articular cartilage with cadaveric donor specimens^[42]. Some surgeons prefer this procedure over AOT because it avoids donor site morbidity^[24]. Although frozen grafts may be used, the decline in the viability of chondrocytes within the graft tissue has led to an increase in the use of fresh allografts.

Reported success rates are highly variable within the literature. El-Rashidy *et al*^[43] performed one of the largest studies published on patients who received small cylindrical allografts and reported positive outcomes in 28 of 38 patients at a mean follow-up of 37.7 mo. Raikin^[44] evaluated patients who received bulk allografts and demonstrated improved AOFAS scores in 15 patients at a mean follow-up of 44 mo. Lastly, Haene *et al*^[45] reported in a case series that only ten of 17 cases who underwent allograft transplantation had good or excellent results at an average follow-up of 4.1 years. Although clinical evidence suggests osteochondral allograft transplantation to be effective in the treatment of larger OLT, this evidence is limited as it consists primarily of case series with reported variable success rates.

Autologous chondrocyte implantation

Autologous chondrocyte implantation (ACI) is a cell-based, two-stage procedure that can be used as an alternative to osteochondral grafting techniques.

This technique involves harvesting healthy articular cartilage for chondrocyte cultures, which are grown for approximately 30 d^[46]. These cultures are implanted into the defect site. The aim of ACI is to promote the development of hyaline-like repair tissue. ACI is typically indicated for full-thickness cartilage defects with an intact SCB plate with stable edges of the surrounding cartilage^[47].

A systematic review by Harris *et al.*^[48] analyzed 82 studies (5276 subjects; 6080 defects) and reported a low failure rate of 1.5%-7.7% following ACI in the knee. Similar outcomes have been shown in the ankle. A meta-analysis by Niemeyer *et al.*^[49] reported a clinical success rate of 89.9% in 213 patients following ACI. Gobbi *et al.*^[50] reported no difference in AOFAS scores following chondroplasty, microfracture, and AOT. Disadvantages of ACI include the cost of culturing hyaline cells, the need for two surgical procedures, hypertrophy of the graft and the durability of the graft^[2].

Although many studies have published promising results, the available evidence to date is of poor quality due to the level of evidence, low patient number, and use of variable outcome parameters^[47]. Therefore, randomized clinical trials are necessary to determine the superiority of ACI over other more established techniques.

Matrix-induced autologous chondrocyte implantation

Matrix-induced autologous chondrocyte implantation (MACI) is a second generation of ACI whereby cells are embedded into a bioabsorbable matrix^[24]. This membrane is placed over the talar cartilage defect. This procedure avoids periosteal graft harvesting and allows for a more even cell distribution^[51]. In addition, a fibrin sealant can be utilized to secure the defect, reducing the need for suture fixation.

Evidence in the literature has demonstrated arthroscopic MACI as a safe alternative for the treatment of OLT with good overall clinical and radiologic results. Aurich *et al.*^[52] reported in a case series of 19 patients, significant improvement in AOFAS clinical scores following MACI at a mean follow-up of 24 mo. Giannini *et al.*^[53] also reported positive clinical and histologic outcome scores at 36 mo post-operatively.

Evidence has demonstrated MACI to be a promising new treatment method for large OLT. Future research should attempt to compare radiological, clinical, and histological MACI to conventional treatment.

BIOLOGIC AUGUMENTATION FOR CARTILAGE REPAIR

Platelet-rich plasma

Platelet-rich plasma (PRP) is an autologous blood product that contains at least twice the concentration of platelets compared to baseline values, or $> 1.1 \times 10^6$ platelets/ μL ^[54]. Platelets contain numerous growth factors and cytokines which have been shown to induce

human-MSc proliferation and promote tissue healing^[55]. There has been evidence in the literature that demonstrates positive effects of PRP on cartilage repair. Smyth *et al.*^[56] showed in a systematic review that 18 of 21 (85.7%) basic science papers reported positive effects of PRP on cartilage repair. Additionally, Smyth *et al.*^[57] found in a rabbit model, that application of PRP at time of AOT improved the integration of the osteochondral graft at the cartilage interface and decreased graft degeneration. In clinical studies, Guney *et al.*^[58] performed a randomized control trial in 19 OLT patients and reported that BMS with PRP had better functional outcomes when compared with BMS alone. Görmeli *et al.*^[59] compared the effect of PRP and HA following BMS for OLT and found at 15.3-mo follow-up, clinical improvement after PRP with HA when compared to HA or saline injection alone.

Despite successful reported outcome following PRP adjuvants, the effect of PRP on OLT is still controversial because of several concerns. Currently there has been no proposed standard method for PRP harvesting. There are a variety of commercially-available centrifugation systems with various timing protocols and activation methods^[60]. In addition, plasma contains differing concentrations of platelets, cells, growth factors, and cytokine, which are variable even within a single individual^[60]. Several studies have evaluated the anti-inflammatory effects of different leukocyte concentrated PRP on cartilage repair^[61,62]. However, to our knowledge, there has been no study that has investigated the effect of leukocyte concentration in PRP in the treatment of ankle OLT. In conclusion, the published literature suggests that utilizing PRP in the operative treatment for OLT can improve clinical and functional outcomes. The evidence for PRP is promising; however, well-designed clinical trials are necessary to determine its efficacy in the clinical setting.

Concentrated bone marrow aspirate

Concentrated Bone Marrow Aspirate (cBMA) is a blood product produced by centrifuging bone marrow typically aspirated from the iliac crest^[63]. cBMA contains a variety of bioactive cytokines, as well as MSCs, which have the ability to undergo chondrocyte differentiation. In addition, most recent studies have shown that cBMA includes an abundant concentration of interleukin-1 receptor antagonist proteins (IL-1Ra), which are the primary anti-inflammatory cytokines^[63].

A few studies have demonstrated the ability of cBMA to promote the chondrogenic cascade which can be beneficial in the treatment of osteochondral lesions. Improved cartilage healing has been demonstrated in the equine model, with improvements histologically and radiographically in groups receiving cBMA at the time of BMS^[64]. In addition, similar results were reported in a goat model when using BMS combination with cBMA and HA^[65]. Clinically, Hannon *et al.*^[66] reported that mean FAOS improved significantly pre- to post-

operatively at 48.3 mo in groups receiving cBMA with BMS. They also demonstrated that groups with cBMA had improved integration of the repair tissue with MRI demonstrating less fissuring and fibrillation. Kennedy *et al*^[6] demonstrated improved restoration of radius curvature and color stratification similar to that of native cartilage on MRI using T2 mapping in patients treated with cBMA and AOT. Overall, current evidence suggests that cBMA can improve cartilage repair in OLT, but future clinical research and clinical trials are necessary for better comparison of outcomes with other biological adjuncts.

CONCLUSION

OLT present a challenge and optimal treatment remains controversial. Although future randomized clinical trials are needed to establish evidence of the most effective treatment, both reparative and replacement procedures remain feasible options. The literature supports treatment with BMS for lesions of smaller sizes, whereas treatment with AOT may be utilized for larger or cystic lesions. Cell-based techniques and allograft transplantation may be utilized in failed primary procedures. Although biologic augmentation offers promising results, well-designed clinical trials are necessary to determine efficacy in the clinical setting.

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Foot and ankle history and clinical examination: A guide to everyday practice

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Abstract

This review summarises the key points in taking a history and performing a comprehensive clinical examination for patients with foot and/or ankle problems. It is a useful guide for residents who are preparing for their specialty exams, as well as family doctors and any other doctor who has to deal with foot and ankle problems in adults.

Key words: Foot; Ankle; History; Examination and clinical assessment

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Core tip: Patients present with foot and ankle problems can have either single or multiple pathologies. Obtaining adequate history and performing good clinical examination is a key in reaching the accurate diagnosis. Adjuvant tools like radiological images can be used to confirm what has been clinically suspected.

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INTRODUCTION

Patients commonly present with foot and ankle problems, either in primary or secondary care clinics. However, many physicians find it challenging to assess these patients^[1]. This is probably related to the complexity and multiplicity of joints in this part of the body.

There are 26 bones, 33 Joints and more than 100

ligaments, tendons and muscles in each foot^[2]. On average, we walk 10000 steps per day, 1000000 steps per year and 115000 miles in our lifetime. The foot stands 3-4 times body weight during running.

This review summarises the keys points in taking a full history and performing a systematic clinical examination for patients with foot and ankle problem. It is a useful guide for residents who are preparing for their specialty exams, but also for any doctor who may have to deal with these problems in practice.

HISTORY

The common reasons for patient's presenting to the foot and ankle clinic are: Pain, swelling, deformity, stiffness, instability and/or abnormal gait^[2]. For new patients or when the diagnosis has not been confirmed before, we recommend that the examiner should not read the previous notes prior seeing the patient. This good practice allows the examiner to have more lateral thinking, with fresh eyes looking into the problem.

Pain

Ask the patient to finger point to the exact site of the maximum pain. If the pain was diffuse and not localized to one spot, try to identify the area/side of maximum discomfort. Correlate the site with the anatomical location as described in Table 1. Ask about the radiation of pain and quality or nature of it (sharp, dull or burning), whether it is related to weight bearing (degenerative changes, stress fracture or Inflammatory conditions like plantar fasciitis), the radiation (towards the toes or up the leg), severity of the pain (0-10), prevents activity, waking up during the night, time (early morning or night pain which disturbs the sleep), duration, pattern (constant/intermittent), aggravating factors (like walking distance, walking on flat or uneven floor; Going up and down the stairs; relation with shoes), and any alleviating factors (rest, analgesia, preferred type of foot wear)^[3].

The chronicity and the severity of the pain can help to establish whether there is an element of central sensitization where by the patient becomes more sensitive and experiences more pain with less provocation. Factors like sleep deprivation and depression can drive central sensitization^[4]. Finally, it is important to clarify what is the patients' belief about their foot pain.

Deformity

Enquire about the duration and when the patient or their family member first noticed the deformity, which area it involves, is it progressing, and whether it associated with other symptoms (for example, skin ulcer, pain, recurrent infection, rapid wear of shoes, or cosmetic).

Table 1 Correlations between the anatomical site of the pain and the possible underlying causes^[6]

Location of pain	Common possible pathology	
Anterior ankle pain	Degenerative disease	Impingement Ankle joint capsule injury ex. Sport injury with maximum ankle joint plantar flexion
Medial pain below the medial malleolus	Sinus tarsi syndrome Subtalar degenerative changes Tarsal coalition of mid facet	Spring ligament or deltoid ligament pathology Tibialis posterior pathology or medial impingement
Postero-medial pain	Tibialis posterior tendonitis	Flexor hallucis longus Tarsal tunnel syndrome Os trigonum pathology
Posterior pain	Achilles tendinopathy Posterior impingement	
Postero-lateral pain	Peroneal tendon	
Lateral pain	Stress fracture of distal fibula ATFL injury Lateral impingement	Sinus tarsi syndrome Subtalar pathology Calcaneal fracture malunion
Heel pain	Plantar fasciitis Calcaneal stress fracture Entrapment of first branch of lateral plantar nerve	Fat pad atrophy/contusion Tarsal tunnel syndrome Foreign body reaction Plantar fascia rupture
Mid foot pain	Degenerative disease Post traumatic arthritis	Tarsal bones stress fracture Ligament injury ex Lisfranc injury Insertional tendinopathy of peroneal brevis
Forefoot pain	Metatarsalgia Morton neuropathy Stress fracture Freiberg disease	Metatarsophalangeal joint synovitis Nail pathology
Forefoot pain - big toe	Hallux valgus/rigidus Inflamed bunion	Sesamoiditis Sesamoid fracture
Forefoot pain - 2 nd , 3 rd and 4 th toe	Claw toe Hammer toe	Mallet toe
Forefoot pain - little toe	Inflamed bunionette	

ATFL: Anterior inferior tibiofibular ligament.

Swelling

It is important to establish whether the swelling is localized to one area or the whole leg or ankle, whether it is uni- or bilateral, associated with activities, as well as the frequency and the duration of swelling. Generalized bilateral swelling that involves the whole foot and ankle is usually related to more systematic pathology, such as cardiac or renal problems. Swelling which includes the area only around the ankle joint may be related to the tibio-talar joint (for example, degenerative changes or inflammatory arthropathy). On other hand, localized swelling is more likely result from a specific local pathology. As an example, swelling anterior to the distal fibula may indicate chronic injury of the anterior inferior tibio fibular ligament (ATFL) and swelling posterior to the distal fibula may indicate peroneal tendon pathology^[5]. Acute painful or painless swelling with or

Table 2 Important points not to miss during the history taking^[6]

Important key points not to be missed in general medical history
Age
Occupation
Participation in sports
History of lower back pain
History of problems with other joints (for example, hip and knee)
Diabetes
Peripheral neuropathy
Peripheral vascular disease
Inflammatory arthropathy
Rheumatoid arthritis
Vasculitis

without the deformity of the mid foot deformity could result from Charcot neuropathy.

Instability

Enquire as to when the first episode of instability or sprain occurred, how often it happens and what can precipitate it^[6].

History of trauma

History of trauma with details of immediate symptoms and treatment, surgery, injections or infection with date and details of any identified.

Associated symptoms

It is important to look out for red flags symptoms such as night sweating, temperature or weight loss, which may be related to an infection or neoplasm. Neurological symptoms like numbness, limb weaknesses or burning sensation are usually related either to spinal problem or peripheral neuropathy.

General medical history

It is important to cover all the key points that are summarised in Table 2.

CLINICAL EXAMINATION

The examination begins from the first moment of meeting the patient by observing the gait and whether he/she uses any walking aids. The patient should be adequately exposed and ideally patients should wear shorts with bare feet. Ask for chaperone if appropriate.

Inspection of the patients footwear, insole, and walking aides

Start by examining the patient shoes and whether they are commercial or surgical shoes. Look at the pattern of the wear, which usually involves the outside of the shoe heel. Different patterns of wear indicate abnormal contact of the foot with the ground. Early lateral, proximal, and mid shoe wear, indicates a supination deformity; wear on the medial border indicates a pronation deformity^[2]. In case of absence of any

Table 3 Correlations between the different gait patterns and the functional assessment

Examination of gait	Assessing the following aspects
Tiptoe walking	Ankle flexibility Posterior impingement Achilles/tibialis post function Midfoot function MTPJ problems Fractures (Stress) S1/2 function
Heel walking	Ankle mobility Anterior impingement Tibialis anterior function L4/5 EHL/EDL function Plantar fasciitis/heel problems
Inner borders (inversion)/ outer borders (eversion) foot walking	Sub talar mobility Tibialis posterior function Peroneal tendons function 5 th ray problems Medial and lateral gutter impingement 1 st ray problem

wear, it may simply reflect new or unused pair of foot wears. Look for any orthosis or walking aides. Inspect any insole and ask the patient which type of insole is comfortable and which type is painful.

Examination in a standing position

In most clinical setting the patient is sitting on the chair at the start of the examination. First ask the patient to stand up, and assess the alignment of the lower limbs as a whole. In particular look for any excessive varus or valgus knee deformity. Inspect the alignment of the spine in case of scoliosis, and look for any pelvic tilt. Inspect for any thigh or calf muscles wasting^[7].

Look from the side for the feet arches (is there any pes cavus or pes planus), any swelling or scars. Inspect for any big toe deformity (hallus valgus, hallux valgus interphalangeus or hallus varus), lesser toes deformity (mallet toe, hammer toes, claw toes)^[1]. In normal ankle, you should not be able to see the heel pad on the medial side when you inspect from the front. If this was visible then it is called "peek a boo" sign which exists with pes cavus^[2]. It is important to compare both sides as a false-positive sign may be caused by a very large heel pad or significant metatarsus adductus^[8].

Inspect the ankle from the back for any bony bumps like calcaneal boss^[1]. The normal ankle alignment is neutral. Also notice if there is a "too many toes" sign. In a normal foot you should not be able to see more than 5th and 4th toes when you look at it from behind. If there were more toes visible (3rd or 3rd and 2nd), then it is called "too many toes" sign which can indicate an increased heel valgus angle.

Ask the patient to stand onto tiptoes. Both ankles should turn into varus. This indicates normal subtalar movement and, in case of flat feet, if a medial arch

Table 4 Different types of abnormal gaits

Type of the gait	Physical findings and observations	Possible cause
Antalgic gait	Short stance phase of the affected side Decrease of the swing phase of the normal side	Pain on weight bearing could be any reason from Back pathology to toe problem, <i>e.g.</i> , degenerative hip joint
Ataxic (stamping) gait	Unsteady and uncoordinated walk with a wide base	Cerebral cause Tabes dorsalis
Equinus (tiptoes) gait	Walking on tiptoes	Weak dorsiflexion and/or plantar contractures
Equinovarus gait	Walking on the out border of the foot	CETV
Hemiplegic (circumductory) gait	Moving the whole leg in a half circle path	Spastic muscle
Rocking horse (gluteus maximum) gait	The body shift backward at heel strike then move forward	Weak or hypotonic gluteus maximum
Quadriceps gait	The body leans forward with hyperextension of the knee in the affected side	Radiculopathy or spinal cord pathology
Scissoring gait	One leg crosses over the other	Bilateral spastic adductors
Short leg (Equinus) gait (more than 3 cm)	Minimum: Dropping the pelvis on the affected side Moderate: Walks on forefoot of the short limb Severe: Combination of both	Leg length discrepancy
Steppage gait (high stepping - slapping - foot drop)	No heel strike The foot lands on the floor with a sound like a slap	Foot drop Polio Tibialis anterior dysfunction
Trendelenburg (lurching) gait	Trunk deviation towards the normal side When the foot of the affected side leaves the floor, the pelvis on this side drops	Weak gluteus medius
Waddling gait	Lateral deviation of the trunk with an exaggerated elevation of the hip	Muscular dystrophy

Table 5 Movements of the ankle joint and possible causes of restrictions^[3,9]

Movement	Normal range of motion	Possible causes of restriction
Dorsiflexion	0-20 degrees	Tight Achilles tendon Tightness of the posterior ligaments Loss of flexibility in the ankle syndesmosis Impingement of anterior soft tissue or osteophytes
Plantar flexion	0-50 degrees	Anterior capsule/ligaments contractures Posterior impingement
Inversion	0-35 degrees	Tension in the joint capsules and the lateral ligaments ¹
Eversion	0-15 degrees	Tension in the joint capsules and the medial ligaments ¹

¹Inversion and eversion is mostly the motion of subtalar joint, the most common causes of restriction including subtalar arthritis, tarsal coalitions or calcaneal fracture malunion.

forms on standing on tip toes then this is a flexible pes planus^[1].

Gait: Enquire if the patient can walk without a support and be prepared to provide support for elderly patients and those who may unsteady on their feet. Ask the patient to walk as per their normal gait. Observing the gait from the front and the back help to assess the shoulder and pelvic tilt. Looking from at the hip movements, knee movements, initial contact, three rockers, stride length, cadence and antalgia.

The patient should then be asked to walk on his/her tiptoes, then heels, inner borders and finally the outer borders of the feet. Correlate your finding with possible

causes as described in Tables 3 and 4. Beware not to miss a foot drop.

Examination in a sitting position

By this stage, a fair idea of the possible diagnosis may have been established. Hence, you should be able to direct the rest of the examination accordingly. We recommend at this stage to ask the patient to sit on the examining couch, with the legs hanging loosely from the side. Raise the bed so the patient’s foot is at the level of the examiner’s hand, and sit on a chair opposite the patient.

Look: Start with meticulous inspection of the sole then the rest of the foot. Look for skin discoloration, scar, ulcer, lack of hair (circulatory changes), nails, any skin thickening (callosity), hard/soft corns and any signs of infection^[7].

Feel: First ask the patient if there are any areas which are painful to touch, so you can try to avoid causing pain during the examination. Then you start with gentle feel of the skin temperature, always comparing to the other side.

The second part of the palpation is to establish area of tenderness. Always follow a systematic method of palpation so you will not miss any part. We recommend to start the palpation for tenderness from proximal fibula, Achilles tendon, distal fibula, peroneal tendons, PTFL, CFL, ATFL, AITFL, Sinus tarsi, Calcaneum, Calcaneocuboid (CC) joint, Cuboid, lesser Metatarsals, Phalanges, 1st IP and MTP joint, 1st ray, TMT joints, Cuneiforms, Navicular, TN joint, Talus, Ankle

Table 6 Examination techniques of muscles functions^[3]

Muscle	Ankle position	Manoeuvre of the test
Tibialis Anterior	Maximum Dorsiflexion and inversion	Try to plantar flex the ankle with your hand and ask the patient to resist, use your second hand on the tendon to feel the contraction (Figure 1)
Tibialis posterior	Plantar flexion and inversion	Patient inverts the foot in full plantar flexion whilst the examiner pushes laterally against the medial border of the patient's foot (in an attempt to evert the foot). The examiner needs to use second hand on the tendon to feel the contraction (Figure 2)
Peroneal longus and peroneal brevis	Plantar flexion and eversion	Patient everts the foot in full plantar flexion and the examiner pushes medially against the lateral border of the patient's foot (in an attempt to invert the foot) (Figure 3)
Extensor hallucis longus	Neutral	Patient extends the great toe and the examiner try to planter flex it (Figure 4)
Extensor digitorum longus	Neutral	Patient extends the lesser toes and the examiner try to planter flex it ¹ (Figure 5)
Flexor hallucis longus and flexor digitorum longus	Neutral	Patient curls the toes downward and the examiner tries to dorsiflex them ¹

¹It can be difficult to neutralize the intrinsic muscles completely.

Table 7 Examination techniques of performing the foot and ankle special tests^[2,3,9,10]

Name of the test	Purpose of the test	Maneuver
Anterior drawer test	Lateral ligament complex	The leg hangs loosely off the table The examiner hold the patient's leg just above the ankle joint with one hand The examiner uses the other hand to hold the ankle in plantar flexion and try to gently to pull the ankle forward - anterior translation (Figure 6) Look at the skin over the anterolateral dome of the talus to watch for anterior motion of the talus with this maneuver - sulcus sign
Inversion stress test	Stability of the lateral ankle ligaments (ATFL)	The knee is flexed 90 degree With one hand perform inversion stress by pushing the calcaneus and talus into inversion while holding the leg from the medial side with the other hand (Figure 7) The test is positive when there is excessive inversion and/or pain
Calf compression or "squeeze" test	Syndesmotic injury	The leg hangs loosely off the table - knee flexed The examiner uses both hand to squeeze at midpoint of the tibia and fibula Pain caused by this maneuver indicates Syndesmotic injury
External rotation stress	Syndesmotic injury	The leg hangs loosely off the table - knee flexed and foot fully dorsiflexed The examiner uses one hand to stabilize the lower leg With the other hand they externally rotate the foot Pain caused by this maneuver indicates Syndesmotic injury
Coleman block test	To assess the flexibility of the hindfoot, <i>i.e.</i> , whether the cavus foot is caused by the forefoot or the hindfoot	A block is placed under the lateral border of the patients foot The medial forefoot is allowed to hang over the side The first metatarsal will be able to drop below the level of the block, <i>i.e.</i> , eliminate the contribution by the first ray (Figure 8) With a flexible hindfoot, the heel will fall into valgus or neutral termed forefoot-driven hindfoot varus In case of rigid hindfoot or hindfoot-driven hindfoot varus the heel will remain in varus, and no correction will be happen
Semmes-weinstein monofilament test	To assess the degree of sensory deficit	Pressure testing using a 10 g Semmes-Weinstein mono- filament. Especially useful in diabetic charcot feet (Figure 9)



Figure 1 Test for tibialis anterior muscle.



Figure 2 Test for tibialis posterior muscle.

Table 8 Examination techniques of performing the foot and ankle special tests^[2,3,9,10]

Name of the test	Purpose of the test	Manoeuvre
Silfverskiold test	Differentiate between a tight gastrocnemius and a tight soleus muscle	The leg hangs loosely off the table - knee flexed Dorsiflex the ankle to the maximum Patient should then extend their knee Repeat the ankle dorsiflexion (Figure 10) If there was more ankle dorsiflexion with the knee flexed then there is gastrocnemius tightness
Thompson's test	Achilles' tendon rupture	Patient lies is prone on the bed or kneel on a chair The examiner gently squeeze the gastrosoleus muscle (calf) If the tendon is intact, then the foot passively plantar flexes when the calf is squeezed
Test for tarsal tunnel syndrome	Compressions of the posterior tibial nerve underneath the flexor retinaculum at the tarsal tunnel	Tap inferior to the inferior to the medial malleolus to produce Tinel's sign
Test for flat foot	Differentiate between flexible <i>vs</i> rigid	Ask patient to stand on tiptoes If the medial arch forms and heel going into varus then it is flexible flat foot Beware of rupture tibialis posterior tendon or tarsal coalition
Test for stress fractures	Stress fractures	Place a tuning fork onto the painful area If it increases the pain, then it is positive Other test: One spot tenderness on palpation with finger
Babinski's response	Upper motor neuron disease	Scratch the lateral border of the sole of the foot A positive response is dorsiflexion of the great toe
Oppenheim's test	Upper motor neuron disease	Run a knuckle or fingernail up the anterior tibial surface A positive response is dorsiflexion of the great toe
Mulder's test	Morton's neuroma	A mass felt or audible Click is elicited by palpating (grasping) the forefoot (web space) with the index finger and thumb of the examiner

joint, Medial malleolus, Tibialis post, Tibialis anterior, extensors and other flexors and finally plantar fascia.

Move: Start with active movement by asking the patient to perform dorsiflexion, plantar flexion, inversion, and eversion. Always compare both sides (Table 5).

This will be followed by passive movement of dor-siflexion: As the patient is already sitting, the knee is flexed to 90 degrees then repeat the test with knee straight (Silfverskiold test). Keep the foot in a neutral position (0 degree of inversion and eversion), hold the back of the leg with one hand and use the palm of the other hand to push the sole of the examined foot^[9].

Table 9 Three common pathologies and the related necessary clinical tests^[7]

Special pathology	Required tests
Pes cavus	Claw toes Examine peroneal tendons Tibialis anterior and posterior Coleman block test Examine the Achilles tendon Full lower and upper limb neurological examination Hand - inspect for muscle wasting Spine
Pes planus	Single leg sustained tip toe test Testing tibialis posterior power Too many toes sign Examine the Achilles tendon
Hallux valgus/ rigidus	Dorsal osteophyte Passive ROM Grind tests Correct the deformity Examine the Achilles tendon

Table 10 Medical Research Council scale to assess the strength of muscle^[8]

Grade	Description
Grade 0	No contraction
Grade 1	Flicker or trace of contraction
Grade 2	Active movement with gravity eliminated
Grade 3	Active movement against gravity
Grade 4	Active movement against gravity and resistance
Grade 5	Normal power

Now move the palm of the hand to the dorsum of the examined foot to produce the passive plantar flexion.

Supination and pronation are triplanar movements. Supination is the combination of Inversion, Plantar-flexion and adduction. Pronation is the combination of Eversion, Dorsiflexion and Abduction.

Inversion: Place one hand over the back of the leg and use your other hand to grasp the calcaneus between your index finger and thumb and use your forearm to fully dorsiflex and lock the talus in the ankle. Rotate the calcaneus in a medial direction to test for inversion and move your hand in a lateral direction to test for Eversion^[9].

Midfoot movements: Stabilize the calcaneus and talus with one hand and use the other hand to move the foot medially to test for Adduction). Move the foot laterally to test for the abduction^[9]. It is also important to examine the motion of midfoot (transverse tarsal joint) on sagittal plane (specially for patients with end stage ankle arthritis). The motion of 1st TMT joint should be examined as well (for patients with hallux valgus or flexible flatfoot).

Forefoot movements (metatarsophalangeal and interphalangeal joints): You should test the



Figure 3 Test for the peroneal tendons.



Figure 4 Test for extensor hallucis longus.



Figure 6 Anterior drawer test.



Figure 5 Test for extensor digitorum longus.



Figure 7 Inversion stress test.

movement in each joint separately. If there is any deformity, try to find whether it is correctable or not (for example, a fixed flexion deformity).

The examination of muscular function and the special tests should be the next step of the assessment. Both of these aspects are summarised in Tables 6, 7, 8 and 9. The strength of each muscle is assessed using the medical research council (MRC) scale Table 10.

The examination of the foot and ankle is not complete until you perform neurovascular examination, an examination of the spine (deformity like scoliosis, hair

tuft on the lower back), leg length, hip joint examination and knee joint examination.

Finally, it is important to consider Functional testing which is important and needs to be appropriate to the level and background of the patient for instance, a single leg squat or squat jump for higher level athletes may indicate issues not obvious with more static tests.

CONCLUSION

The assessment of foot and ankle pathology can



Figure 8 Coleman block test.



Figure 9 Semmes - weinstein monofilament test.



Figure 10 Silverskiold test.

be challenging, hence the importance of following a systematic method for its clinical assessment. We have described here one way of performing the clinical examination. It has been built using the best available evidence, and has been tested and evolved through the experience of the senior author. We recommend this approach for residents who are preparing for their specialty exams, for clinicians in family or sports medicine, and for any physician who has to deal with foot and ankle patients.

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Case Control Study

Digital templating in total hip arthroplasty: Additional anteroposterior hip view increases the accuracy

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Abstract

AIM

To analyze planning total hip arthroplasty (THA) with an additional anteroposterior hip view may increase the accuracy of preoperative planning in THA.

METHODS

We conducted prospective digital planning in 100 consecutive patients: 50 of these procedures were planned using pelvic overview only (first group), and the other 50 procedures were planned using pelvic overview plus antero-posterior (a.p.) hip view (second group). The planning and the procedure of each patient were performed exclusively by the senior surgeon. Fifty procedures with retrospective analogues planning were used as the control group (group zero). After the procedure, the planning was compared with the eventually implanted components (cup and stem). For statistic analysis the χ^2 test was used for nominal variables and the *t* test was used for a comparison of continuous variables.

RESULTS

Preoperative planning with an additional a.p. hip view (second group) significantly increased the exact component correlation when compared to pelvic overview only (first group) for both the acetabular cup and the femoral stem (76% cup and 66% stem vs 54% cup and 32% stem). When considering planning \pm 1 size, the accuracy in the second group was 96% (48 of 50 patients) for the cup and 94% for the stem (47 of 50

patients). In the analogue control group (group zero), an exact correlation was observed in only 1/3 of the cases.

CONCLUSION

Digital THA planning performed by the operating surgeon and based on additional a.p. hip view significantly increases the correlation between preoperative planning and eventual implant sizes.

Key words: Digital; Templating; Preoperative planning; Hip view; Total hip arthroplasty

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Core tip: Preoperative planning is an essential practice carried out prior to total hip arthroplasty (THA). However, the accuracy of digital preoperative planning in THA is variable and often lacks sufficient precision. Our prospective study analysed that preoperative planning with an additional antero-posterior hip view significantly increased the exact component correlation when compared to pelvic overview only for both the acetabular cup and the femoral.

Stigler SK, Müller FJ, Pfau S, Zellner M, Füchtmeier B. Digital templating in total hip arthroplasty: Additional anteroposterior hip view increases the accuracy. *World J Orthop* 2017; 8(1): 30-35 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/30.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.30>

INTRODUCTION

Preoperative planning for elective total hip arthroplasty (THA) is of paramount importance, irrespective of the level of difficulty. Not only does it prevent complications, but it also helps to optimise important geometric parameters such as leg length, centre of rotation, and femoro-acetabular offset adjustment by determining such components^[1-4].

Previously, conventional X-ray images and measuring templates were used for this purpose. However, according to the literature, these practices resulted in low levels of correlation with the sizes of the eventually implanted devices in most cases^[2]. With the increasing use of digital radiography, more and more digital planning software programmes are being offered, which, in theory, should deliver higher precision. However, it has been reported that there were only a few cases for which digital planning has resulted in more than low correlation between planning and implanted sizes^[4-6].

Therefore, we conducted a comparative case-control study based on the null hypothesis that planning precision regarding the eventually implanted components can be increased with an additional antero-posterior (a.p.) hip view. This was based on the fact that the a.p. hip view with a central X-ray beam (directed

to the proximal femur) reduces parallax shifts and rotational deviations^[7].

MATERIALS AND METHODS

Since 2014, we have exclusively performed preoperative THA planning in our hospital using digital software (MediCAD, HECTEC GmbH, Landshut, Germany). The digital planning has been performed using a 17-inch LCD screen with a resolution of at least 1.024 × 768 pixels.

We used three groups for this comparative study: The first group included digital planning in 50 consecutive patients (who underwent surgery in 2015) using digital pelvic overview only (Figure 1). The second group also included digital planning in 50 consecutive patients (within the same year), but with an additional a.p. hip view for planning (Figure 2). All X-ray examinations (pelvic overview) were performed using a standardised technique with the patients in the supine position with a film-focus distance of 115 cm, a 10- to 15-degree internal rotation of the hip joint, and the central X-ray beam directed to the pubic symphysis.

A 25-mm external calibration marker (scaling sphere) was used for planning in both groups, and it was placed laterally from the hip joint requiring surgery or centred between the legs at the joint level at the height of the trochanter major. Moreover, surgeries in both groups were exclusively performed by the senior consultant surgeon who operated on the patients on the following day. Access to the hip was achieved exclusively in the lateral position using the minimally invasive technique according to Bertin and Röttinger^[8]. The planning steps were performed according to the procedure described by Bono^[3], Dastane *et al.*^[9], and Unnanuntana *et al.*^[10] (Figures 1 and 2).

Fifty consecutive patients with analogue planning (who underwent surgery the year before the digital software had become available) served as the control group (group zero). Here, the individual planning steps had been performed according to Egli *et al.*^[11].

The indications for the 150 patients who received a cementless THA for both acetabular cup and femoral stem were primary osteoarthritis ($n = 133$), avascular femoral head necrosis ($n = 11$), and dysplasia ($n = 6$). The exclusion criteria were as follows: History of cemented or hybrid arthroplasty, additional osteotomies, and revision surgery for any reason.

Preoperative planning, surgical reports, and post-operative X-ray (within 6 wk) for the first and second group were performed prospectively, and group zero was evaluated retrospectively. The cup component was a Fitmore or an Allofit press-fit cup (Zimmer, Freiburg, Germany), and the stem was a CLS Spotorno (Zimmer), exclusively in all three of the groups. The study was approved by the local ethics committee.

Statistical analysis

SPSS version 23 (SPSS, Chicago, IL, United States) was

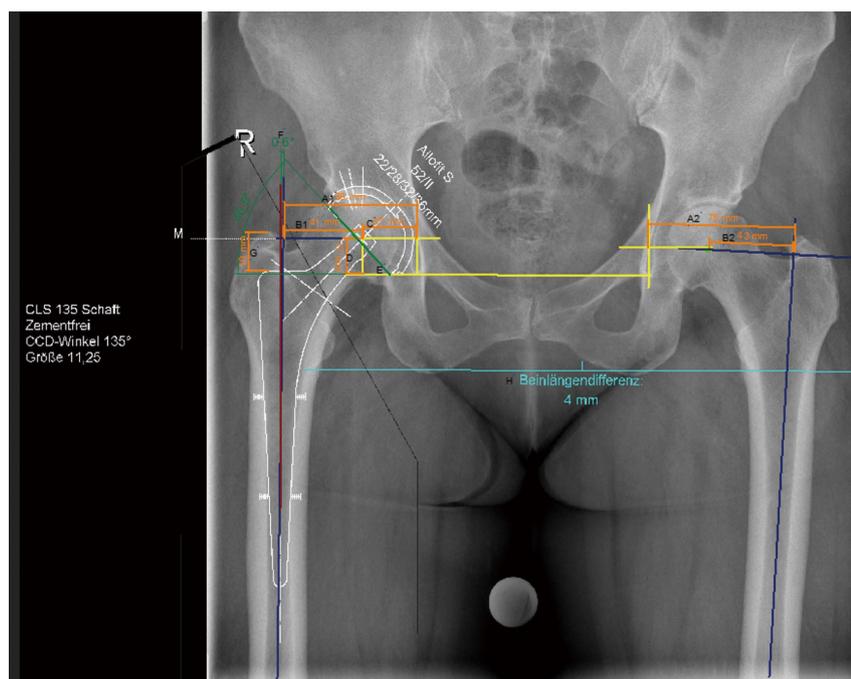


Figure 1 Digital planning of cup and stem for total hip arthroplasty of the right side (group 1). A1: Hip offset: Perpendicular line from the teardrops through the centre of rotation to the femoral shaft axis, *i.e.*, line B1 + C; A2: Contralateral hip offset; B1: Femoral offset: Perpendicular line from the centre of rotation to the axis of the femur; B2: Contralateral femoral offset; C: Horizontal position of the centre of rotation: Distance determined by the centre of rotation and one line perpendicular to the teardrops drawn through the centre of the teardrop; D: Vertical position of the centre of rotation: Line determined by the inter-teardrop line and the centre of rotation; E: Inclination angle: Angle determined by the inter-teardrop line and one axis extending through the cup opening; F: Stem orientation: Angle between femoral shaft axis and implant shaft axis; G: Implantation depth: Line between the upper edge of the prosthesis and the tip of the greater trochanter; H: Leg length difference: Quantified by subtracting the perpendicular distance from the bischial line to the proximal corner of the minor trochanters of both sides (measurements according to Bono, Dastane, Unnanuntana, Eggli^(3,9-11)).

used for statistical analysis. Descriptive analysis was performed by determination of values, averages, and standard deviations. Differences were compared using the χ^2 test for nominal variables. The *t*-test was used for a comparison of continuous variables. A *P* value of < 0.05 was set as the significance threshold.

RESULTS

Among the 150 patients who underwent cementless THA, 63 were female, 87 were male, and the mean age was 63 years (30 to 83). No patient received bilateral THA. The descriptive data (sex, age, BMI, indications, and duration of surgery) within the three groups were not significantly different (*P* > 0.05).

For all 150 patients, no major postoperative complications, *e.g.*, periprosthetic fracture, fracture of the trochanter tip, or hip dislocation - were documented.

Acetabular cup size

The exact acetabular cup sizes within the three groups are shown in Table 1. The size increments within the two cups are 2 mm. Within the second group, including additional a.p. hip view, a total of 48 out of 50 (96%) were predicted within \pm one size without a significant difference between both of the utilised components (Allofit or Fitmore). The results for exact size accuracy between the three groups were significantly different (*P*

= 0.02).

Femoral stem size

The exact femoral stem sizes within the three groups are shown in Table 2. The increments of the femoral stems are between 1 and 1.25 mm. Within the second group that included an additional a.p. hip view, a total of 47 out of 50 (94%) were predicted within a one size deviation. The results for exact size accuracy between the first and the second group were significantly different (*P* < 0.001).

Centre of rotation

A distance of \leq 5 mm between the vertical and horizontal centre of rotation after implantation when compared to the scheduled position was found in a total of 48% (*n* = 24) of patients in group zero and in a total of 72% (*n* = 36) of patients in the digital group. The planning accuracy difference between both groups was significantly different (*P* = 0.014).

Femoral and hip offset

A femoral offset of \leq 5 mm when compared to the scheduled position was found in a total of 68% (*n* = 34) in the analogue planning group and in a total of 70% (*n* = 35) in the digital group. The hip offset was scheduled \leq 5 mm in 50% of patients (*n* = 25) of both groups (both with analogue and digital planning).

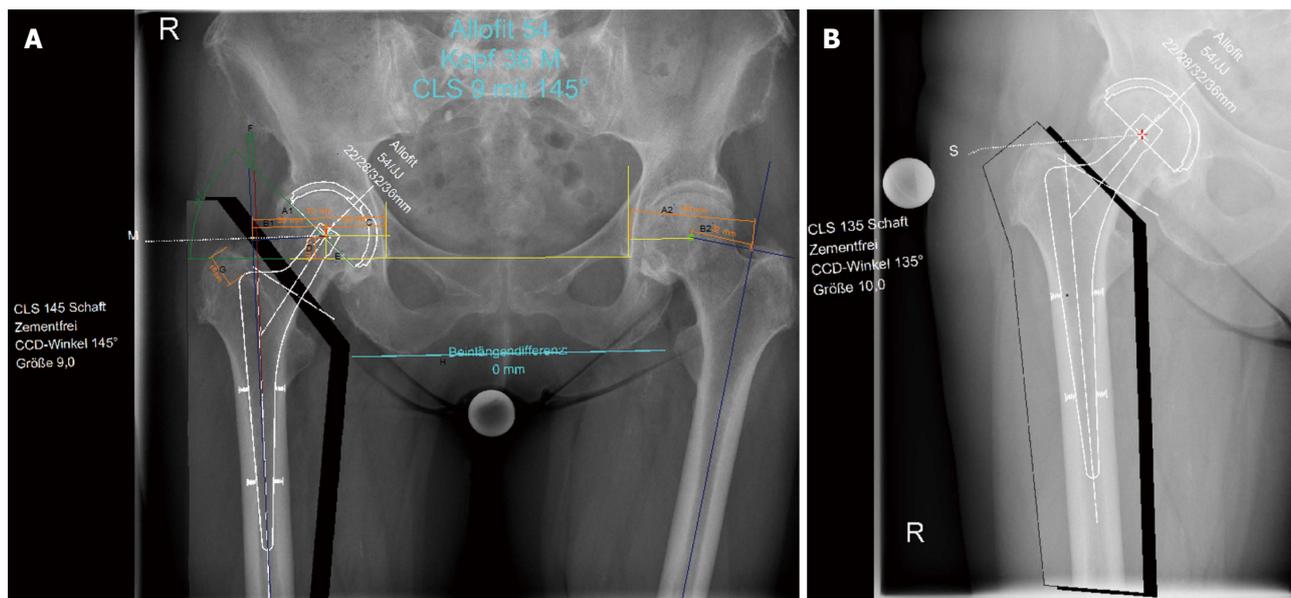


Figure 2 Pelvic overview plus antero-posterior hip view (group 2). A: Digital planning of cup and stem for total hip arthroplasty of the right side; B: Additional antero-posterior hip view for planning. With this true antero-posterior view of the hip, planning is more accurate.

Table 1 Accuracy of acetabular cup n (%)			
Preoperative planning vs implant used	Group zero n = 50	First group n = 50	Second group n = 50
- 2 sizes smaller	-	-	-
- 1 size smaller	6 (12)	8 (16)	5 (10)
Exact size	17 (34)	27 (54)	38 (76)
+ 1 size larger	15 (30)	12 (24)	5 (10)
+ 2 sizes larger	9 (18)	2 (4)	2 (4)
+ 3 sizes larger	2 (4)	1 (2)	-
+ 4 sizes larger	1 (2)	-	-

Table 2 Accuracy of femoral stem n (%)			
Preoperative planning vs implant used	Group zero n = 50	First group n = 50	Second group n = 50
- 2 sizes smaller	1 (2)	3 (6)	3 (6)
- 1 size smaller	11 (22)	20 (40)	9 (18)
Exact size	16 (32)	16 (32)	33 (66)
+ 1 size larger	17 (34)	10 (20)	5 (10)
+ 2 sizes larger	5 (10)	1 (2)	-

Acetabular cup inclination

The mean inclination angle of the acetabular cup was 44.5° (SD ± 4.2°) in group zero and 45° (SD ± 5.8°) in the digital planning group, and there was no significant difference between the two groups.

A total of 88% of the prostheses (n = 44) in the analogue planning group and 92% (n = 46) in the digital planning group were implanted at angles between 30° und 50°.

Leg length difference

The mean postoperative leg length difference (LLD) was 4.6 mm in the analogue planning group (SD ± 5.0 mm) and 2.7 mm in the digital planning group (SD ± 3.4 mm). A total of 80% of patients in group zero and 90% in the digital planning group had postoperative leg length differences of < 10 mm.

DISCUSSION

This study covers multiple aspects of preoperative planning: Although several studies of analogue planning have been previously reported^[11,12], our study offers an additional direct comparison with digital planning. Few

studies have compared analogue and digital planning procedures. Surprisingly, their results varied: González Della Valle *et al.*^[13] demonstrated that analogue planning resulted in a higher planning accuracy for both cup and femoral stem. However, The *et al.*^[1] concluded that digital planning was superior to analogue planning in regard to both components. In contrast, Gamble *et al.*^[6] found a significantly higher accuracy only for the acetabular cup when digital planning was used, whereas identical results were achieved with femoral stems. The results of the latter study are similar to ours: We also found an equally low exact precision (32%) for the femoral stem with both analogue and digital planning (when only a pelvic overview was used). However, in total, our data clearly showed that analogue planning offered the lowest levels of results for both exact precision and deviation by one size.

However, digital planning of the acetabular cup resulted in a clearly higher exact size determination (54%) in our study when compared to the results of other recent studies that reported an accuracy of only 34% to 42%^[4,6,10]. Nevertheless, this result is still not satisfactory for several reasons: First, whether the scaling sphere was actually placed in the correct plane cannot be retrospectively evaluated^[14]. Accordingly,

inaccurate positioning and an inappropriately rotated femur have detrimental effects on X-ray imaging quality and, thus, on planning precision. The femoral stem component is more prone to such effects than the cup^[15]. This may explain the lower planning accuracy with regard to the stem component. In our study, it was more common that a smaller-than-needed size of the femoral stem component was selected (though the difference was only one size) when compared to a larger-than-needed size (40% vs 20%). Kniesel *et al.*^[16] reported similar results. In their evaluation of different calibration methods, Franken *et al.*^[17] also found that there was a tendency to underestimate the real dimensions when the reference sphere was placed in the centre between the patient's legs. Furthermore bone density is a crucial criterion when selecting the stem component: It is common that larger components are selected for patients with lower bone density^[4].

Second, we were able to demonstrate for the first time that the exact correlation between planning and eventually implanted components (cup and stem) can be significantly increased to more than 2/3 of the cases with an additional a.p. hip view. When a size deviation of \pm one size is also taken into account, an accuracy level of above 90% can be achieved for both the cup and the stem. Hip view with central X-ray beam targeting the proximal femur results in the minimisation of parallax shifts with reduction of rotational deviations^[7], which may explain the higher planning precision. However, there are no data currently available with regard to an additional centred hip view for component planning.

In addition to component selection, it is clear that leg length difference is another very important preoperative planning parameter, even though a maximum clinical difference of 10 mm is generally considered to be acceptable^[18]. The validation of different measurement methods for leg length differences has been the subject of multiple studies, with various results. Meermans *et al.*^[19] found that the horizontal line through the teardrops offers a more accurate reference marker when compared to the line between the two ischial tuberosities. However, Tripuraneni *et al.*^[20] concluded that the teardrop line is most commonly prone to measurement errors and that the obturator line would be the most accurate reference. In our study, the bisischial line was used as an anatomical landmark for LLD assessment. We found a significant difference in planning accuracy in favour of the digital method: 90% of the patients showed a postoperative leg length difference of less than 10 mm, which is in line with the results reported in the studies of Unnanuntana *et al.*^[10] or González Della Valle *et al.*^[21]. However, it must be emphasised that complete compensation of leg length differences is not always practical and necessary, particularly in elderly patients with scoliotic deformities. With regard to offset, analogue and digital procedures were found to be equivalent in terms of planning and correlation with implant positions. The digital method

was significantly superior to the analogue method in terms of planning vertical and horizontal positions of the rotation centre. Good results were achieved for both cup planning and implantation when the inclination angle was within the "safe zone" (30°-50°) according to Lewinnek *et al.*^[22]. This was observed in both groups. Implantation outside of this range is known to promote abrasion and prosthesis loosening in the mid and long term^[23].

Finally, it is necessary to address the weaknesses of the present study: Digital planning was performed by the senior surgeon who then also operated the patients. Hence, it is possible that the use of the initially scheduled component size was "enforced" during surgery. However, severe post-surgery complications, *e.g.*, hip dislocation, periprosthetic fractures or stem loosening were reported in none of the 100 patients with digital planning and implantation. Conversely, a common sentiment in the literature is that planning should be performed by the operating surgeon^[1,18], and this procedure has been propagated by the authors in those studies.

Moreover, an advancement of the digital two-dimensional planning is already underway using a three-dimensional CT. However, this method can expose patients to high levels of radiation and is probably not necessary for most THA patients with osteoarthritis^[24]. In contrast, the addition of the a.p. hip view confers a negligible radiation exposure of only 0.05 mSv. Because our study exclusively investigated cementless total hip arthroplasties, the results cannot be completely transferred to cemented THA or to other components. To date, it also remains unclear if the commonly occurring minor differences between planning and surgery cause long-term clinical consequences. Studies on this aspect are not available yet and are needed.

In conclusion, the digital planning of cementless THA performed by the surgeon based on additional antero-posterior hip view significantly increases the correlation between preoperative planning and eventual implant sizes. Therefore, we recommend that it should be implemented as a standard in preoperative planning.

COMMENTS

Background

Digital preoperative planning is an essential practice in total hip arthroplasty (THA). However, the accuracy is variable and often insufficient.

Research frontiers

The current research hotspot is the analysis and the improvement of preoperative planning in THA.

Innovations and breakthroughs

This case-control study could represent that digital THA planning performed by the operating surgeon and based on additional antero-posterior hip view increases the accuracy of preoperative planning in THA.

Applications

An additional antero-posterior hip view should be implemented as a standard in preoperative planning.

Peer-review

The authors present a nice prospective study about accuracy in digital planning of cementless total hip replacement.

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Retrospective Study

Heterotopic ossification after the use of recombinant human bone morphogenetic protein-7

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Abstract**AIM**

To present the incidence of heterotopic ossification after the use of recombinant human bone morphogenetic protein-7 (rhBMP-7) for the treatment of nonunions.

METHODS

Bone morphogenetic proteins (BMPs) promote bone formation by auto-induction. Recombinant human BMP-7 in combination with bone grafts was used in 84 patients for the treatment of long bone nonunions. All patients were evaluated radiographically for the development of heterotopic ossification during the standard assessment for the nonunion healing. In all patients (80.9%) with radiographic signs of heterotopic ossification, a CT scan was performed. Nonunion site palpation and ROM evaluation of the adjacent joints

were also carried out. Factors related to the patient (age, gender), the nonunion (location, size, chronicity, number of previous procedures, infection, surrounding tissues condition) and the surgical procedure (graft and fixation type, amount of rhBMP-7) were correlated with the development of heterotopic ossification and statistical analysis with Pearsons χ^2 test was performed.

RESULTS

Eighty point nine percent of the nonunions treated with rhBMP-7, healed with no need for further procedures. Heterotopic bone formation occurred in 15 of 84 patients (17.8%) and it was apparent in the routine radiological evaluation of the nonunion site, in a mean time of 5.5 mo after the rhBMP-7 application (range 3-12). The heterotopic ossification was located at the femur in 8 cases, at the tibia in 6, and at the humerus in one patient. In 4 patients a palpable mass was present and only in one patient, with a para-articular knee nonunion treated with rhBMP-7, the size of heterotopic ossification affected the knee range of motion. All the patients with heterotopic ossification were male. Statistical analysis proved that patient's gender was the only important factor for the development of heterotopic ossification ($P = 0.007$).

CONCLUSION

Heterotopic ossification after the use of rhBMP-7 in nonunions was common but it did not compromise the final clinical outcome in most cases, and affected only male patients.

Key words: Nonunion; Bone morphogenetic protein; Recombinant human bone morphogenetic protein-7; Heterotopic ossification; Long bone; Bone graft; Osteoinduction

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Core tip: Bone morphogenetic proteins are identified as factors promoting osteogenesis. In this study an attempt was made to estimate the rate of heterotopic bone formation in patients with long bone nonunions treated with recombinant human bone morphogenetic protein-7 (rhBMP-7), and to identify predisposing factors, related to the patient, the nonunion characteristics, and the surgical procedure. Eighteen percent of the patients developed heterotopic ossification on the radiographs, without functional limitations. All patients that developed heterotopic ossification were male. This rate of heterotopic ossification after rhBMP-7 use for the treatment of long bone nonunions is higher than the rates reported in literature.

Papanagiotou M, Dailiana ZH, Karachalios T, Varitimidis S, Hantes M, Dimakopoulos G, Vlychou M, Malizos KN. Heterotopic ossification after the use of recombinant human bone morphogenetic protein-7. *World J Orthop* 2017; 8(1): 36-41 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/36.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.36>

INTRODUCTION

Heterotopic ossification is commonly complicating orthopaedic procedures and trauma but its highest incidence occurs after brain injuries. The hip, the elbow, and the knee are the most commonly affected joints after muscle damage, intramuscular hematoma and brain trauma^[1-7]. Depending on the site and the location of the heterotopic bone, it may interfere with muscle and tendon function and limit the range of joint motion^[3,4]. In experimental models, heterotopic bone is induced after implantation of bone marrow cells in muscle or in the peritoneal cavity^[7] and allo-transplantation of demineralized bone matrix^[8]. The later is linked to the activity of Bone Morphogenetic Proteins (BMPs) as factors promoting osteogenesis by auto-induction in extra-skeletal sites, as described by Urist *et al*^[8].

Since their identification BMPs have been isolated and experimentally applied in several preclinical models. Recombinant (rh) forms are available for two of the BMPs (rhBMP-2 and rhBMP-7), and have been licensed by the american food and drug administration for clinical use in tibia nonunions (rhBMP-7)^[9-11], and acute tibia fractures (rhBMP-2)^[12,13]. Although the formation of heterotopic bone after the rhBMPs application in experimental animal models is well known^[14], only a few reports confirm these findings in the clinical practice.

The aim of our study is to describe the development of heterotopic ossification in a series of 84 patients with long bone nonunions treated with bone graft and rhBMP-7, and to identify risk factors related to the patient, the nonunion and the surgical procedure.

MATERIALS AND METHODS

Eighty-four patients (60 men and 24 women), with long bone nonunions treated with the combination of bone grafts and rhBMP-7 (Osigraft, Stryker Pharmaceutical) between 2004 and 2008^[15] were evaluated for the development of heterotopic ossification. Nonunions were located in the upper (13) and lower (71) extremity and all patients had undergone at least one previous failed procedure for the treatment of the nonunion. The product used consisted of 3.3 mg of lyophilized rhBMP-7 combined with 6.7 mg of type I bovine collagen. The standard surgical procedure consisted of debridement of the nonunion site till normal viable bone margins. RhBMP-7 was applied mixed with bone grafts^[15]. After rhBMP-7 implantation, irrigation was avoided, so as to prevent product leakage at the surrounding tissues.

Heterotopic ossification was diagnosed as a delayed postoperative complication, during the standard postoperative radiographic evaluation for the assessment of healing of the nonunion. The efficacy of rhBMP-7 on the treatment of long bone nonunions, in this series



Figure 1 Heterotopic ossification in a 28-year-old male patient treated for femoral nonunion (3D CT reconstruction).



Figure 2 Heterotopic ossification in a 51-year-old male patient treated for femoral nonunion (3D CT reconstruction).

of patients, has already been published in a previous study^[15]. In all patients with apparent signs of heterotopic bone formation on the radiographs, a quantitative computed tomography (Q-CT) and 3D-CT reconstruction (employing Osirix software) were obtained to confirm the diagnosis. The patients with heterotopic ossification were additionally evaluated clinically by palpation and examination of the range of motion of the adjacent joints.

Factors related to the patient (age, gender), the nonunion (location, size, chronicity, number of previous failed procedures, presence of infection, and condition of the surrounding soft tissues) and the type of the index surgical procedure (type of graft and amount of rhBMP-7 used), were also analyzed and correlated with the presence of heterotopic ossification.

Statistical analysis was performed with the Pearson χ^2 test and with a logistic regression model under Firth's correction (Stata version 10).

RESULTS

Heterotopic bone formation was diagnosed as a delayed complication within the first postoperative year in 15 patients (17.8%) (Figures 1-3). All patients were male (Figure 4) and the mean time to heterotopic ossification radiographic appearance was 5.5 mo (3 to 12 mo) after the index procedure. The heterotopic ossification was located at the lower extremity in 14 cases, 6 of them at the tibia and in 8 at the femur. In one case heterotopic ossification developed in a patient with a humeral nonunion. The ectopic bone was palpable in 4 patients, but only one had a limitation of the range of motion after the treatment of a para-articular distal femoral nonunion. This patient developed a significant restriction of flexion and extension of the knee joint (Figure 3).

The results were presented with the use of means and standard deviations or counts and percentages, where appropriate. The effect of categorical variables on

the main outcome was examined with the use of the χ^2 test, while the effect of scale variables with the use of the *t* test for independent samples or the Mann-Whitney test where normality did not hold, after implementation of the Shapiro Wilk test. The variables were then used in a logistic regression model under Firth's correction. Significance was in all cases set at 0.05. The analysis was carried out with the use of the software Stata v.10.0.

Statistical analysis with the use of χ^2 test, proved that patient's gender was the only factor significantly correlating with the development of heterotopic ossification with statistical significance ($P = 0.007$) (Table 1 and Figure 4), while no other parameter had any effect on the development of this complication. The logistic regression model which was used, under Firth's correction, did not show any parameter significantly affecting heterotopic bone formation, probably due to the small number of patients who developed this complication (Table 1).

DISCUSSION

The incidence of heterotopic bone formation in this series is relatively high (17.8%), but in the majority of cases (14 of 15) it did not compromise the functional outcome of the limb. This high incidence may be attributed to the preexisting muscle trauma and extensive excision of the scar at the site of rhBMP-7 application, as these patients had undergone several operations prior to the index procedure. It has been demonstrated that repeated blunt trauma in the extremities, may induce degenerative changes in the muscle predisposing to ectopic bone formation^[3,7,16].

The development of heterotopic ossification has been studied in several experimental models, however the exact pathophysiology of this process has not been completely elucidated. According to the rhBMP-7 commercial product's safety database, the rate of undesirable effects (erythema, tenderness swelling and

Table 1 Analysis of the parameters affecting the development of heterotopic ossification

Parameter	No. of patients	HO	HO rate (%)	P value (χ^2)	P value (logistic regression firth's correction)	
Gender	Male	60	15	25	0.007	0.081
	Female	24	0	0.0		
Age	≤ 30	20	6	30.0	0.067	0.205
	31-55	39	8	20.5		
Extremity	≥ 56	25	1	4.0	0.298	0.733
	Upper	13	1	7.7		
Defect size	Lower	71	14	19.7	0.776	0.997
	Critical	42	8	19.0		
Chronicity	Non critical	42	7	16.0	0.229	0.731
	> 1 yr	33	4	12.1		
Infection	< 1 yr	51	11	20.3	0.420	0.451
	Yes	30	4	13.3		
Soft tissue defects	No	54	11	20.3	0.200	0.287
	Yes	9	3	33.3		
Previous procedures	No	75	12	16.0	0.227	0.315
	1	56	8	14.3		
Graft type	2-3	28	7	25.0	0.463	0.663
	Autograft	67	13	19.4		
Amount of rhBMP-7	Allograft	9	0	0	0.576	0.629
	No graft	8	2	25.0		
	1 vial	75	14	18.6		
	2 vials	9	1	11.1		

P values with the use of χ^2 test and with the use of logistic regression model under Firth's correction. HO: Heterotopic ossification; rhBMP-7: Recombinant human bone morphogenetic protein-7.



Figure 3 Heterotopic ossification in a para-articular femoral nonunion in a 44-year-old male patient, affecting knee joint range of motion (3D CT reconstruction).

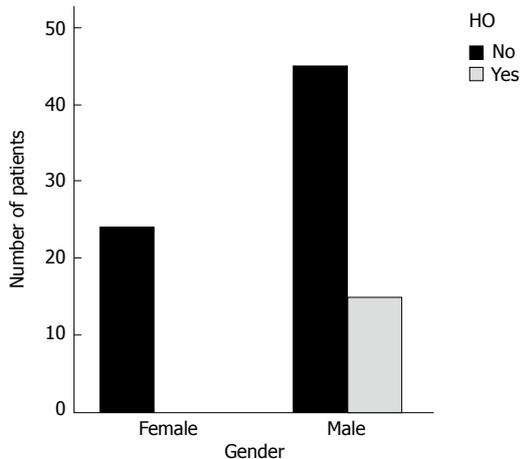


Figure 4 Gender effect on the development of heterotopic ossification after the use of recombinant human bone morphogenetic protein-7.

ectopic ossification) ranges from 1% to 10%^[17].

Male gender significantly influenced the appearance of heterotopic bone. In a study evaluating the osteogenic capacity of mice skeletal muscle-derived stem cells (MDSCs), the male MDSCs revealed significantly greater ALP activity and expression of osteogenic genes when stimulated with rhBMP-4 *in vitro*. In addition, the implantation of these cells into intramuscular pockets in the mice led to more bone formation in the male mice compared to the female regardless of the implanted cells gender^[18]. In a recent study in mice with cranial defect treated with MDSCs after transduction with a

retrovirus encoding BMP-4, male mice demonstrated more rapid bone formation and larger volumes of ectopic bone than female^[19]. These findings suggest a specific effect of the gender in the heterotopic ossification development.

The potential of mesenchymal progenitor cells to differentiate into osteoprogenitor cells in muscles, has been shown in animal models^[20-22]. In a recent *in vitro* study human skeletal muscle-derived progenitor cells have been isolated and characterized for their osteogenic properties indicating a potential effect on heterotopic bone formation^[23]. These cells were identified as PDGFR α^+ cells, able to differentiate into

osteoprogenitor cells under the stimulation of bone morphogenetic proteins in mice^[21]. The role of BMPs in the heterotopic bone formation has also been elucidated in the fibrodysplasia ossificans progressiva, where BMPs were found to promote muscle mesenchymal stem cells differentiation in preosteoblasts and osteoblasts^[24].

Since 2001, when the use of rhBMP-7 was approved by the American Food and Drug Administration and the European Medicines Agency (European Marketing Authorization Number: EU/1/01/179/001) for the treatment of tibia nonunions, its use was extended to skeletal nonunions and spinal fusions with successful outcomes presented in several series^[25-27]. Although rhBMP-7 has been widely used in the clinical practice, only few cases of heterotopic bone formation were reported in the literature after 2006. A case of myositis ossificans in a 49-year old woman, who underwent L4-L5 decompression and fusion with the use of rhBMP-7 was presented by Bennet *et al.*^[28]. The first case of heterotopic ossification in a long bone (distal humerus nonunion) after the use of rhBMP-7 was reported by Wysocki *et al.*^[29]. The patient gradually developed elbow stiffness from an extensive heterotopic ossification in the triceps muscle. Another small series of four patients that developed heterotopic ossification after the use of rhBMP-7 (3 patients) and rhBMP-2 (one patient) for the treatment of acute fractures or nonunions of the humerus was presented by Axelrad *et al.*^[30]. All patients had painful restriction of motion and underwent surgical excision of the heterotopic bone with good postoperative outcome. Heterotopic ossification after the use of rhBMP-7 for the treatment of femoral head osteonecrosis was also reported. In this case, in this series the majority of patients developed heterotopic ossification at the lateral surface of the femur around the entry point of core decompression and fibula insertion, which, however, did not affect the range of motion^[31].

The main limitation of this study is the lack of a control group of patients who did not receive rhBMP-7. As all patients had several previous unsuccessful surgical procedures, the treating physicians decided to use all available means to treat the nonunions and considered unethical the deprivation of rhBMP-7 in the patients of a control group.

In conclusion, heterotopic ossification following the use of rhBMP-7 for the treatment of long bone nonunions was a relatively common complication. Also, a positive correlation between the male gender and the development of this side effect was found. Careful observation of postoperative radiographs may increase the reported heterotopic ossification rates in the literature as the majority of cases lack clinical relevance.

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COMMENTS

Background

Bone morphogenetic proteins (BMPs) have been identified as factors promoting osteogenesis by auto-induction in extra-skeletal sites. In the recent years they have been used in the treatment of long bone nonunions in combination with bone grafts. In this study, the rate of heterotopic ossification occurring after the use of commercially available recombinant human bone morphogenetic protein-7 (rhBMP-7) for the treatment of long bone nonunions was estimated. In addition, the correlation between the development of heterotopic ossification and factors related to the patient (age, gender), the nonunion (location, size, chronicity, previous procedures, infection, surrounding tissues condition), and the surgical procedure (graft type, amount of rhBMP-7) was evaluated.

Research frontiers

BMPs and especially rhBMP-2 and rhBMP-7 have been used in several clinical studies but there are only few reported data related to the complications related to their use.

Innovations and breakthroughs

In this study, heterotopic ossification was a relatively common complication of the use of rhBMP-7, with higher rates than the ones reported in literature. In addition, a significant correlation between patient's gender and the development of this complication was found.

Applications

This study suggests that heterotopic ossification is a relatively common complication after the use of rhBMP-7 for the treatment of nonunions, related significantly with patient's gender. Although not clinically significant in the majority of cases, this complication should be acknowledged to the patients, especially the male, before rhBMP-7 use.

Terminology

rhBMP-7: Recombinant human bone morphogenetic protein-7; HO: Heterotopic ossification.

Peer-review

The rate of heterotopic ossification after the use of rhBMP-7 was higher in the present series than the rates reported in the literature and a significant correlation between male gender and the development of this complication was found. The lack of any clinical relevance of this complication in the vast majority of cases may be the reason of the low reported rates up to now. Thus, careful evaluation of postoperative radiographs may increase the reported rates.

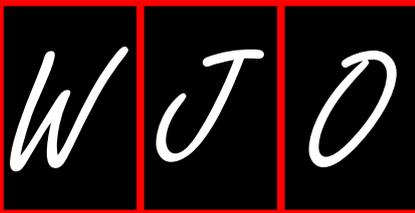
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Retrospective Study

Unhappy triad in limb reconstruction: Management by Ilizarov method

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Author contributions: El-Alfy BS performed the surgery in all cases, designed the study and wrote the paper.

Institutional review board statement: The study was approved by the ethical committee in our institution.

Informed consent statement: All patients gave their informed consent before being included in the study.

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Abstract

AIM

To evaluate the results of the Ilizarov method in management of cases with bone loss, soft tissue loss and infection.

METHODS

Twenty eight patients with severe leg trauma complicated by bone loss, soft tissue loss and infection were managed by distraction osteogenesis in our institution. After radical debridement of all the infected and dead tissues the Ilizarov frame was applied, corticotomy was done and bone transport started. The wounds were left open to drain. Partial limb shortening was done in seven cases to reduce the size of both the skeletal and soft tissue defects. The average follow up period was 39 mo (range 27-56 mo).

RESULTS

The infection was eradicated in all cases. All the soft tissue defects healed during bone transport and plastic surgery was only required in 2 cases. Skeletal defects were treated in all cases. All patients required another surgery at the docking site to fashion the soft tissue and to cover the bone ends. The external fixation time ranged from 9 to 17 mo with an average of 13 mo. The complications included pin tract infection in 16 cases, wire breakage in 2 cases, unstable scar in 4 cases and chronic edema in 3 cases. According to the association for study and application of methods of Ilizarov score the bone results were excellent in 10, good in 16 and fair in 2 cases while the functional results were excellent in 8, good in 17 and fair in 3 cases.

CONCLUSION

Distraction osteogenesis is a good method that can treat the three problems of this triad simultaneously.

Key words: Ilizarov methods; Bone defect; Soft tissue

reconstruction; Open bone transport

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Core tip: Bone and soft tissue loss represent a true challenge for both the orthopedic and plastic surgeons. The presence of bone and soft tissue infection further complicates limb reconstruction. In this study a series of 28 patients with severe lower limb trauma were managed by the Ilizarov method without the need for major plastic surgery. The results were encouraging.

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INTRODUCTION

Bone loss represents a true challenge for orthopedic surgeons. Soft tissue loss may complicate the condition and makes reconstruction more difficult. Bone infection may further complicate the condition and makes reconstruction extremely difficult^[1-4]. So, the triad of bone loss, soft tissue loss and infection is considered to be an unhappy triad in the field of limb reconstruction. In the presence of this triad the scope for reconstruction becomes very narrow and amputation may be the end result.

It is important to restore a healthy soft tissue envelope for proper treatment of this complex problem. This could be done by major plastic surgery in the form of local myocutaneous flaps, or free flaps. But, in the presence of infection the chance for success of these plastic surgeries becomes very limited^[5,6]. During distraction osteogenesis all the tissues are lengthened including the bone, vessels, nerves, muscles and skin. This gradual lengthening may lead to spontaneous closure of the soft tissue defects without the need for plastic surgery^[7-9].

The aim of this study is to evaluate the results of distraction osteogenesis in management of cases with severe leg trauma complicated by bone loss, soft tissue loss and infection.

MATERIALS AND METHODS

Between April 2007 and Jun 2014, twenty eight patients with bone loss, soft tissue loss and infection were treated by distraction osteogenesis in our institution. The average age of the patients was 37 years (range: 16-58 years). There were 23 males and 5 females. The etiology of this complex problem was trauma sequelae in all of the cases. Plastic surgery was performed in 12 cases but it failed because of infection. After radical

debridement, the average size of the skeletal defects was 8 cm (range: 6 to 14 cm) and the soft tissue defects ranged from 3 cm × 4 cm to 6 cm × 11 cm, with an average of 5 cm × 7 cm. The defects were located in the proximal third of the leg in 6 patients, middle third in 13 patients and distal third in 9 patients. All cases were infected with an active discharge. The ethical committee in our institution approved this study. Informed consent was taken from the patients before being included in the study. Under general or spinal anesthesia, the infected and dense fibrous tissues were excised. The infected and necrotic bone ends were debrided down to a healthy bleeding surface. Further debridement of the exposed bone ends was done until they became well covered by the skin and soft tissue. The Ilizarov frame was applied and corticotomy was performed in a healthy bone segment. The wounds were left open to drain (Figure 1). Physiotherapy was started early in the postoperative period to avoid joint contracture. It involved isometric contraction of the quadriceps muscles, active and passive range of movement and stretching exercises for the hamstring and gastrocnemius complex. Bone transport was started after a latent period of about one week. Patients were discharged after an average of 8 d and followed up regularly in the outpatient clinic. During bone transport the bone segment carries its surrounding soft tissues with it and the soft tissue defects gradually close. As transport is done without sufficient soft tissue coverage it is called open bone transport. At the time of docking the skin becomes incarcerated between the bone ends (Figure 1D). At this stage the patient is taken to theater again where the soft tissue is removed from the docking site and the skin is fashioned to cover the bone ends. Transverse skin incision is preferred in this step to facilitate skin closure. It was made along the bone ends of the proximal and distal fragments. The incision was deepened down to the bone and the soft tissues were removed from the docking site. The bone ends were freshened and compressed against each other by the frame. This compression approximates the skin edges together and facilitates their closure over the bone ends (Figure 2). Bone graft was done at this time to stimulate bone healing in 15 cases. Partial limb shortening was done in 7 cases to reduce the size of both the soft tissue and bone gaps. After docking, bone lengthening was continued to equalize the limb lengths in those cases.

The frame was removed after healing of the docking site and full maturation of the regenerated bone. The average follow up period was 39 mo (range: 27 to 56 mo). The results were evaluated according to the association for study and application of methods of Ilizarov (ASAMI) scoring system^[10]. In this system the results are divided into bone results and functional results. The bone results are evaluated according to union, infection, deformity and limb length discrepancy while the functional results are evaluated according to daily activities, joint stiffness, limp, pain and presence of



Figure 1 Surgical technique. The infected and necrotic bones are excised (A) and further debridement of the bone ends is done until they recessed under the skin and soft tissues (B); C: The Ilizarov frame is applied and bone transport started; D: At the time of docking the skin is invaginated between the bone ends.

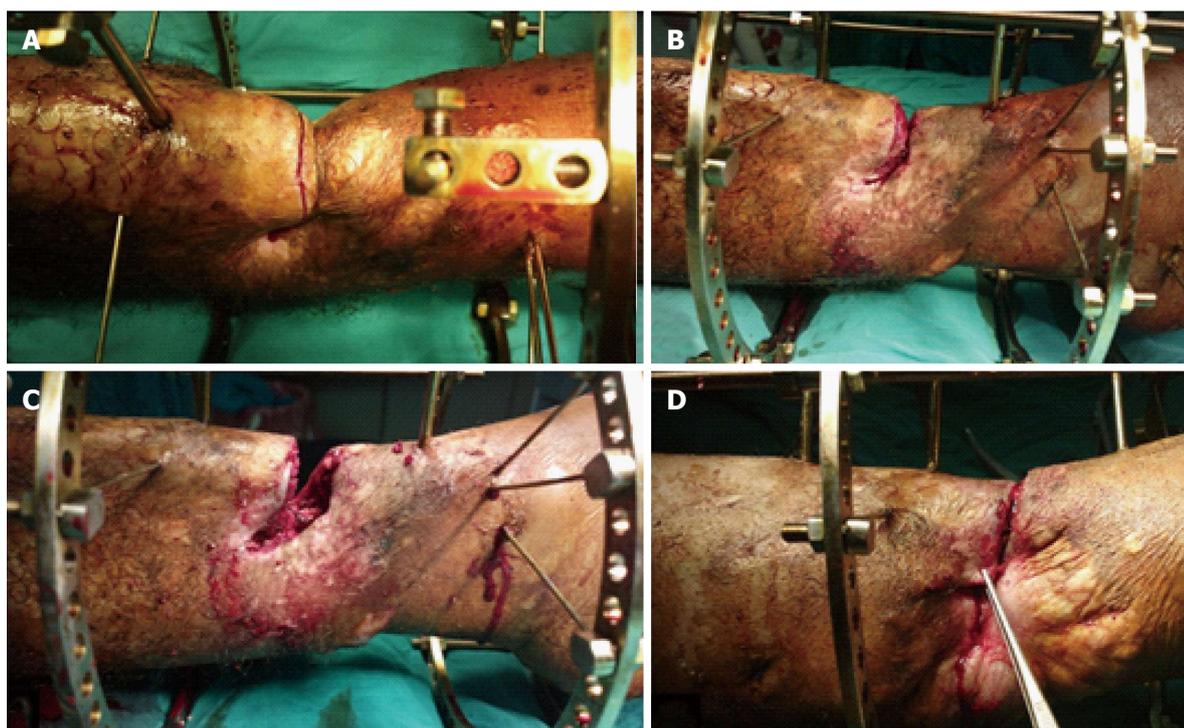


Figure 2 Management of the docking site. A: Transverse skin incision is made along the bone ends at the docking site; B: The incision is deepened down to the bone and the soft tissues are removed from the docking site; C: The bone ends are freshened and compressed against each other by the frame; D: This compression approximates the skin edges together and facilitates their closure over the bone ends.

reflex sympathetic dystrophy.

RESULTS

The infection was eradicated in all of the cases. All the soft tissue defects healed during the process of bone transport and plastic surgery was only required in two cases. Bone defects were bridged in all cases (Figure 3). All patients required another surgery at the time of

docking to fashion the soft tissue and to cover the bone ends. The docking sites united without the need for bone graft in 13 cases and with bone graft in 15 cases. The average time of external fixation was 13 mo (range: 9 to 17 mo). The complications in this study were pin tract infection in 16 cases (treated by local care and oral antibiotics), wire breakage in 2 cases (treated by reinsertion of new wires), unstable scar in 4 cases and chronic edema in 3 cases. The limb length discrepancy

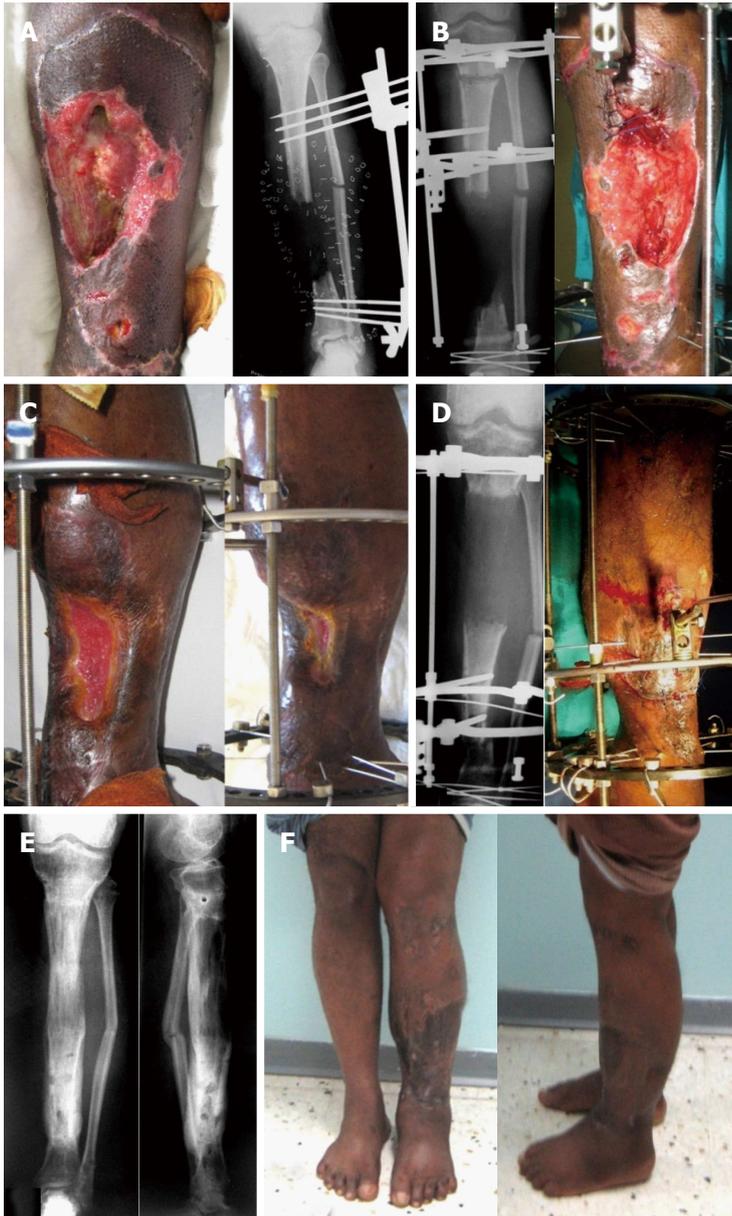


Figure 3 Middle third bone and soft tissue defects. A: Forty-seven year old male patient with combined bone loss, soft tissue loss and infection of his left leg as a complication of an open fracture of the tibia and fibula; B: Debridement of the bone ends was done, Ilizarov frame applied and bone transport started; C: During bone transport the soft tissue defect gradually closes; D: At the time of docking the skin was fashioned over the bone ends; E: After removal of the frame with good bone healing; F: The patient with good alignment and complete healing of the soft tissue.

did not exceed 2.5 cm except in one case. No cases were complicated by amputation or reflex sympathetic dystrophy. Using the ASAMI scoring system, the bone results were excellent in 10, good in 16 and fair in 2 cases while the functional results were excellent in 8, good in 17 and fair in 3 cases.

DISCUSSION

The tibia is the most common site for open fracture of the long bones due to its anatomic location and scanty soft tissue coverage. Also it is more liable for complications due to its poor blood supply. These complications include soft tissue necrosis, bone loss and infection^[11-13]. Successful treatment of the soft tissue loss is vital for bone healing. This could be done by free or local myocutaneous flaps. But, in certain situations these major plastic surgeries may be not feasible or they may endanger the limb survival. These conditions

include severe infection and local vascular problems. In the presence of infection the chance for success of plastic surgery is limited and additional surgery may be required to control infection prior to the major plastic surgery^[5,14,15]. After severe trauma some limbs may be left with only one blood vessel and if it is used as a feeding artery for the graft this may threaten the limb life. In case of failure of these surgeries the choice between amputation and another modality of reconstruction should be made.

In this study, 28 patients with the complex problem of bone loss, soft tissue loss and infection were treated by the Ilizarov method with satisfactory results in most of them. All the wounds healed during bone transport and plastic surgery was only required in two cases. We found that it was not necessary to restore the soft tissue coverage before skeletal reconstruction. After thorough debridement the combined bone and soft tissue gaps could be treated simultaneously by the process of

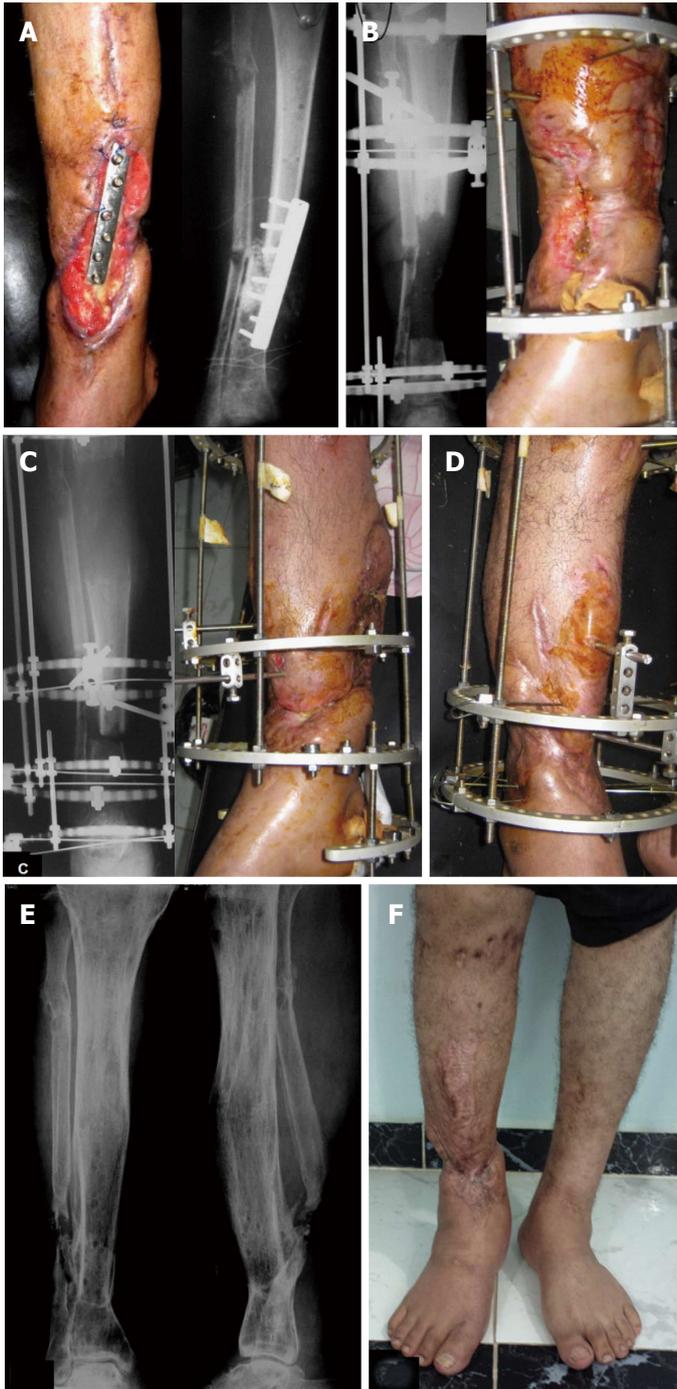


Figure 4 Lower third bone and soft tissue defects. A: Thirty-nine year old male patient with skin loss, infection and exposed plate in the lower third of his right leg; B: After radical debridement and application of the Ilizarov external fixator; At the time of docking the skin was fashioned to cover the bone ends (C) and it healed completely (D); After removal of the frame with good bone healing (E) and the patient with good alignment and complete healing of the soft tissue (F).

distraction osteogenesis. In the two cases that required plastic surgery, the soft tissue defects were big - 4 cm × 7 cm and 5 cm × 9 cm, respectively. During bone transport the defects decreased but did not close completely. The infection was eradicated in both of them and they were easily treated by local muscle flaps.

To avoid protrusion of the bone fragment from the wound during distraction the bone ends must be debrided until they become well covered by the skin. So, when distraction is started the bone fragment carries its surrounding soft tissue with it and the soft tissue creeps gradually until the defect heals spontaneously^[9].

The soft tissue defects in the lower third of the leg

are difficult to treat. Free-flaps is the best method for coverage of soft tissue defects in this area but the procedure is technically difficult, requires skilled surgeons and the recipient site should have suitable vessels which is a big problem in major tibial fractures^[16-18]. Perforator-based flaps or a distally-based soleus flap may be suitable for the lower third of the leg but the results are controversial^[19-21]. Karbalaiekhani *et al*^[21] used a soleus flap to treat soft tissue defects in the middle and lower third of the leg and reported a high failure rate in the distal third. They recommend preoperative assessment by angiography before surgery.

In this study, the defects were present in the distal

third of the leg in 9 patients. All of them were treated by the Ilizarov method and none of them required plastic surgery (Figure 4). Partial shortening of the limb helps to reduce the size of the bone and soft tissue defects and decreases the time required for soft tissue healing. After docking the frame must be adjusted to allow for further lengthening to restore the limb length.

Bone graft was required in 15 cases to stimulate bone healing at the docking site. In such cases small amounts of cancellous bone graft were sufficient for this purpose. The unstable scar is an important problem with this technique. It happened in four of our patients early in the course of this study. It usually occurs at the docking site because the skin is thin and adherent in this area. This skin is liable to injury and chronic ulceration due to minor trauma. Prolonged protection of the skin is required to prevent it from injury. We could avoid this complication by resection of more bone at the time of docking until thick healthy skin meets each other over the bone at the docking site.

The method of Ilizarov is good for reconstruction of patients with bone loss, soft tissue loss and infection. The three problems could be treated simultaneously without the need for major plastic surgery. Infection is treated by radical debridement while the bone and soft tissue defects are managed by bone and soft tissue transport. Good experience with the Ilizarov frame, better understanding of the distraction process and proper handling of the soft tissues are required to get the best results.

COMMENTS

Background

Bone and soft tissue loss are common after major limb trauma. The presence of infection will further complicate limb reconstruction. The healthy soft tissue envelope is essential for bone healing. This could be achieved by either local or free myocutaneous flaps. Unfortunately these surgeries are technically demanding, time consuming and may be associated with major complications.

Research frontiers

During distraction osteogenesis both the bone and soft tissue are lengthened which may help in spontaneous closure of the soft tissue defect.

Innovations and breakthroughs

In this study the complex problem of combined bone loss, soft tissue loss and infection was treated by distraction osteogenesis without the need for major plastic surgery except in 2 cases.

Applications

This method could be used for treatment of cases with post traumatic bone and soft tissue loss with or without infection. It is not necessary to restore the soft tissue envelope before osseous reconstruction. During bone transport both the bone and soft tissue defects will heal spontaneously. It is highly indicated after failure of plastic surgeries and for cases with a poor vascular bed that does not allow major plastic surgery to be done.

Terminology

Distraction osteogenesis is the mechanical induction of new bone formation between two bony surfaces when they are gradually pulled apart. It was developed by Ilizarov in the fifties of the last century. A low grade cortical

osteotomy is made in a healthy bone segment and the circular external fixator is usually used to apply the distraction force. It is also known as Ilizarov method; Bone transport: A condition in which a healthy bone segment is transported locally and gradually through the soft tissue to bridge a bone defect; The docking site is the site where the bone ends come to meet each other after bone transport.

Peer-review

The paper reports a good method for the treatment of lower limb tissue loss. It is interesting and well written. References are adequate.

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Clinical Trials Study

Microvascular response to transfusion in elective spine surgery

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Abstract

AIM

To investigate the microvascular (skeletal muscle tissue oxygenation; SmO₂) response to transfusion in patients undergoing elective complex spine surgery.

METHODS

After IRB approval and written informed consent, 20 patients aged 18 to 85 years of age undergoing > 3

level anterior and posterior spine fusion surgery were enrolled in the study. Patients were followed throughout the operative procedure, and for 12 h postoperatively. In addition to standard American Society of Anesthesiologists monitors, invasive measurements including central venous pressure, continual analysis of stroke volume (SV), cardiac output (CO), cardiac index (CI), and stroke volume variability (SVV) was performed. To measure skeletal muscle oxygen saturation (SmO₂) during the study period, a non-invasive adhesive skin sensor based on Near Infrared Spectroscopy was placed over the deltoid muscle for continuous recording of optical spectra. All administration of fluids and blood products followed standard procedures at the Hospital for Special Surgery, without deviation from usual standards of care at the discretion of the Attending Anesthesiologist based on individual patient comorbidities, hemodynamic status, and laboratory data. Time stamps were collected for administration of colloids and blood products, to allow for analysis of SmO₂ immediately before, during, and after administration of these fluids, and to allow for analysis of hemodynamic data around the same time points. Hemodynamic and oxygenation variables were collected continuously throughout the surgery, including heart rate, blood pressure, mean arterial pressure, SV, CO, CI, SVV, and SmO₂. Bivariate analyses were conducted to examine the potential associations between the outcome of interest, SmO₂, and each hemodynamic parameter measured using Pearson's correlation coefficient, both for the overall cohort and within-patients individually. The association between receipt of packed red blood cells and SmO₂ was performed by running an interrupted time series model, with SmO₂ as our outcome, controlling for the amount of time spent in surgery before and after receipt of PRBC and for the inherent correlation between observations. Our model was fit using PROC AUTOREG in SAS version 9.2. All other analyses were also conducted in SAS version 9.2 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Pearson correlation coefficients varied widely between SmO₂ and each hemodynamic parameter examined. The strongest positive correlations existed between ScvO₂ ($P = 0.41$) and SV ($P = 0.31$) and SmO₂; the strongest negative correlations were seen between albumin ($P = -0.43$) and cell saver ($P = -0.37$) and SmO₂. Correlations for other laboratory parameters studied were weak and only based on a few observations. In the final model we found a small, but significant increase in SmO₂ at the time of PRBC administration by 1.29 units ($P = 0.0002$). SmO₂ values did not change over time prior to PRBC administration ($P = 0.6658$) but following PRBC administration, SmO₂ values declined significantly by 0.015 units ($P < 0.0001$).

CONCLUSION

Intra-operative measurement of SmO₂ during large volume, yet controlled hemorrhage, does not show a statistically significant correlation with either invasive

hemodynamic, or laboratory parameters in patients undergoing elective complex spine surgery.

Key words: Transfusion; Complex spine surgery; Near infrared spectroscopy; Microvascular blood flow; Hemodynamic monitoring

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Core tip: Tissue oxygenation determined by Near Infrared Spectroscopy has been used to assess the adequacy of end-organ perfusion in models of trauma and sepsis and has been shown to correlate with stroke volume in models of hemorrhagic shock. We sought to investigate muscle tissue oxygenation (SmO₂) during transfusion in patients undergoing complex spine surgery, and to study the association of SmO₂ with invasive hemodynamic parameters in the clinical setting. In our study, we were unable to demonstrate a statistically significant correlation between SmO₂ and either invasive hemodynamic, or laboratory parameters in patients undergoing elective complex spine surgery.

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INTRODUCTION

Over 400000 elective spine fusion surgeries are performed annually in the United States^[1]. Blood loss during complex spine surgery can be significant, and these patients frequently undergo either homologous or autologous blood transfusion, with the aim of preserving patient hemodynamics and adequate end-organ perfusion. While the transfusion of blood products is clearly indicated in situations of severe anemia associated with hemodynamic instability, the individual threshold at which a patient should undergo transfusion is less clear. Due to the properties of stored blood, unloading of oxygen may be impaired^[2-4], and transfusion may thus not achieve the desired effect of optimizing oxygen supply to the tissues. Furthermore, liberal blood transfusions in patients undergoing elective orthopedic surgery are not associated with improved outcomes even in patients at high risk for cardiac complications, and may cause adverse side effects such as an increase in surgical site infections, pulmonary complications, and increased length of hospital stay in general patient populations undergoing non-cardiac surgery^[5,6]. In addition, blood transfusions can cause a significant economic burden on the healthcare system if not clearly indicated^[7].

Tissue oxygenation determined non-invasively by Near Infrared Spectroscopy (NIRS) has been suggested as one possible modality to determine the adequacy of end-organ perfusion in models of trauma and sepsis^[8,9], and has been shown to correlate well with stroke volume in states of acute, untreated hypovolemia in models of hemorrhagic shock outside of the clinical arena^[10]. We sought to investigate the microvascular (skeletal muscle tissue oxygenation; SmO₂) response to transfusion in patients undergoing elective complex spine surgery, and to study the association of muscle tissue oxygenation with invasive hemodynamic parameters obtained by pulse contour analysis in the clinical setting, thereby providing guidance as to when to transfuse a patient.

MATERIALS AND METHODS

Study design

After obtaining approval from the Institutional Review Board (Hospital for Special Surgery, New York, NY), potential participants were identified by review of the surgical schedule and approached on the day of surgery in the preoperative holding area. Twenty patients aged 18 to 85 years of age undergoing > 3 level anterior and posterior spine fusion surgery were enrolled. Exclusion criteria included minors, mentally disabled patients, pregnant women, employees, and prisoners. In addition, patients with skin lesions at the sensor placement site, and a history of allergies to skin adhesives were excluded from the study. Patients enrolled in the study were followed throughout the operative procedure, and for 12 h postoperatively.

Procedures and data collection

After informed consent was obtained, patients were taken to the operating room where general anesthesia was induced in standard fashion. In addition to standard American Society of Anesthesiologists (ASA) monitors, patients received an invasive arterial blood pressure catheter (Edwards Lifesciences, Irvine, CA) in the radial artery position, as well as a multi-lumen central venous catheter (Arrow International, Reading, PA) for administration of fluids, blood products, blood sampling, and measurement of central venous pressure. The arterial pressure transducer was connected to a pulse contour analysis module (FloTrac, Edwards Vigileo[®], Edwards Lifesciences, Irvine, CA) for continual analysis of stroke volume (SV), cardiac output (CO), cardiac index (CI), and stroke volume variability (SVV). To measure skeletal muscle oxygen saturation (SmO₂) during the study period, a non-invasive adhesive skin sensor based on NIRS (CareGuide, Reflectance Medical, Westborough, MA) was placed over the deltoid muscle. After a 5-min period to obtain a stable baseline signal, continuous recording of optical spectra was performed throughout the operative procedure. Measurements were interrupted during prone positioning of the patient (anterior-posterior procedures), and during patient

transport.

Central venous and mean arterial pressures were recorded with every routine lab draw during the procedure, and no less than every two hours intra-operatively. Lactate, hematocrit, base excess, arterial blood gases and central venous oxygen saturation were determined from blood samples that were drawn as part of routine care, and no less than every two hours intra-operatively.

Fluid administration and blood transfusion

No standardized protocol for administration of crystalloids, colloids, and blood products was used for the purpose of this study. Administration of fluids and blood products was performed at the discretion of the Attending Anesthesiologist based on individual patient comorbidities, hemodynamic status, and laboratory data. Crystalloid solutions were administered in the form of Lactated Ringer's. The colloid administered during the study period was human albumin 5% in 250 mL aliquots. Blood products transfused were either autologous blood from cell saver (Hemonetics, Braintree, MA) in 125 mL aliquots, or allogenic packed red blood cells (PRBC) from the blood bank. No specific transfusion triggers were used, and the healthcare team was blinded to the collection of NIRS spectra. All administration of fluids and blood products followed standard procedures at the Hospital for Special Surgery, without deviation from usual standards of care. Time stamps were collected for administration of colloids and blood products, to allow for analysis of SmO₂ immediately before, during, and after administration of these fluids, and to allow for analysis of hemodynamic data around the same time points. In general, PRBC were infused using pressure infusion bags (Vital Signs Inc, Totowa, NJ), whilst blood processed with the cell saver system was infused as a free flowing infusion.

Statistical analysis

Data on stroke volume, SmO₂, transfusion, and blood gas were collected on a total of 20 patients. Several variables were collected on a continuously throughout the surgery and included heart rate, blood pressure, mean arterial pressure, SV, CO, CI, SVV and SmO₂. These variables were identified at each time point with a time recording out to seconds. Patient data from the four sources was merged by a unique patient ID and timed at which the measurement occurred rounded to the nearest minute. Bivariate analyses were conducted to examine the potential associations between the outcome of interest, SmO₂, and each hemodynamic parameter measured using Pearson's correlation coefficient, both for the overall cohort and within-patients individually.

To examine the association between receipt of packed red blood cells and SmO₂, we created a dataset that included 11 patients who had received PRBC with documented administration times. After conducting an exploratory data analysis on SmO₂ using graphical techniques and percentile ranges, we excluded SmO₂

Table 1 Patient demographics

	Age (yr)	Height (cm)	Weight (kg)	BMI	Sex (m/f)
Mean (SD)	59.80 (10.96)	165.99 (9.83)	75.84 (15.75)	27.58 (5.45)	5/15

Table 2 Correlations with SmO₂

Variable	ρ (correlation)	No. of observations ¹
ScvO ₂	0.40704	92
SV	0.30967	8490
PvO ₂	0.20475	92
HCT	0.19402	89
CO	0.06498	8490
Lactate	0.0609	61
CI	0.05839	8490
pH A	0.0578	92
SVV	-0.10652	8490
RBC	-0.25085	18
Cell saver	-0.37471	37
Albumin	-0.42714	29

¹Eight thousand four hundred and ninety total observations within 20 patients (not all hemodynamic parameters were examined at each observation).

values ≤ 30 as well as values that jumped by $> 10\%$ from one time point to the next, unless the jump in values was typical for that specific patient. Due to the few occurrences of multiple PRBC administration during surgery in our data, we only focused on the first PRBC event.

A variable, "timecount", was created to standardize the time units, where the first minute of each patient surgery in our data was equal to one and subsequently increased by one unit for every minute until the end of the surgery. A second variable was created to flag the time at which PRBC was administered, where the variable was equal to 0 until the time at which PRBC were administered and 1 at every time point thereafter. Finally, an additional time variable, "postcount", was created to count the time after PRBC was administered, where postcount = 1 referred to the minute at which PRBC was given and increased by one unit per minute of time remaining in surgery for each subsequent measurement. These flagging variables allowed us to run an interrupted time series model, with SmO₂ as our outcome, controlling for the amount of time spent in surgery before and after receipt of PRBC and for the inherent correlation between observations. Our model was fit using PROC AUTOREG in SAS version 9.2. All other analyses were also conducted in SAS version 9.2 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Summative patient demographics are presented in Table 1. Pearson correlation coefficients varied widely between SmO₂ and each hemodynamic parameter examined. When examined for the overall cohort,

Table 3 SmO₂ statistics for individual patients and overall

Patient	No. of observations (time counts)	SmO ₂ statistics			
		Mean	Std Dev	Minimum	Maximum
1	1609	47.30205	4.231185	39.24457	59.81775
2	261	54.48111	4.559080	41.36314	60.91571
3	110	58.08155	3.474810	49.92571	63.56974
4	1061	59.45269	5.814339	42.39521	67.48903
5	333	59.86487	6.765487	43.87553	70.40168
6	284	60.44015	2.490064	53.33939	68.04648
7	486	60.78656	13.90398	30.77515	75.79442
8	1440	60.95438	4.090378	48.86891	73.39652
9	420	61.17271	2.276567	54.89989	65.64407
10	1470	61.18899	2.880967	52.65419	69.78379
11	203	61.95770	3.067270	47.69575	71.06789
Total	7677	57.63074	7.677996	30.77515	75.79442

Sorted by mean SmO₂.

where each unit of time served as an observation, the maximum number of observations was 8490 among the 20 participants. Several parameters, including central venous oxygen saturation ScvO₂, lactate, venous blood oxygen tension (PvO₂), arterial pH (pH-A), hematocrit, PRBC, cell saver, and albumin had less than 100 observations, among all participants. The strongest positive correlations existed between ScvO₂ ($P = 0.41$) and SV ($P = 0.31$) and SmO₂; the strongest negative correlations were seen between albumin ($P = -0.43$) and cell saver ($P = -0.37$) and SmO₂. Correlations for other laboratory parameters studied were weak and only based on a few observations (Table 2). When correlations were examined within individual patients, values varied widely; for example, correlations for SV varied from 0.40590 to -0.66903 for 18 patients with recorded SV values (data not shown).

Average SmO₂ for the 11 patients included in the final modeling was 57.63 (\pm SD 7.68), with a range of mean values from 47.30-61.92. The total number of observations analyzed was 7677, representing 7677 time counts, or minutes, of surgery over all patients included. Individual patient time counts ranged from 110 to 1609 (Table 3).

The final model showed a small, but significant increase in SmO₂ at the time of PRBC administration by 1.29 units ($P = 0.0002$). SmO₂ values did not change over time prior to PRBC administration ($P = 0.6658$) but following PRBC administration, SmO₂ values declined significantly by 0.015 units ($P < 0.0001$).

DISCUSSION

The key finding of our study is that when compared to experimental^[11], and clinical settings of uncontrolled hemorrhagic shock^[8], intra-operative measurement of SmO₂ during large volume, yet controlled hemorrhage does not show a statistically significant correlation with either invasive hemodynamic, or laboratory parameters in patients undergoing elective complex spine surgery.

The non-invasive assessment of tissue perfusion

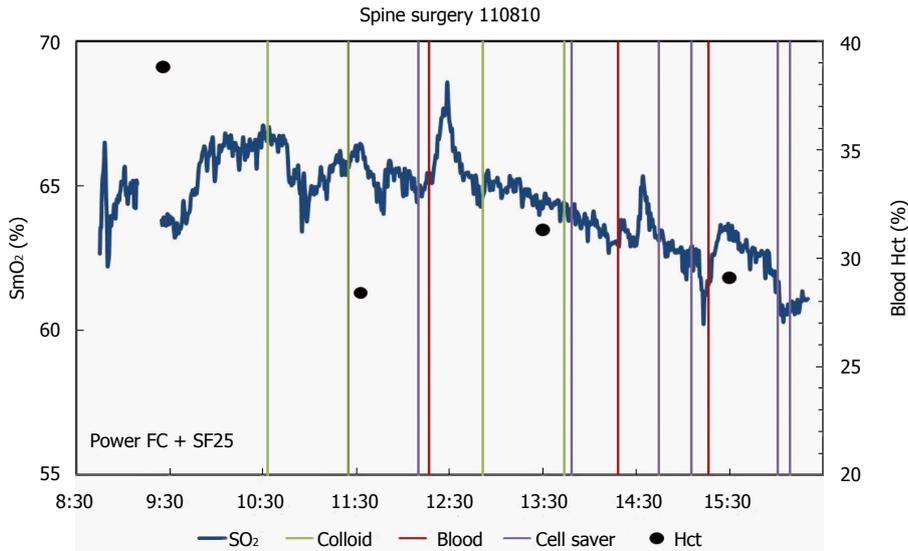


Figure 1 Representative SmO₂ response to infusion of colloid, cell saver, and homologous blood in one of the study patients. Notice the apparent lack of correlation between SmO₂ and HCT.

has garnered increasing interest in acute care medicine, based on the fact that traditional hemodynamic and oxygenation parameters such as blood pressure, central venous pressure, pulse oximetry, and central venous oxygen saturation are not necessarily reflective of the actual amount of blood loss, or the degree of shock a patient is experiencing. Furthermore, monitoring the macrocirculation with standard blood pressure, and heart rate monitors may not provide the clinician with relevant information about the adequacy of end-organ perfusion in certain disease states.

The ability of SmO₂ values derived by NIRS to track the adequacy of fluid resuscitation has been demonstrated in a model of swine hemorrhagic shock^[12], and a NIRS-derived variable of tissue oxygenation (StO₂) has been used to guide closed-loop fluid resuscitation in animal models^[13]. SmO₂ has also been shown to have a strong correlation with stroke volume in a human model of acute central hypovolemia^[14]. Recently, Bohula May and coworkers were able to demonstrate correlation of SmO₂ with invasively-measured SvO₂, and cardiac index (CI) in patients hospitalized with heart failure and cardiogenic shock^[15].

In disease states such as septic shock and traumatic hemorrhage, low tissue oxygen saturation determined by modalities such as NIRS, and persistent alterations in microcirculatory blood flow determined with OPS-imaging have been shown to correlate with severity of illness, and to be associated with organ failure, and death^[9,16-18].

While we were able to demonstrate a positive correlation between SmO₂ and SV, no statistical significance was found in our study, despite significant blood loss experienced by some of the patients. It is important to note however that data generated in models of acute, un-resuscitated shock may not be comparable to the situation found during elective surgery, where

patients undergo continuous administration of crystalloid, colloids, and blood products. The same is likely true for patients in cardiogenic shock on vasopressor therapy, where accumulation of significant oxygen debt is not uncommon, and is more likely to negatively affect tissue oxygenation.

No definitive transfusion triggers exist to guide clinicians during the intraoperative period, particularly during surgical procedures associated with substantial blood loss such as complex spine surgery. There is compelling retrospective data suggesting that intraoperative transfusion of blood in patients with anemia undergoing non-cardiac surgery, including orthopedic surgery is associated with an increase in morbidity and mortality^[19]. The situation is different for post-operative patients, including those admitted to an intensive care unit with severe sepsis, as well as patients with active gastrointestinal hemorrhage outside the operating room. Several prospective, randomized controlled trials have shown that restrictive transfusion strategies are either superior, or non-inferior to liberal transfusion strategies with respect to outcomes such as in-hospital and 90-d mortality, infection, cardiac ischemia, and in-hospital acute myocardial infarction^[5,6,20,21].

The most recent clinical practice guideline for perioperative blood management by ASA recommends that monitoring perfusion and oxygenation of vital organs should be continuous, and may include cerebral oximetry, and NIRS, in addition to standard hemodynamic monitors^[22]. While conceptually attractive due to its non-invasive nature, and the ability to reliably monitor the microcirculation in a variety of tissue beds, data on the ability of NIRS to provide clinically relevant information in the intraoperative period during elective surgery is sparse, and is mostly restricted to the monitoring of cerebral oxygenation.

The microvascular response to red blood cell trans-

fusion has been studied in patients with severe sepsis and trauma, however to our knowledge, no such data has been collected in patients undergoing elective orthopedic surgery associated with significant blood loss to date. Sakr and coworkers analyzed the microvascular response to transfusion in patients with severe sepsis. The authors were unable to demonstrate an overall effect of transfusion on sublingual microvascular perfusion as assessed with OPS-imaging. However, baseline microvascular blood flow predicted the microvascular response to transfusion. Those patients who were shown to have reduced microvascular blood flow at baseline demonstrated improved perfusion with transfusion whereas those with normal perfusion suffered a decrease in microvascular blood flow after transfusion^[23]. The same pattern has been demonstrated in trauma patients using Sidestream Dark Field imaging, with some decline in microvascular blood flow in response to transfusion of stored RBC in patients who had normal sublingual perfusion patterns at baseline^[24]. More recent investigations using NIRS-based technology to analyze the microvascular response to transfusion in trauma patients suggest that increasing age of transfused RBC results in decreased StO₂ levels. This effect was demonstrated both in critically injured, as well as stable, but anemic patients^[25,26]. These effects are likely attributable to “storage defects” of red blood cells, which decrease post-transfusion RBC survival. Changes that have been reported in the literature include depletion of adenosine triphosphate, and 2,3 diphosphoglycerate (2,3 DPG), a decrease in pH, release of potassium, reduced nitric oxide, increased cell volume, and reduced RBC deformability^[27]. Further experimental evidence in support of a negative impact on physiologic properties of stored RBC comes from a recent analysis of the impact of exchange transfusion in a rat model using intravital microscopy among other techniques. Yalcin and coworkers were able to demonstrate that exchange transfusion with stored RBC’s produced microcirculatory vasoconstriction resulting in decreased blood flow and oxygen delivery that was not found in anemia alone, or transfusion with fresh red blood cells. In addition, the authors showed that stored RBC’s have a shorter circulating lifetime, and appear to be removed from circulating blood due to their impaired elastic, and hydrodynamic behavior^[28].

In conclusion, while we detected a short-lived increase in SmO₂ in response to transfusion of PRBC, we were unable to detect a sustained, and relevant change in SmO₂ signal in a patient population subjected to significant intra-operative blood loss. The reasons for the short-lived increase (Figure 1) remain speculative, but might be explained by the aforementioned changes found in stored RBC’s.

Study limitations

The limitations of our study are significant, and include the small number of subjects enrolled, and the fact that there were no specific treatment algorithms or outcomes

studied in this proof-of-concept design. In addition, the age of transfused PRBC was not documented in our study protocol, which may limit the interpretability of our results. We were able however to evaluate a promising, non-invasive technology based on near-infrared spectroscopy in a “real-world” clinical setting, combined with a complex statistical analysis of continual oxygenation data. The results of this prospective, observational pilot study may provide a framework for future studies looking at specific patient outcomes associated with a hemodynamic management strategy incorporating real-time, microvascular blood flow data based on NIRS.

COMMENTS

Background

The assessment of the adequacy of end-organ perfusion in states of shock from sepsis or hemorrhage remain a challenge, as global hemodynamic measurements such as blood pressure, and cardiac filling pressures may not be reflective of perturbations of microcirculatory blood flow, and hence inadequate oxygen supply to critical end organs. Furthermore, standard physiologic parameters may not be sensitive to the early changes associated with hypovolemia from hemorrhage or anemia resulting in undetected tissue hypoxemia. Various technologies have been tested in both, exercise physiology laboratories as well as the clinical arena in an attempt to provide clinicians with more complete information regarding the state of the (micro) circulation, and oxygen supply to critical end organs. At the same time, individualized transfusion triggers based on objective data remain elusive, and there is ongoing research to determine rational, and safe transfusion patterns for hemodynamic impairment in states of shock from both, hemorrhagic, and non-hemorrhagic causes.

Research frontiers

One of the non-invasive technologies, which have shown promise in experimental settings both in the laboratory, as well as the clinical arena, is based on Near Infrared Spectroscopy (NIRS). The technology allows for accurate assessment of skeletal muscle oxygen saturation (SmO₂), which has been demonstrated to be a very early indicator of central hypovolemia in humans in a model of lower body negative pressure. It also shows excellent correlation with non-invasively measured stroke volume in the same model. A decrease in peripheral muscle NIR spectra is reflective of a decrease in tissue blood volume, and increased oxygen extraction by the peripheral tissues. NIRS has shown promise as an adjunct monitoring system for patients undergoing emergency surgery for trauma, or during treatment of patients in septic shock in addition to standard physiologic monitors for hemodynamic evaluation.

Innovations and breakthroughs

This study is the first to investigate tissue oxygenation based on NIRS in orthopedic patients undergoing elective complex spine surgery with anticipated high volumes of blood loss. While restrictive transfusion strategies appear safe in high-risk patients undergoing hip surgery, intra-operative blood loss during these procedures is usually much lower compared to estimated blood loss incurred during complex spine surgery. Optimal transfusion strategies during the latter type of surgery remain elusive, and largely based on experience and local practice patterns. The authors sought to determine in this observational pilot study if NIRS derived data on microcirculatory blood flow may provide useful objective information on the microcirculatory response to transfusion, which could guide subsequent prospective randomized controlled clinical trials on rational transfusion strategies in patients undergoing complex spine surgery. They also developed a complex statistical model for the analysis of continuous NIR spectra and their correlation with invasive hemodynamic and laboratory parameters, which can serve as a template for future trials in this area.

Application

As they were unable to detect a sustained, and relevant change in SmO₂ signal in a patient population subjected to significant intra-operative blood loss, the

role of NIRS during elective surgery associated with large volume blood loss will require further investigation.

Terminology

Light emitted in the near infrared spectrum from 700 to 1000 nm near infrared spectroscopy can penetrate deep in to the muscle, and be reflected back to a sensor bundle providing information on the absorption spectra of hemoglobin, and de-oxyhemoglobin. This spectral information allows for the calculation of skeletal muscle tissue oxygenation with great accuracy. The sensor used in this clinical study also allows for correction of fat thickness and skin pigmentation, thus further increasing the accuracy of the spectral information derived from the tissues.

Peer-review

This manuscript is a well-written report of an original study, with good analysis and methodology, informative tables, and clear results.

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Observational Study

“Meniscal” scar as a landmark for the joint line in revision total knee replacement

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Author contributions: Khan WS participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Bhamra J and Williams R participated in the drafting of the initial manuscript; Morgan-Jones R was the guarantor and designed the study; all authors reviewed and revised the article critically for important intellectual content; all authors approved the final submitted version.

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Abstract

AIM

To determine whether tissue identified at the joint line was actually remnant “meniscal” scar tissue or not.

METHODS

Nine patients undergoing revision knee surgery following informed consent had meniscal scar tissue sent to the histology department for analyses. All revisions were performed where joint line had been raised or lowered at earlier surgery. Although preoperative radiographic evaluations suggested that the joint line had been altered, intraoperatively there was scar tissue at the level of the recreated joint line. This scar tissue has traditionally been described as meniscal scar, and to identify the origins of this tissue, samples were sent for histological analyses. The tissue samples were stored in formalin, and embedded and sectioned before undergoing histochemical staining. All samples underwent macroscopic and microscopic examination by a histopathologist who was blind to the study aims. The specific features that were examined included tissue organisation, surface and central composition, cellular distribution including histiocytes, nuclear ratio and vasculature. Atypical and malignant features, inflammation and degeneration were specifically looked for. A statistical review of the study was performed by a biomedical statistician.

RESULTS

The histological findings for the nine patients showing

the macroscopic and microscopic findings, and the conclusion are outlined in a Table. The histological analyses were reviewed to determine whether the tissue samples were likely to be meniscal scar tissue. The response was yes (2, 22%), no (6, 67%) and maybe (1, 11%) based on the conclusions. The results were "yes" when on macroscopy, firm cream tissue was identified. In these two "yes" samples, microscopic analyses showed organised fibrous tissue with focal degenerative areas with laminated pattern associated with histiocytes peripherally but no inflammation. The "no" samples were assessed macroscopically and microscopically and were deemed to have appearances representing fibrous synovial tissue and features in keeping with degenerate scar tissue or connective tissue. One sample was indeterminate and microscopically contained fibro-collagenous tissue with synovial hyperplasia. It also contained some degenerate hyalinised tissue that may represent cartilage, but the appearances were not specific.

CONCLUSION

Based on our pilot study, we recommend reliance on a number of markers to identify the joint line as outlined above, and to exercise caution in using the "meniscal" scar.

Key words: Meniscal scar; Joint line; Revision surgery; Knee; Histology

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Core tip: Our findings suggests that the structure identified as the "meniscal" scar may actually represent scar tissue that forms in the available space of the recreated joint line rather than actually represent the level of the native joint line where the meniscus once attached.

Khan WS, Bhamra J, Williams R, Morgan-Jones R. "Meniscal" scar as a landmark for the joint line in revision total knee replacement. *World J Orthop* 2017; 8(1): 57-61 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/57.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.57>

INTRODUCTION

Revision total knee arthroplasty (TKA) is a complex procedure that generally does not achieve the same good results as primary knee replacement. There are a number of reasons for this and include the complexity of the revision procedure making it difficult to restore the joint line^[1-3]. Restoring the joint line is associated with improved clinical outcomes, functional knee scores and range of motion as well as decreased anterior knee pain^[4]. In revision surgery the joint line can more commonly become elevated due to distorted anatomical

landmarks, excessive distal femoral bone resection and using an excessively thicker a tibial insert. Excessive distal femoral bone loss may be due to excessive bone resection at the primary joint replacement or as a result of deficient bone stock from infection, osteolysis, peri-prosthetic fracture, component migration or iatrogenic damage when attempting to remove implants and cement in revision surgery^[1,3]. It is therefore proposed that distal femoral augments should be used rather than thicker polyethylene to avoid elevation of the joint line.

A number of landmarks have been described in the literature to facilitate the accurate reproduction of the joint line in revision TKA and include the (1) the "meniscal" scar; (2) 1.5-2 cm proximal to the fibular head; (3) 2 cm proximal to the tibial tubercle; (4) 2-2.5 cm distal to the lateral femoral epicondyle; and (5) 2.5-3 cm distal to the medial femoral epicondyle^[5,6]. Other measurements used include two finger breadths above the tibial tubercle or 2 cm below the inferior patella pole in extension^[7]. Less commonly used reference points include the adductor tubercle^[7,8]. Some surgeons obtain historical radiographs of the ipsilateral, or up-to-date radiographs of the contralateral knee to help identify the location of the joint line relative to fixed bony landmarks^[4,7]. Variations in technique exist when measuring from radiographs and other potential drawbacks include malrotation and magnification that can cause inaccurate measurements^[5].

The bony and radiological methods described to identify the joint line can be unreliable and are not standardised or reproducible. The bony landmarks may not be easily accessible or identifiable intraoperatively and hence the greater reliance on the "meniscal" scar. We performed a histological study to determine whether tissue identified at the joint line was actually remnant "meniscal" scar tissue or fibrous tissue formed at the level of the recreated joint line from the previous surgery.

MATERIALS AND METHODS

Nine patients undergoing revision knee surgery following informed consent had "meniscal" scar tissue sent to the histology department for analyses. All revisions were performed where joint line had been raised or lowered at earlier surgery. Although preoperative radiographic evaluations suggested that the joint line had been altered, intraoperatively there was scar tissue at the level of the recreated joint line. This scar tissue has traditionally been described as meniscal scar but to identify the origins of this tissue, samples were sent for histological analyses.

The tissue samples were stored in formalin, embedded and sectioned before undergoing histochemical staining. All samples underwent macroscopic and microscopic examination by a histopathologist who was blind to the study aims. The specific features that were examined included tissue organisation, surface

Table 1 Histological reports for nine patients showing the macroscopic and microscopic findings, and the conclusion

Patient	Macroscopy	Microscopy	Conclusion	Is the tissue likely to be meniscal scar tissue?
1	Cream tissue	Organised fibrous tissue and synovial surface. No atypical features	Appearances likely represent fibrous synovial tissue	No
2	Yellow and white tissue	Fragments of fibrous tissue partly lined by synovium show focal areas of denuded surface with acellular fibrinoid exudate. No significant inflammation	Features in keeping with degenerate scar tissue	No
3	Firm cream tissue	Fibrous tissue with focal degenerate area. No inflammation seen	Meniscal tissue	Yes
4	Firm cream tissue	Sections showing organised fibrous tissue and laminated pattern associated with foamy histiocytes at the periphery under the synovial surface. In areas the fibrous tissue lack nuclei	Appearances likely represent meniscal remnants with degenerate features	Yes
5	Firm cream tissue	Fragments of connective tissue. No features of atypia, malignancy, or significant inflammation	Connective tissue	No
6	Cream tissue	Fragments of fibrous tissue with overlying synovium. There is a mild inflammatory infiltrate	Features in keeping with fibrous scar tissue	No
7	Firm cream tissue	Sections show fragments of connective tissue. No evidence of atypia or malignancy. No significant inflammation is identified. There is a small collection of blood vessels seen in one edge	Connective/scar tissue	No
8	Cream tissue	Fibro-collagenous tissue with synovial hyperplasia. Some degenerate hyalinised tissue that may represent cartilage, but the appearances are not specific	Features in keeping with non-specific articular tissue	Maybe
9	Yellow and white tissue	Fibrous tissue with no significant inflammation	Degenerate scar tissue	No

The histological analyses were reviewed to determine whether the tissue reported was likely to be meniscal scar tissue.

and central composition, cellular distribution including histiocytes, nuclear ratio and vasculature. Atypical and malignant features, inflammation and degeneration was specifically looked for. A statistical review of the study was performed by a biomedical statistician.

RESULTS

The histological findings for nine patients showing the macroscopic and microscopic findings as well as the conclusion are outlined in Table 1. The histological analyses were reviewed to determine whether the tissue samples were likely to be meniscal scar tissue. The response was yes (2, 22%), no (6, 67%) and maybe (1, 11%).

DISCUSSION

Restoring the joint line is important in knee surgery. Joint line elevation can cause patella baja, patella button impingement, accelerated wear and loosening, quadriceps weakness, anterior knee pain, laxity in knee mid-flexion, varus-valgus instability and hyperextension instability^[1]. It also results in decreased knee range of motion caused by impingement of the patellar implant on the tibial component^[9,10]. Mid-flexion instability is caused by tight posterior structures that provide stability in extension and at 90 degrees of flexion^[6]. A recent review of studies demonstrated elevation of the joint line in 79% of revision TKAs by 3-13 mm^[2,5,7]. Singerman *et al*^[11] demonstrated that raising or lowering the joint line in revision TKA by more than

8 mm resulted in a decreased range of motion and lower modified Mayo Clinic knee scores. In another study, elevation greater than 8 mm was associated with reduced mean Knee Society scores of 141 vs 125^[3]. Several studies have shown that elevation more than 5 mm significantly affects the functional outcome in revision TKA^[1]. Mason *et al*^[5] showed a significant difference in total Bristol knee scores and the functional component of the score when there was more than 5 mm elevation of the joint line. Proximal joint line displacement of more than 5 mm caused decreased knee flexion, increased patellofemoral forces that can cause pain, subluxation, dislocation, fracture and increased varus-valgus instability particularly in mid-flexion in cadaveric knees^[12]. A less common occurrence of distal placement of the joint line, patella alta, can alter tracking of the extensor mechanism that can cause increased patellar strain^[11]. Although Scuderi and Insall suggest that elevation of the joint line by 10 mm has no significant clinical effect^[13], and Partington *et al*^[3] demonstrated only a marginal statistical significance in clinical scores in a series of 99 revision TKA cases with more than 8 mm elevation of the joint line the overwhelming evidence points to the restoration of the joint line being important for a good clinical result.

The "meniscal" scar is increasingly being used to identify the level of the native joint line in revision knee surgery. The menisci are two fibrocartilagenous, semilunar concave shaped tissues that rest on the medial and lateral tibial plateau. Functions of the menisci include assistance in joint stability, to bear and transmit loads within the knee and to act as "shock

absorbers"^[14]. The normal meniscus contains two cell populations, fibroblasts on the meniscal surface and fibrochondrocytes in the inner surface. Meniscus tissue has a complicated shape and anchoring network, but displays great regional variation in its extracellular matrix components. The menisci consist of water (75%), water (20%), type I collagen and other substances (5%); including proteoglycans, elastin and type II collagen. The majority of collagen fibres are arranged circumferentially with some running radially. The meniscal periphery is highly fibrous and abundant in cells and collagen type I, with the inner portion of the tissue resembles hyaline cartilage with fewer cells, type II collagen and higher proteoglycan content. The outer portion of the meniscal tissue is highly vascularized, in comparison to the inner menisci that is devoid of blood vessels^[14]. There are several morphological variations in meniscal tissue with cells being classified as fibroblasts, fibrocytes, chondrocytes, fibro-chondrocytes and meniscus cells by researchers. However these morphologies have various cell profiles. Cells in the superficial meniscal layer are oval or fusiform in shape and represent fibroblast morphology. Cells in the deeper meniscal layer have a more spherical appearance similar to chondrocytes. The outer proportion of meniscus contains type I collagen predominantly with fibrocartilaginous matrix. The inner meniscus is more hyaline-like consisting of predominantly type II collagen and contains chondrocyte-like cells^[14]. Meniscal tissue may contain few or no intrinsic viable cells^[15].

These features suggest that it is reliable histologically to identify meniscal tissue. Our pilot study only identified 33% of samples as potentially being of meniscal origin. The remaining 67% were not likely to be of meniscal origin. This suggests that the structure identified as the "meniscal" scar may actually represent scar tissue that forms in the available space of the joint line rather than actually represent the level of the native joint line where the meniscus once attached. This has significant implications on restoring the joint line. We recommend reliance on a number of markers to identify the joint line as outlined above and to exercise caution in using the "meniscal" scar.

COMMENTS

Background

During primary and revision knee surgery, it is important to restore the joint line but this can be difficult especially where there has been previous trauma, surgery or infection. A number of landmarks have been described in the literature to facilitate the accurate reproduction of the joint line in revision total knee arthroplasty (TKA) and include the "meniscal" scar amongst others.

Research frontiers

A number of landmarks have been described in the literature to facilitate the accurate reproduction of the joint line in revision TKA but none of them are absolutely accurate. The bony and radiological methods to identify the joint line can be unreliable, and are not standardised or reproducible. The bony landmarks may not be easily accessible or identifiable intraoperatively and hence the greater reliance on the "meniscal" scar.

Innovations and breakthroughs

The authors' findings suggest that the structure identified as the "meniscal" scar may actually represent scar tissue that forms in the available space of the recreated joint line rather than actually represent the level of the native joint line where the meniscus once attached.

Applications

The research has significant implications on restoring the joint line. The authors recommend reliance on a number of markers to identify the joint line as outlined in this paper, and to exercise caution in using the "meniscal" scar.

Terminology

The "meniscal" scar is the remnant soft tissue on the peripheries of the knee joint after excision of the menisci during earlier knee arthroplasty surgery.

Peer-review

The present study described the "meniscal" scar as one of many landmarks used to identify the native joint line. It's a very well written paper.

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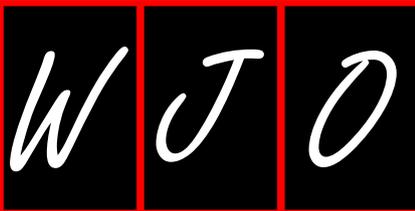
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Observational Study

Tourniquets do not increase the total blood loss or re-amputation risk in transtibial amputations

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Informed consent statement: Our retrospective study contained data from medical records only. The study was registered at the regional data protection agency (04.12.2012) (j. no. 01975 HVH-2012-053).

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Abstract

AIM

To investigate the total blood loss (TBL) and the safety with respect to the re-amputation rate after transtibial amputation (TTA) conducted with and without a tourniquet.

METHODS

The study was a single-centre retrospective cohort study of patients with a primary TTA admitted between January 2013 and April 2015. All patients with a primary TTA were assessed for inclusion if the amputation was performed because of arteriosclerosis or diabetic complications. All patients underwent a standardized TTA procedure that was performed approximately 10 cm below the knee joint and performed with sagittal

flaps. The pneumatic tourniquet, when used, was inflated around the femur to a pressure of 100 mmHg above the systolic blood pressure. The number of blood transfusions within the first four postoperative days was recorded. The intraoperative blood loss (OBL), which is defined as the volume of blood lost during surgery, was determined from the suction volume and by the weight difference of the surgical dressings. The trigger for a blood transfusion was set at a decrease in the Hgb level < 9.67 g/dL (6 mmol/L). Transfusions were performed with pooled red blood cells containing 245 mL per portion, which equals 55 g/L of haemoglobin. The TBL during the first four postoperative days was calculated based on the haemoglobin level and the estimated blood volume. The re-amputation rate was evaluated within 30 d.

RESULTS

Seventy-four out of 86 consecutive patients who underwent TTA within the two-year study period were included in the analysis. Of these, 38 were operated on using a tourniquet and 36 were operated on without using a tourniquet. There were no significant preoperative differences between the groups. The patients in both groups had a postoperative decrease in their Hgb level compared with preoperative baseline values. The patients operated on using a tourniquet received approximately three millilitres less blood transfusion per kilogram body weight compared with patients operated on without a tourniquet. The duration of surgery was shorter and the OBL was less for the tourniquet group than the non-tourniquet group, whereas no significant difference was observed for the TBL. The TBL median was 859 mL (IQR: 383-1315) in the non-tourniquet group *vs* 737 mL (IQR: 331-1218) in the tourniquet group ($P = 0.754$). Within the 30-d follow-up period, 9 patients in the tourniquet group and 11 in the non-tourniquet group underwent a re-amputation at the trans-femoral level. The use of a tourniquet showed no statistically significant association with the 30-d re-amputation at the femur level in the multiple logistic regression model ($P = 0.78$). The only variable with a significant association with re-amputation was age (OR = 1.07; $P = 0.02$).

CONCLUSION

The results indicate that tourniquets do not cause severe vascular damage with an increased postoperative bleeding or failure rate as the result.

Key words: Total blood loss; Intraoperative blood loss; Transtibial amputation; Lower extremity amputation; Pneumatic tourniquet; Re-amputation

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Core tip: The authors performed a retrospective cohort study on the use of tourniquets during transtibial amputation with the primary aim of comparing various estimates of blood loss and re-operation between

the groups with or without a tourniquet. The basis for investigating this subject is the theoretical risk of increased bleeding due to vascular damage in the tourniquet group, which may, in turn, lead to increased risk of re-amputation due to local oedema, among other factors. We found no significant difference in the total blood loss when calculated on day four after surgery or in the 30-d re-amputation rate between the tourniquet and the non-tourniquet group.

Wied C, Tengberg PT, Holm G, Kallelose T, Foss NB, Troelsen A, Kristensen MT. Tourniquets do not increase the total blood loss or re-amputation risk in transtibial amputations. *World J Orthop* 2017; 8(1): 62-67 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/62.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.62>

INTRODUCTION

Recent studies have illuminated the challenges in lower extremity amputation surgery where a high short-term amputation failure rate is especially notable^[1,2]. No clear explanation for this result has yet been established. With this retrospective cohort study, we aimed to investigate if the possible cause is related to the use of a pneumatic tourniquet during amputation. Studies have shown that the use of a tourniquet reduces the intraoperative blood loss (OBL) and facilitates the procedure (decreases the duration of surgery) during transtibial amputations (TTA)^[3]. However, despite this advantage, the use of tourniquets remains a controversial topic in amputation surgery due to potential complications^[4,5]. There is a theoretical risk that the tourniquet could aggravate the blood loss during the first postoperative days. When the tourniquet pressure is applied to arteriosclerotic vessels, there is a risk of causing minor lesions and, as a result, seepage of blood. This seepage could be unrecognized by the operating surgeons due to the late onset re-perfusion of the limb after the release of the tourniquet^[6] and cause severe postoperative bleeding. Such "hidden blood loss" could potentially lead to oedema of the stump and maybe associated with an increased risk of early re-amputation.

The aims of this study were (1) to compare the total blood loss (TBL) evaluated on the fourth postoperative day in patients operated with or without the use of a tourniquet and (2) to evaluate if the use of tourniquet increases the risk of re-amputation within the first 30 d after TTA performed with sagittal flaps (ad modum Persson).

MATERIALS AND METHODS

The study was a single-centre retrospective cohort study of patients with a primary TTA admitted between January 2013 and April 2015. All patients with primary TTA were assessed for inclusion if amputated because

of arteriosclerosis or diabetic complications. Exclusion criteria were a bilateral amputation procedure, on-going gastrointestinal bleeding, amputation due to trauma or incomplete data or death before the final measurement of haemoglobin (Hgb).

All patients underwent a standardized TTA procedure^[7] performed approximately 10 cm below the knee joint and performed with sagittal flaps. The pneumatic tourniquet, when used, was inflated around the femur to a pressure of 100 mmHg greater than the systolic blood pressure^[8]. It was released again at the end of the procedure but before final closure to secure haemostasis. The decision to use a tourniquet relied on the surgeons. Standardized care was provided for all patients regarding bandages, pain management, rehabilitation, fluid replacement, pausation of antiplatelet drugs, treatment with blood transfusions and thromboprophylaxis^[9]. Tranexamic acid was not administered.

Blood loss

The number of blood transfusions within the first four postoperative days was recorded where day 0 is the day of surgery (after the start of the surgical procedure). The OBL, which is defined as the volume of blood lost during surgery, was determined from the suction volume and by the weight difference of the surgical dressings. The trigger for a blood transfusion was set at a decrease in the Hgb level < 9.67 g/dL (6 mmol/L). Transfusions were performed with pooled red blood cells containing 245 mL/portion, which equals 55 g/L of haemoglobin. The TBL during the first four postoperative days was calculated based on the haemoglobin level and the estimated blood volume. The blood volume and loss was determined according to gender, weight, height and the Hgb of the patient using formulae described in previous studies^[10,11]:

Blood volume (l) = height (m)³ × 0.356 + weight (kg) × 0.033 + 0.183 for women, and Blood volume (l) = height (m)³ × 0.367 + weight (kg) × 0.032 + 0.604 for men. $Hgb_{loss} = \text{blood volume} \times (Hgb_{adm} - Hgb_{fin}) + Hgb_{trans}$, where Hgb loss is the calculated total haemoglobin loss (g), Hgb_{adm} is the haemoglobin value on admission, Hgb_{fin} is the final recorded haemoglobin value on day four and Hgb_{trans} is the total amount of haemoglobin (in grams) in the transfused red blood cells before the measurement of Hgb_{fin} . The calculated blood loss was estimated using the following formula:
Blood loss in millilitre = $(Hgb_{loss}/Hgb_{adm}) \times 1000$.

Other variables

Eight predictor variables (age, gender, body mass index, ASA score, duration of surgery, the rank of surgeon, intraoperative blood loss, and anti-fibrinolytic medication) were included in the TBL analysis due to their previously established influence on patient outcome^[10,12]. Re-amputations were included if performed within 30 d following the index amputation. Six patients died within the 30-d follow-up period, and of these six patients, all underwent re-amputation; these patients were still

included in the re-amputation model.

Statistical analysis

Continuous data are presented as median values with interquartile ranges (IQRs) or mean values with standard deviations. Differences between the groups were tested using a *t* test or a Mann-Whitney *U* test based on the normal distribution assumption. Categorical data are presented as numbers and were compared using the χ^2 test or Fisher's exact test in cases with cell counts of five or less. The associations of TBL and OBL with tourniquets were analysed using univariable and multivariable linear regression. The models use either TBL or OBL as the dependent variable and all previously mentioned predictor variables along with tourniquets as independent variables. The residuals in the models were tested and found to be normally distributed. A logistic regression model with tourniquet as the dependent variable was performed to identify potential inherent selection bias. The association between the 30-d re-amputation and the use of tourniquet was analysed using a multiple logistic regression model. The fit of the model was evaluated using a Hosmer-Lemeshow goodness of fit test. A *P* value of 0.05 was considered statistically significant. All analyses were performed by a biostatistician working in R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 74 out of 86 consecutive patients who underwent TTA within the two-year study period were included in the analysis. Of these, 38 were operated on using tourniquets and 36 without. Six patients died before the 30-d follow-up ($n = 3$ in the tourniquet group and $n = 3$ in the non-tourniquet group). Trained residents or senior consultants performed the surgical procedures. Reasons for exclusion were bilateral amputation ($n = 8$), trauma ($n = 2$), and death before the fourth postoperative day ($n = 2$). There were no significant preoperative differences between the groups (Table 1). The patients in both groups had a postoperative decrease in their Hgb level compared with the preoperative baseline values, as illustrated in Figure 1A. The patients operated on using tourniquets received approximately three millilitres less transfusion blood per kilogram body weight than the patients operated on without using a tourniquet (Figure 1B, $P \leq 0.03$ for all days). The duration of surgery was shorter, and the OBL was less for the tourniquet group compared with the non-tourniquet group, whereas no significant difference was observed for the TBL. When the median OBL was subtracted from the median TBL for all the patients in the two groups, no significant difference was found (Table 2, $P = 0.241$). Within the 30-d follow-up, 9 patients in the tourniquet group and 11 in the non-tourniquet group had a re-amputation at the transfemoral level.

The logistic regression analysis with tourniquet as

Table 1 Demographic of the included patients

Variables	All patients <i>n</i> = 74	Tourniquet group <i>n</i> = 38	Non-tourniquet <i>n</i> = 36	<i>P</i> value
Sex (female/male)	25/49	11/27	14/22	0.511
Age (yr)	72.3 ± 11.0	71.3 ± 9.8	73.4 ± 12.1	0.415
Height (cm)	172 ± 9	173 ± 9	171 ± 9	0.178
Weight (kg)	74.2 ± 18.8	78.2 ± 18.6	70.1 ± 18.4	0.065
Body mass index	25.0 ± 5.4	25.9 ± 5.5	23.9 ± 5.2	0.112
Cause of amputation (diabetes/arteriosclerosis)	39/35	19/19	20/16	0.806
ASA group 1-2/3-4	13/60	5/32	8/28	0.374
Rank of surgeon, (resident/consultant)	49/25	24/14	25/11	0.745
Preoperative hemoglobin (g/dL)	10.9 ± 1.6	11.2 ± 1.6	10.8 ± 1.4	0.246
Preoperative	368 ± 150	352 ± 121	380 ± 169	0.481
Thrombocyte (× 10 ⁹ /L)				
NSAID or acetylsalicylic acid (yes/no)	40/34	20/18	20/16	0.985
Clopidogrel (yes/no)	14/60	8/30	6/30	0.854

Data are presented as numbers or mean values with standard deviations. ASA: American Society of anesthesiologists; NSAID: Nonsteroidal anti-inflammatory drug.

Table 2 Perioperative data from included patients

All patients	<i>n</i> = 71 ¹	Tourniquet <i>n</i> = 35	Non-tourniquet <i>n</i> = 36	<i>P</i> value
Duration of surgery (min)	82 (66-106)	78 (60-97)	88 (72-112)	0.041
Duration of Tourniquet (min)		30 (18-42)		
Intraoperative blood loss (mL)	250 (150-500)	200 (100-300)	300 (225-600)	< 0.001
Total blood loss from day 0-4 (mL)	773 (336-1218)	737 (331-1218)	859 (383-1315)	0.754
Delta TBL-OBL (mL)	479 (66-855)	495 (115-900)	296 (-30-803)	0.241

Data are presented as median values with interquartile range. ¹Three patients missing due to no registration of the intraoperative blood loss. TBL: Total blood loss; OBL: Intraoperative blood loss.

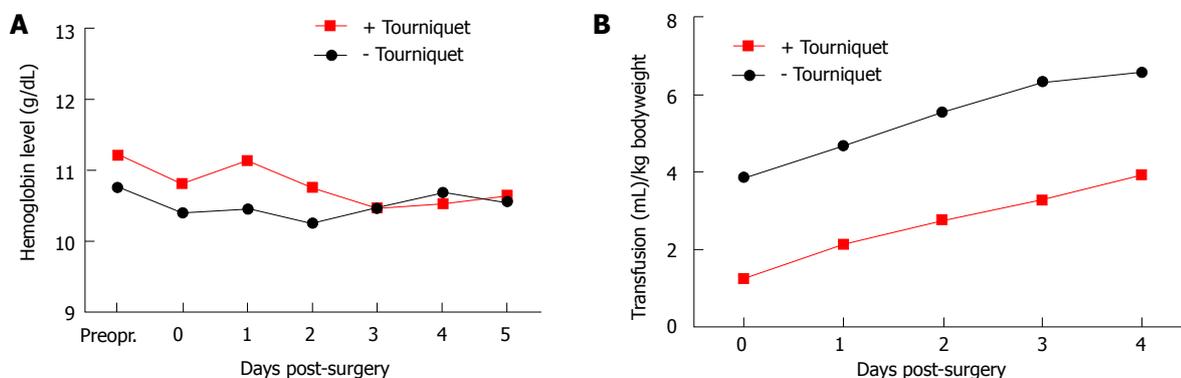


Figure 1 The patients in both groups had a postoperative decrease in their Hgb level compared with the preoperative baseline values. A: Development in Haemoglobin, Day 0 = day of surgery; B: Transfusion requirements.

the dependent variable identified no potential selection bias. However, there was a tendency that patients with a greater body mass index more often had a tourniquet installed during surgery ($P = 0.059$). The univariable linear regression analysis revealed no significant effect on the TBL from any of the selected variables. Still, the average TBL was lower for women and when consultants performed the procedures (Table 3). The multiple linear regression model of factors influencing the OBL showed that the non-tourniquet group, on average, experienced a greater OBL (mean of 243 mL, $P = 0.004$) compared with the tourniquet group. No other variables showed a significant association with

OBL. There was no significant difference between the two groups regarding the TBL (Table 3). The use of a tourniquet showed no statistically significant association with a 30-d re-amputation at the femur level in the multiple logistic regression model ($P = 0.78$). The only variable with a significant association with re-amputation was age (OR = 1.07; $P = 0.02$). The Hosmer-Lemeshow goodness of fit test had a P -value of 0.06 in the re-amputation model.

DISCUSSION

We found that the use of a pneumatic tourniquet in

Table 3 Univariable and multivariate analysis with linear regression of association between risk factors for the total blood loss in the 74 patients

	Univariable estimate (95%CI)	P value	Multivariable estimate (95%CI)	P value
Tourniquet (used)	-39 (-370-293)	0.810	-78 (-431-275)	0.659
Age (per year older)	-10 (-25-5)	0.210	-7 (-23-9)	0.384
Women/men (men)	320 (-22-662)	0.066	221 (-149-590)	0.237
Specialist registrar/consultant (consultant)	-335 (-676-6)	0.054	-324 (-689-41)	0.081
Clopidogrel (in treatment)	33 (-390-456)	0.876	-86 (-520-349)	0.696
NSAID/ acetylsalicylic acid (in treatment)	205 (-124-534)	0.218	223 (-126-572)	0.206
Duration of surgery (per minute)	1 (-5-7)	0.752	-3 (-10-5)	0.482
ASA-1-2/ ASA 3-4 (ASA 3-4)	-1 (424-422)	0.995	-66 (-506-373)	0.764
Body mass index (per one unit)	21 (-9-52)	0.162	17 (-17-50)	0.322

Variables in parenthesis = reference; NSAID: Nonsteroidal anti-inflammatory drug; ASA: American society of anesthesiologists.

dysvascular TTA surgery ad modum Persson does reduce the duration of surgery, the blood transfusion rate (millilitres of blood transfusion per kilogram bodyweight) and the OBL, but there was no significant difference in the TBL when evaluated on the fourth postoperative day. We found no evidence that the tourniquet causes severe damage to vessels and, therefore, an increased postoperative blood loss. However, although not significant, we did find that patients who were operated by a consultant experienced a lower blood loss than those operated by surgeons with less experience. We found no difference between the groups regarding re-amputation at the femur level within 30-d follow-up. This finding is similar to studies on (ad modum Burgess) amputations with long posterior flaps and tourniquets^[13,14].

Patients who require a TTA due to diabetes-related complications or severe arteriosclerosis are often old and have several co-morbidities^[15]. Recent studies suggest that a more restrictive strategy towards blood transfusions in patients undergoing major amputations would be appropriate since blood transfusions appear to be associated with post-operative complications, such as acute renal failure and pneumonia^[16,17]. The use of a pneumatic tourniquet around the femur can reduce the OBL and, therefore, the transfusion rate and risk of transfusion-related complications^[13]. However, the effect of the tourniquet in TTA surgery is not thoroughly described, and the focus has primarily been towards the ability to reduce the OBL.

Our findings of a reduction in the OBL using a tourniquet are similar to the findings from a 2006 randomized controlled trial^[13]. These findings are of no surprise since the major vessels are strangulated by the tourniquet and under-tied with sutures by the surgeons. It is reasonable to assume that the reduction in the OBL will reduce the transfusion rate^[14]. Our concern was that the tourniquet could aggravate the seepage of blood from the wounds due to damage to the vessels during the time when the tourniquet is inflated. However, we found no statistically significant difference between the groups when the TBL was calculated on the fourth postoperative day indicating no radical change in blood loss.

The fact that the non-tourniquet group had a greater OBL and received more blood transfusions but had a similar TBL as the tourniquet group is a dilemma. This result could illustrate a late onset drop in Hgb level in the patients operated on using tourniquets, pointing at increased postoperative bleeding. Thus, it has been shown that an exsanguinated human limb will swell by approximately 10% of its original volume after the release of a pneumatic tourniquet and mainly due to the return of the exsanguinated blood volume^[6]. This delayed reperfusion, which is associated with the duration of use of the tourniquet, creates a potential source of continuous minor bleeding if the surgeons overlook minor vessels not recognized during the time when the tourniquet is inflated^[18]. Even if the surgical field is inspected for minutes after the release of the tourniquet, the possible delayed re-perfusion might still cause the non-under tied vessels to begin leaking when the patients are moved from the operating room. However, if serious seepage due to damaged vessels was the case, we would have expected a more dramatic drop in Hgb and a steeper development in the transfusion curve.

This study has some limitations. Although the formula used to calculate the TBL has been used widely in other orthopaedic sub-specialties^[10,19], it has limitations in amputation surgery due to the changes in the body surface area after amputation. The patients will, because of this, have a different blood volume after surgery, which is difficult to correct in the equations. However, since we compared two groups with similar baseline values and our interests are the change in the values between the groups, we believe that the calculations are acceptable to illuminate the objectives of our study. Potential biases include the operating surgeons and the selection of patients for surgery with a tourniquet. However, the logistic regression model with respect to this matter showed no evidence that a specific patient's characteristics triggers the surgeons to use a tourniquet.

In conclusion, the use of a tourniquet reduces the duration of surgery, the OBL, and the transfusion rate in dysvascular TTA amputations. We found no significant

difference in the TBL when it is calculated on day four after surgery or in the 30-d re-amputation rate between the tourniquet and the non-tourniquet group. From a haemodynamics point of view, it appears to be advantageous and safe to use a tourniquet during ad modum Persson TTA amputations.

COMMENTS

Background

There is an increasing number of high-risk elderly and severely comorbid patients scheduled for dysvascular lower extremity amputations. Continuous optimization of current procedures is necessary. The use of a tourniquet in dysvascular amputees is considered controversial due to fear of vascular damage and potentially increased postoperative bleeding. The primary aim of this study was to compare the total blood loss after transtibial amputation conducted with and without tourniquets, and the secondary aim was to illuminate the safety aspect regarding the re-amputation rate following (ad modum Persson) transtibial amputations.

Research frontiers

The authors have reported the first series in the literature of patients with lower extremity amputations who were evaluated with the use of calculated total blood loss on day four after amputation. The approach provides valuable information regarding the blood loss when a tourniquet is applied during transtibial amputations.

Innovations and breakthroughs

The authors found that the use of a pneumatic tourniquet in dysvascular transtibial amputation surgery (ad modum Persson) does reduce the duration of surgery, the blood transfusion rate (millilitres of blood transfusion per kilogram bodyweight) and the intraoperative blood loss but without a significant difference in the total blood loss when evaluated on the fourth postoperative day. The authors found no evidence that the tourniquet causes severe damage to vessels and, therefore, an increased postoperative blood loss. The authors found no difference between the groups regarding re-amputation at the femur level within the 30-d follow-up. This finding is similar to studies on ad modum Burgess amputations with long posterior flaps and tourniquets.

Applications

The tourniquet can be considered during transtibial amputations to secure minimal blood loss and duration of surgery.

Peer-review

The study is valuable in showing that the total blood loss is not increased by either method.

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Observational Study

Reliability and concurrent validity of postural asymmetry measurement in adolescent idiopathic scoliosis

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Institutional review board statement: The study was reviewed and approved by the Swedish Research Council Regional Ethics Committee in Stockholm, Sweden (Dnr: 2012/172-31/4) and from Bond University Health Research Ethics Committee in 2014 (RO 1896).

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at allan.abbott@liu.se. Participants gave informed consent for data

sharing of anonymized data.

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Abstract

AIM

To investigate the reliability and concurrent validity of the Baseline[®] Body Level/Scoliosis meter for adolescent idiopathic scoliosis postural assessment in three anatomical planes.

METHODS

This is an observational reliability and concurrent validity study of adolescent referrals to the Orthopaedic department for scoliosis screening at Karolinska

University Hospital, Stockholm, Sweden between March-May 2012. A total of 31 adolescents with idiopathic scoliosis (13.6 ± 0.6 years old) of mild-moderate curvatures ($25^\circ \pm 12^\circ$) were consecutively recruited. Measurement of cervical, thoracic and lumbar curvatures, pelvic and shoulder tilt, and axial thoracic rotation (ATR) were performed by two trained physiotherapists in one day. The intraclass correlation coefficient (ICC) was used to determine the inter-examiner reliability (ICC_{2,1}) and the intra-rater reliability (ICC_{3,3}) of the Baseline[®] Body Level/Scoliosis meter. Spearman's correlation analyses were used to estimate concurrent validity between the Baseline[®] Body Level/Scoliosis meter and Gold Standard Cobb angles from radiographs and the Orthopaedic Systems Inc. Scoliometer.

RESULTS

There was excellent reliability between examiners for thoracic kyphosis (ICC_{2,1} = 0.94), ATR (ICC_{2,1} = 0.92) and lumbar lordosis (ICC_{2,1} = 0.79). There was adequate reliability between examiners for cervical lordosis (ICC_{2,1} = 0.51), however poor reliability for pelvic and shoulder tilt. Both devices were reproducible in the measurement of ATR when repeated by one examiner (ICC_{3,3} 0.98-1.00). The device had a good correlation with the Scoliometer ($\rho = 0.78$). When compared with Cobb angle from radiographs, there was a moderate correlation for ATR ($\rho = 0.627$).

CONCLUSION

The Baseline[®] Body Level/Scoliosis meter provides reliable transverse and sagittal cervical, thoracic and lumbar measurements and valid transverse plan measurements of mild-moderate scoliosis deformity.

Key words: Reliability; Validity; Scoliosis; Posture; Assessment

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Core tip: The Baseline[®] Body Level/Scoliosis meter is inexpensive, easily administered and provides reliable transverse and sagittal cervical, thoracic and lumbar measurements as well as valid transverse plan measurements of mild-moderate scoliosis deformity.

Prowse A, Aslaksen B, Kierkegaard M, Furness J, Gerdhem P, Abbott A. Reliability and concurrent validity of postural asymmetry measurement in adolescent idiopathic scoliosis. *World J Orthop* 2017; 8(1): 68-76 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/68.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.68>

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a three-dimensional (3D) structural deformation of the spine in otherwise normal adolescents during puberty^[1]. AIS

is characterized as: (1) a lateral spinal curvature in the frontal plane (Cobb angle $> 10^\circ$); (2) a disturbance of spinal curvatures in the sagittal plane; and (3) an axial rotation of vertebrae in the transverse plane. In the majority of cases, spinal asymmetry is noted during primary health care screening^[2], and the patients are referred to specialist orthopaedic clinics for assessment, longitudinal observation and treatment^[3].

Methods for the clinical evaluation of trunk deformity that are reliable, valid, feasible and acceptable is of great importance for patients and clinicians to evaluate and monitor aspects of AIS^[4]. Methods that are easy to administer and inexpensive could provide essential information replacing the need for repeated radiation from radiographs and also expensive surface topography equipment. An easy to administer and inexpensive test for scoliosis is measuring the axial thoracic rotation (ATR) using a Scoliometer^[5]. The inter-observer and intra-observer reliability of Scoliometer assessments have in several studies ranged from very good to excellent, and the tool is reportedly useful as a screening device^[6]. Further, the validity of the Scoliometer when correlated to the Gold Standard Cobb angle from radiographs has been found to be fair to very good^[6,7]. A limitation with the Scoliometer ATR measurement and Cobb angle from radiographs is however that it only measures deformity in a single anatomical plane when scoliosis is a 3D deformity.

To obtain a better description of scoliosis related morphologic deformity in several anatomical planes and reduce the need of radiographic exposure, techniques such as 3D postural analysis systems have been developed^[8]. However, these measurement systems are not accessible for most clinicians and require specialized training and complex data processing. Thus, a simpler, inexpensive 3D tool is needed to measure scoliosis morphology in a clinical setting. A thorough literature search^[9] revealed no published research investigating the reliability and/or validity of simpler, inexpensive 3D tools. The Baseline[®] Body Level/Scoliosis meter is an inexpensive and easy to administer clinical tool that can be used to obtain quick measurements of scoliosis morphology in three anatomical planes.

The primary objective of this study was to investigate the inter-examiner reliability for the Baseline[®] Body Level/Scoliosis meter for the following parameters: Cervical, thoracic and lumbar curve in the sagittal plane; pelvic and shoulder tilt in the frontal plane as well as the inter-examiner and intra-examiner reliability for ATR in the transverse plane. A secondary objective was to investigate the concurrent validity of the Baseline[®] Body Level/Scoliosis meter compared to Orthopaedic Systems Inc. Scoliometer and Cobb angle from radiographs and discuss its clinical utility.

MATERIALS AND METHODS

Research design

This is an observational reliability and concurrent validity

Table 1 Patient demographic and descriptive data

	Mean (\pm SD)	n (%)
Age (yr)	13.6 (0.6)	
Sex		
Males		4 (13)
Females		27 (87)
Primary curve Cobbs angle (degrees)	25 (12)	
Scoliosis type (Lenke classification)		
Main thoracic (1AN)		22 (71)
Thoracolumbar/lumbar (5CN)		9 (29)

study. All study participants, or their legal guardian, provided informed written consent prior to study enrolment. The study received ethical approval from the Swedish Research Council Regional Ethics Committee in Stockholm, Sweden (Dnr: 2012/172-31/4) and from Bond University Health Research Ethics Committee in 2014 (RO 1896). The study followed Guidelines for Reporting Reliability and Agreement Studies, which contains issues to be addressed when reliability and agreement studies are reported^[10].

Participants

Recruitment was achieved through consecutive adolescent referrals to the Orthopaedic department for scoliosis screening at Karolinska University Hospital, Stockholm, Sweden between March-May 2012. Informed consent was obtained from individuals that fulfilled the inclusion criteria to participate in the study. Inclusion criteria included: (1) diagnosis of idiopathic scoliosis; and (2) males and females aged 9-17 years. Exclusion criteria included: (1) scoliosis with a possible non-idiopathic aetiology (patients were excluded from the study if the pathogenesis of the scoliosis was due to a neuromuscular, neurological, congenital malformation or trauma related comorbidity); or (2) inability to understand Swedish. Thirty-one patients participated in the study, 27 females and 4 males with a mean age of 13.6 years and mean Cobb angle of 25°. The number of participants was deemed adequate to establish a practically useful clinically important change^[11]. Patient characteristics and demographics are presented in Table 1.

Procedures and instrumentation

Two physiotherapists (10 and 15 years' experience) performed examination of all participants with AIS, using two devices. To standardize their method of assessment the examiners trained in the use of the devices for 5 h before the outset of the study and had clinical experience in the application of the devices. The Baseline® Body Level/Scoliosis meter (Figure 1), developed by Orthopaedics Systems Incorporation®, is a fluid filled inclinometer in which an enclosed ball shows the ATR on a scale of 1 degree increments that range from 0-30 degrees. To improve the conformity of measurements, the recorded value is the one corre-

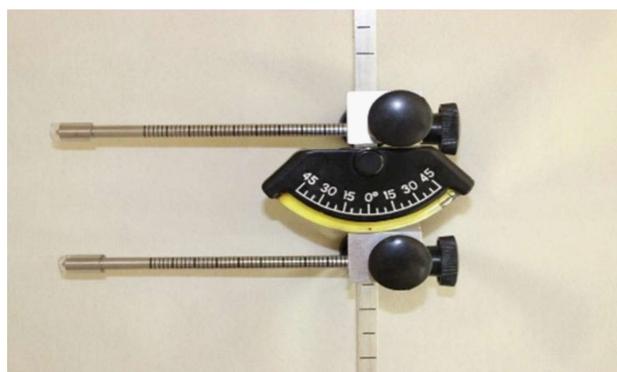


Figure 1 Baseline® Body Level/Scoliosis meter.

sponding to the highest value entirely crossed by the enclosed ball. Measurements of cervical, thoracic, lumbar curvatures and pelvic and shoulder tilt, as well as ATR were performed with the Baseline® Body Level/Scoliosis meter. Measurements of ATR were also performed using the original Orthopaedics Systems Incorporation "Scoliometer". In order to reduce the error associated with the measurement, both examiners used the same devices.

During the measurement, all subjects were barefoot and their back was exposed, which allowed palpation of the entire back. Trousers were lowered to the hip if there was difficulty in palpating the apex of the sacrum or L5. Measurements conducted by both raters were performed within 30 min and were executed in the same order. Examiners had no access to the results of the other measures to avoid recall of the previous values. A protocol that allowed as few manual changes as possible of the Baseline® Body Level/Scoliosis meter was chosen to obtain an efficient examination. The ATR measurements were repeated 3 times, as these measurements were associated with more sources of error. Other measurements were only executed once. Between each evaluation, the subject was instructed to leave the evaluation position to rest. The order of the therapist first taking measurements was randomized. Specific procedures regarding test positions, and device placement were performed according to the following protocol.

Measures using the Baseline® Body Level/Scoliosis meter

Cervical curve in centimetres: The subject was placed in standing position with feet together and asked to "stand straight". The spinous process of C4 was palpated by palpating the process of C2, and then C3 to C4. Then the spinous process of C7 was palpated, the most prominent process in the cervical area, and was distinguished from C6 by bending the head backwards, causing C6 to move anteriorly. After localizing C4 and C7 the rods of the Scoliometer was placed over these spinous processes. The lower rod was unlocked until the gauge indicated 0. Then the rod was locked and the

measurements were recorded in centimetres.

Thoracic curve in centimetres: The patient was placed in a standing position with feet together and asked to "stand straight". The spinous process of C7 was palpated to place the upper rod. The bottom rod was placed at the spinous process of the vertebrae at the apex of the thoracic kyphosis. If there was a deviation of curvature in the frontal plane, the position of the gauge had to be held vertically and therefore the rod could be placed lateral to the spinous process. The lower rod was unlocked until the gauge indicated 0. Then the rod was locked and the measurements were recorded in centimetres.

Anteroposterior angulation L5 and Sacrum in centimetres: The patient was placed in standing position with feet together and asked to "stand straight". The spinous process of L5 was palpated by placing the index fingers over the crest of the ilium and then palpating the spinous process at the same level, that usually is L4, and then the lower process should be L5. The next rod was placed over the most prominent tubercle of the sacral curvature. The lower rod was unlocked until the gauge indicated 0. Then the rod was locked and the measurements were recorded in centimetres.

ATR in degrees: The patient was placed in standing position with feet together and asked to "stand straight", the trunk was anteriorly flexed and almost parallel to the ground, with relaxed arms, hanging perpendicular to the trunk and hands folded. The distance between the rods was set individually for each patient, and placed in the middle of both right and left thorax sides in relation to the spinal column posteriorly level with the apex of the curvature. Both of the rods were locked in the same length and placed over the most prominent point of the curvature. In this position the gauge reading showed the degree of the curvature. Two point five degrees or more was listed.

Pelvic tilt in degrees: The patient was placed in standing position with feet together and asked to "stand straight". Both rods were loosened and placed firmly over each iliac crest and locked with the gauge in the middle. In this position the gauge reading showed the degree of the tilt with 2.5 degrees or more listed.

Shoulder tilt in degrees: The patient was sitting at a 43.5 cm high chair and asked to "sit straight". The sitting position was chosen to avoid the influence of leg length difference. Both rods were loosened and placed firmly over each acromioclavicular articulation and locked with the gauge in the middle. To palpate the acromioclavicular joint (AC joint), find the "soft spot" at the back of the clavicle, anterior to that is the AC joint. In this position the gauge reading showed the degree of

the tilt, anything equal to or greater than 2.5 degrees was listed.

Measures using the Orthopaedics Systems Incorporation Scoliometer

ATR in degrees: The patient was placed in standing position with feet together and asked to "stand straight", with trunk anteriorly flexed and parallel to the ground, with relaxed arms, hanging perpendicular to the trunk and hands folded. The value indicated by the metal sphere after placing the Scoliometer over the spinous process is used to indicate the value of axial trunk rotation. Examiners drew the Scoliometer along the spinous processes to discover the level with the highest reading and measured the axial trunk rotation with 1 degree or more listed.

Measures of radiology Cobb angle in degrees

Standing scoliosis posteroanterior radiographs were performed and measured by a radiologist, and double-checked by the physiotherapist. For the lateral image the feet are together and parallel to the screen. The right side of the body faces the radiation source. The patient was to hold his/her hands on a bar in front of the body and above the shoulders, so that the shoulders and elbows were at 90 degrees flexion. In this position the arms did not obscure the vertebral column. The hands were placed adjacent to one another. If the patient was wearing a brace, it was not to be worn the night prior to the scoliosis radiographs being taken. The Cobb angle was formed by the inclination of the upper end plate of the upper end vertebra and the inclination of the lower end plate of the lower end vertebra measured on posteroanterior view X-ray radiographs^[12].

Statistical analysis

Two independent researchers completed statistical analysis of the data utilizing SPSS software Version 22. The statistics were additionally reviewed by three of the authors who have specific biostatistical competency for reliability and validity studies. Descriptive statistics including means, standard deviations and ranges (minimum and maximum) were calculated for both raters and tabulated as a summary of measurements and patient demographic data. The intraclass correlation coefficient (ICC) is nowadays the preferred retest correlation coefficient and was the method used to determine reliability^[11]. A two-way random analysis of variance and ICC2,1 was used to determine inter-observer reliability in small groups with two test occasions. The intra-observer reliability was determined for ATR with a two way mixed analysis of variance and ICC3,3 using the average of three measurements. The ICC was interpreted with values of < 0.39 as poor, 0.40-0.74 as adequate, and > 0.75 as excellent, as these are considered the minimum standards for reliability coefficients sufficient for research purposes^[13]. A 95%CI for the mean difference between the two

Table 2 Summary of trunk measurements in 3 anatomical planes

	Examiner A						Examiner B					
	Mean	n	SD	Range	Min	Max	Mean	n	SD	Range	Min	Max
Cervical lordosis (cm)	2.5	31	0.8	3	1	4	3.0	31	0.8	4	2	6
Thoracic kyphosis (cm)	3.7	31	1.7	7	1.2	8.2	3.7	31	1.7	7.4	0.6	8
Lumbar lordosis (cm)	3.0	31	1.0	4.2	0.6	4.8	3.5	31	1.0	3.8	1.4	5.2
Pelvic tilt (degrees)	1.8	29	1.9	7.5	0	7.5	3.3	29	2.5	10	0	10
Shoulder tilt (degrees)	1.2	30	1.4	5	0	5	1.3	30	1.7	7.5	-2.5	5
ATR Scoliometer (degrees)	10.2	31	6.1	27.5	0	27.5	10.5	31	6.1	27.5	0	27.5
ATR Baseline Level/Scoliosis meter (degrees)	10.9	31	5.8	24.5	3	27.5	10.3	31	5.6	23.8	0	23.8

ATR: Axial thoracic rotation.

Table 3 Inter-examiner reliability of the Baseline® Body Level/Scoliosis meter measurements

Measures	ICC2,1	95%CI for ICC	Mean difference	95%CI for mean difference	SEM	SRD	95% SRD
Cervical Lordosis (cm)	0.51	0.02-0.76	-0.53	-0.84-0.21	0.82	2.28	-2.81-1.76
Thoracic Kyphosis (cm)	0.94	0.87-0.97	0.013	-0.29-0.31	1.66	4.60	-4.47-4.47
Lumbar Lordosis (cm)	0.79	0.47-0.91	-0.44	-0.71-0.17	0.99	2.74	-3.18-2.3
ATR Scoliometer (degrees)	0.94	0.88-0.97	-0.35	-1.39-0.70	6.07	16.81	-17.16-16.47
ATR Baseline Level/Scoliosis meter (degrees)	0.92	0.84-0.96	0.60	-0.51-1.72	5.67	15.72	-15.12-16.33
Shoulder tilt (degrees)	-0.30	-1.86-0.39	-0.17	-1.05-0.71	1.56	4.33	-4.49-4.49
Pelvic tilt (degrees)	-0.41	-0.89-0.47	-1.47	-0.267-0.26	2.32	6.42	-7.89-4.96

ICC: Intraclass correlation coefficient; ATR: Axial thoracic rotation; SEM: Standard error of measurement; SRD: Smallest real difference.

test occasions was formed with the formula $95\%CI = \text{mean diff} - 2.05 \times \text{standard deviation (SD)}$ to determine if a true systematic difference existed between the two raters^[11]. The mean difference between raters was calculated to evaluate changes in the mean between two test occasions^[11]. To interpret absolute reliability the standard error of measurement (SEM) was calculated using the formula $SEM = \sqrt{WMS}^{[11,14]}$, where WMS is the mean square error term from the analysis of variance^[11]. The smallest real difference (SRD and 95% SRD) was also calculated to determine the magnitude of change that would exceed the threshold of measurement error at the 95% confidence level^[11]. The formula used was $SRD = 1.96 \times SEM \times \sqrt{2}$. To calculate the 95% levels of agreement the formula $\text{mean difference} - 2.05 \times SD$ was applied, where $n = 2.05$ is a good approximation when the number of subjects is > 30 ^[11]. The Spearman’s correlation coefficient was used to analyse the concurrent validity between measurements from the Scoliometer devices and Cobb angles from radiographs, as Spearman’s are not dependent on normality of test data. Correlation values smaller than 0.25 were considered poor, between 0.25 and 0.49 were low, between 0.50 and 0.69 were moderate, between 0.70 and 0.89 were good, and between 0.90 and 1.0 were excellent^[15].

RESULTS

Descriptive results

Table 2 reports a descriptive summary of measurements

taken by each of the raters.

Inter-examiner reliability of the Baseline® Body Level/Scoliosis meter and Scoliometer

Table 3 presents the inter-examiner reliability for the Baseline® Body Level/Scoliosis meter. In the measurement of thoracic kyphosis and ATR, there was excellent reliability between examiners with an ICC2,1 of 0.94 (95%CI: 0.87-0.97) and 0.92 (95%CI: 0.84-0.96) respectively. When taking into consideration excursions in the 95%CI, the method was adequate-to-excellent in the measurement of lumbar lordosis, with an ICC2,1 of 0.79 (95%CI: 0.47-0.91). Furthermore varying adequacy could be seen in the inter-observer reliability in the measurement of cervical lordosis (ICC2,1 = 0.51, 95%CI: 0.02-0.76), and poor inter-examiner reliability when used to measure secondary curves in the frontal plane; pelvic tilt (ICC2.1 = -0.41, 95%CI: -0.89-0.47) and shoulder tilt (ICC2,1 = -0.30, 95%CI: -1.86-0.39). When measurements from the Baseline® Body Level/Scoliosis meter were compared to measurements from the Scoliometer, which is the current Gold Standard to measure ATR, the reliability was similar, with an ICC2,1 of 0.92 (0.84-0.96), compared to the Scoliometer with an ICC2,1 of 0.94 (95%CI: 0.88-0.97).

Systematic error exists between raters in the mean measurements of lumbar lordosis and pelvic tilt when using the Baseline® Body Level/Scoliosis meter, as shown by the 95%CI for mean difference, suggesting non-random error exists. A large measurement error between examiners’ measurements exists for pelvic

Table 4 Intra-examiner reliability of the Baseline® Body Level/Scoliosis meter and Orthopaedic Systems Inc. Scoliometer measurements

Measures	Examiner	ICC3,3	95%CI for ICC		Mean difference	95%CI for mean difference	SEM	SRD	95% SRD
ATR Scoliometer (degrees)	A	0.99	0.99-1.00	A1	0	0	1.35	3.74	-3.74-3.74
				A2	-0.24	-3.00-3.05	1.35	3.75	-4.00-3.51
				A3	-0.32	2.52-2.40	1.33	3.70	-3.37-3.37
	B	0.98	0.97-1.00	B1	0	0	1.39	3.90	-3.87-3.87
				B2	-0.23	-3.08-2.66	1.4	3.87	-3.65-3.65
				B3	0.34	2.63-3.34	1.47	4.07	-3.73-4.41
ATR baseline level scoliosis meter (degrees)	A	1.00	1.00-1.00	A1	0	0	1.37	3.79	-3.38-0.38
				A2	-0.32	-3.03-3.07	1.47	4.07	-4.04-4.04
				A3	-0.05	2.97	1.48	4.09	-4.14-4.14
	B	0.98	0.96-0.99	B1	0	0	1.23	3.40	-3.40-3.40
				B2	0.52	-2.24-2.54	1.35	3.75	-2.88-3.91
				B3	0.53	3.28-3.60	1.50	4.17	-3.63-4.70

ICC: Intraclass correlation coefficient; ATR: Axial thoracic rotation; SEM: Standard error of measurement; SRD: Smallest real difference.

tilt (SEM = 2.3°) and shoulder tilt (SEM = 1.6°). The small 95% SRD between measurements taken by two separate examiners for thoracic kyphosis (-4.5-4.5) and ATR with Baseline® Body Level/Scoliosis meter (-15.1-16.3), and ATR measured with Scoliometer (-17.2-16.5), suggests these measurements are more sensitive and can be considered highly reliable.

Intra-examiner reliability of the Baseline® Body Level/Scoliosis meter and Scoliometer in measuring ATR

Table 4 presents the intra-examiner reliability for the ATR measures. Excellent intra-examiner reliability was seen in ATR measured by the Baseline® Body Level/Scoliosis meter (Examiner A ICC3,3 = 1.00, Examiner B = 0.98) and by the Scoliometer (Examiner A ICC3,3 = 0.99, Examiner B = 0.98).

Concurrent validity of the Baseline® Body Level/Scoliosis meter compared to Scoliometer and Cobb angle from radiographs

Table 5 presents the concurrent validity for the Baseline® Body Level/Scoliosis meter compared to the Scoliometer as well as Cobb angle as measured by radiographs. The correlation between measurements using the Baseline® Body Level/Scoliosis meter and measurements from the Scoliometer for ATR (degrees) was indicated by a Spearman's rho of 0.78 indicating a good, statistically significant correlation between these measures. When ATR measured with the Scoliometer and Baseline® Body Level/Scoliosis meter were each compared to Cobb angle measured from radiographs, there was a moderately significant correlation of rho = 0.58 and rho = 0.63, respectively. When Cobb angles measured from radiographs were compared with thoracic kyphosis in the sagittal plane, there was a low correlation (rho = 0.32).

DISCUSSION

In line with the study's objectives, the reliability and validity of the Baseline® Body Level/Scoliosis meter for measuring scoliosis morphology in three anatomical

planes were studied. Results showed that the Baseline® Body Level/Scoliosis meter was as accurate as the Scoliometer when used repeatedly by the same examiner or by different examiners for the measurement of ATR in the transverse plane on patients with mild-moderate scoliosis. The Baseline® Body Level/Scoliosis meter had similar reliability in the measurement of ATR when compared to other high quality reliability studies assessing the Scoliometer^[6,16,17] and smartphone applications such as the Scolioscreen with an acrylic sleeve^[18].

Based on our results for assessment of the sagittal plane, the Baseline® Body Level/Scoliosis meter can be recommended based on excellent reliability for use by trained examiners for measuring thoracic kyphosis and lumbar lordosis on patients with mild-moderate scoliosis. Furthermore, in the measurement of cervical lordosis on patients with mild-moderate scoliosis, the instrument showed adequate reliability but larger variability in measurements between examiners. Previous research suggests that increased cervical kyphosis is often a secondary coupling effect of increased thoracic kyphosis and coronal plan deformation and that despite this, global spine-pelvis alignment remains well-balanced^[19]. This suggests that for the purpose of screening mild-moderate scoliosis, measurement of thoracic and lumbar sagittal curvature may be suffice, leaving cervical curvature measures redundant in many cases. However the utility of cervical curvature measurement suggests that in may be relevant for some mild-moderate cases and may be of more importance when screening moderate-severe scoliosis.

When compared to the reliability of 3D computerized systems, the Baseline® Body Level/Scoliosis meter had similar reliability for thoracic measures but was less reliable for measuring lordotic sagittal curvatures^[20]. Potential challenges in the accuracy of palpation of anatomical landmarks have been noted in reliability studies to cause observer variations especially in the sagittal and frontal planes^[7,21,22].

A low inter-examiner reliability was found between trained examiners when measuring frontal plane

Table 5 Spearman's bivariate correlations ($n = 31$) of Baseline® Body Level/Scoliosis meter compared to gold standard Cobb angles from radiographs, and compared to Orthopaedic Systems Inc. Scoliometer

Baseline Level/Scoliosis meter	Cobb angle (degrees)
Cervical lordosis (cm)	-0.22
Thoracic kyphosis (cm)	-0.32
Lumbar lordosis (cm)	-0.03
ATR (degrees)	0.63
Pelvic tilt (degrees)	0.13
Shoulder tilt (degrees)	-0.00
ATR Scoliometer (degrees)	0.58
Baseline Level/Scoliosis meter	0.77
ATR (degrees)	

ATR: Axial thoracic rotation.

morphology in patients with mild-moderate scoliosis. The Baseline® Body Level/Scoliosis meter had similar reliability for shoulder and pelvic tilt measurements when compared to previous literature on aesthetic clinical tools, such as the Trunk Aesthetic Clinical Evaluation tool^[21]. A potential source of the low reliability could be a low sensitivity for smaller measures in these frontal plane secondary measures of spinal curvature. For example, examiners in our study reported that when using the Baseline® Body Level/Scoliosis meter the fluid filled ball required 2.5 degrees of deformity in order for the ball to move. Therefore, the device was not sensitive for assessment of smaller secondary measures in the frontal plane for pelvic and shoulder tilt, and a digital recorder may be more precise. Based on our results, one can hypothesize that the Baseline® Body Level/Scoliosis meter may be reliable for larger secondary measures in the frontal plane for pelvic and shoulder tilt that are more common in moderate to severe cases of AIS. Future research should therefore assess the reliability and validity of the Baseline® Body Level/Scoliosis meter for patients with moderate to severe cases of AIS, with curvatures > 30-40 degrees to confirm this hypothesis.

In accordance with the secondary objectives of the study, measurements of ATR with the Baseline® Body Level/Scoliosis showed good correlation with measurements from the Scoliometer as well as the Gold Standard Cobb angles from radiographs. When examined in light of previous literature, the device had a similar correlation with Gold Standard Cobb angle from radiographs as the Scoliometer did^[6,20], and better validity than 2D photography^[23] and trunk surface examination^[24] but lower validity than 3D computerized systems^[20]. Therefore, the Baseline® Body Level/Scoliosis meter could be used for screening, and to monitor curve progression through measurement of ATR. However, ATR measures alone cannot replace Cobb angle measured from radiographs in the diagnosis of the condition, as it has been discussed in statistical literature that greater accuracy is required, with Spearman's correlation of > 0.9, for a measure to be considered accurate for diagnosis^[15]. Furthermore, it is important to note that when screened, not all

adolescents have an ATR of the spine, despite changes in the sagittal and frontal planes. When the apex of the Cobb angle is higher up the thoracic region, less rotation is seen in the spine due to coupled movement^[25].

Additional frontal and sagittal plane measurements provided by the Baseline® Body Level/Scoliosis meter may add important information regarding clinical signs of progression to inform treatment and diagnostic decisions. Cervical and thoracic sagittal curves and frontal plane measures in our study had however low correlation with Cobb angle, perhaps because a Cobb angle of 25° may not have been severe enough and considering we had a larger group of patients with thoracic curves who often have less disturbed lordosis in the cervical and lumbar spine^[25].

This study has its strengths and weaknesses one must consider when interpreting results. A methodological strength of the study was that two physiotherapists performed measurements in 3 anatomical planes for all subjects using the same Baseline® Body Level/Scoliosis meter with no knowledge of results between examiners. The therapists received 5 h training, and were considered proficient with application of the tool. Although there is no recommendation in the literature regarding the training time necessary, previous studies have trained up to 10 h of which the authors suggested contributed to the good to excellent reliability within the study^[26]. The study method aimed to control potential variance in measures caused by fatigue from repeated measures by providing rest periods between measurements. Similarly the study method aimed to control variance due to patient flexibility, body mass index (BMI) or previous activity by re-testing within the same session. The methods lacked however intra-rater reliability measures for sagittal and frontal plan measures which could have provided more thorough information on reliability of the Baseline® Body Level/Scoliosis meter. With regards to sample representativeness it can be considered a strength that our patient sample is consecutively recruited, has a female to male 6.8:1 ratio and main thoracic (1AN) to thoracolumbar/lumbar (5CN) 2:1 curve type ratio representative of the current prevalence of AIS in the population for a mean curvature of 20°-30°^[27]. A possible limitation however is our sample size was not powered for gender or curve type subgroup analysis^[27]. The size of our recruited sample was however adequate to establish group level clinically important change values and the sample was well above the minimum suggested sample size of 15-20 patients for reliability studies with continuous data^[11].

Despite the discussed strengths and weaknesses of the study, the benefits of the Baseline® Body Level/Scoliosis meter outweigh the use of the Scoliometer and Cobb angle for initial screening of mild-moderate scoliosis. This mainly due to it providing reliable, valid, feasible and acceptable measures in several anatomical planes aiding decision making regarding the need for radiographic exposure and potential interventions to prevent AIS progression and dysfunction.

Within the study the authors were able to investigate the manual anthropometric measurement of 3D curvatures in AIS with a device that is inexpensive, easily administered and applicable in a clinical setting. The Baseline[®] Body Level/Scoliosis meter has the ability to provide reliable and valid measurements of mild-moderate scoliosis deformity in transverse and sagittal planes for the cervical, thoracic and lumbar spine, useful for screening scoliosis morphology.

COMMENTS

Background

Adolescent idiopathic scoliosis (AIS) is a structural deformation of the spine in the frontal, sagittal and transverse plans. Methods for the clinical evaluation of trunk deformity in all 3 planes that are reliable, valid, feasible and acceptable are of great importance for the prospective measurement of severity and assessing the need of interventions to prevent deformity progression and dysfunction. Currently repeated radiological exposure or non-radiological methods requiring expensive equipment, specialized training and complex data processing are available.

Research frontiers

Current no published research has investigated the reliability and/or validity and discussed the feasibility and acceptability of simple, inexpensive clinical tools that assess trunk deformity in all 3 anatomical planes.

Innovations and breakthroughs

The Baseline[®] Body Level/Scoliosis meter is an inexpensive and easy to administer clinical tool that can be used to obtain quick measurements of scoliosis morphology in three anatomical planes. It provides reliable transverse and sagittal cervical, thoracic and lumbar measurements as well as valid transverse plane measurements of mild-moderate scoliosis deformity. Poor reliability in frontal plane measures is likely due to the Baseline[®] Body Level/Scoliosis meter not being sensitive in the first 0-2.5 degrees of pelvic and shoulder tilt which was common in mild-moderate AIS.

Applications

The Baseline[®] Body Level/Scoliosis meter is recommended for transverse and sagittal cervical, thoracic and lumbar measurements of mild-moderate scoliosis. It should be combined with a thorough history and physical assessment to aid decision making regarding the need for radiographs and interventions to prevent AIS progression and dysfunction. It is potentially reliable in measuring larger frontal plane deformity of pelvic and shoulder tilt which is more common in moderate-severe scoliosis but research is needed to confirm this.

Terminology

AIS is a three-dimensional structural deformation of the spine in otherwise normal adolescents during puberty. Axial thoracic rotation and Cobbs angle are common single pain measures of scoliosis morphology. Reliability refers to the reproducibility of measurements. Validity describes the extent to which a measure accurately represents the concept it claims to measure.

Peer-review

This is a well performed study with sound statistics and clear reliability tests. This is a non-invasive method for the evaluation of frontal and sagittal curvatures in mild AIS individuals.

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Novel case of Trevor's disease: Adult onset and later recurrence

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Abstract

Dysplasia epiphysealis hemimelica (DEH), or Trevor's disease, is an osteocartilaginous epiphyseal overgrowth typically occurring in children. The literature reports 6 adult cases and none describe recurrence requiring additional procedures. We present a new-onset proximal tibial DEH in an adult recurring approximately 3 years after open excision. A 39-year-old female presented with a history of right knee pain, swelling, and instability. Physical examination revealed a firm proximal tibial mass. Computed tomography (CT) imaging showed an exophytic, lobulated, sclerotic mass involving the anterolateral margin of the lateral tibial plateau. Magnetic resonance imaging was suggestive of an osteochondroma. The patient underwent curettage of the lesion due to its periarticular location. Histology revealed benign and reactive bone and cartilage consistent with periosteal chondroma. Two and a half years later, the patient presented with a firm, palpable mass larger than the initial lesion. CT revealed a lateral tibial plateau sclerotic mass consistent with recurrent intra-articular DEH. A complete excision was performed and histology showed sclerotic bone with overlying cartilage consistent with exostosis. DEH is a rare epiphyseal osteocartilaginous outgrowth frequently occurring in the long bones of children less than 8 years old. DEH resembles an osteochondroma due to its pediatric presentation and similar histologic appearance. Adult-onset cases comprise less than 1% of reported cases. Recurrence rate after surgical intervention is unknown. Only 1 such case, occurring in a child, has been described. Clinicians contemplating operative treatment for DEH should note the potential for recurrence and consider complete excision. A follow-up period of several years may be warranted to identify recurrent lesions.

Key words: Trevor's disease; Dysplasia epiphysealis hemimelica; Adult recurrence; Proximal tibia; Exostosis

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Core tip: Dysplasia epiphysealis hemimelica (DEH), or Trevor's disease, is an osteocartilaginous epiphyseal overgrowth typically occurring in children. The literature reports 6 adult cases and none describe recurrence requiring additional procedures. We present a new-onset proximal tibial DEH in an adult recurring approximately 3 years after open curettage.

Khalsa AS, Kumar NS, Chin MA, Lackman RD. Novel case of Trevor's disease: Adult onset and later recurrence. *World J Orthop* 2017; 8(1): 77-81 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/77.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.77>

INTRODUCTION

Dysplasia Epiphysealis Hemimelica (DEH), otherwise known as Trevor's Disease, is an exceedingly rare disorder of childhood^[1,2]. Characterized by excessive cartilaginous growth from the epiphyseal region, DEH is grossly and histologically similar to osteochondromas found in the metadiaphyseal region^[1]. Patients generally present with localized joint pain, tenderness, and dysfunction, most commonly affecting the foot and ankle but also reported in the knee, hip, and scapula. DEH has an incidence of approximately one in 1000000 with males affected up to three times more frequently than females^[3]. Three types of clinical presentation have been described: Localized to one epiphysis; affecting more than one epiphysis in the same limb; and diffuse disease affecting the entire lower limb^[2].

Though exceedingly rare, DEH usually presents in children before 8 years of age. Only six cases of DEH have ever been reported in individuals over 18 years of age; one in the proximal femur, one in the distal radius, one in the carpus, one in the distal tibia, one in the talus, and one in the proximal tibia^[4-8]. Recurrence in an adult has never been reported nor has recurrence in any population requiring an additional open procedure. This often intra-articular lesion can lead to early degenerative changes if left undiagnosed or untreated and can cause functional debilitation^[9].

We describe the novel case of a 39-year-old female with DEH of the proximal tibia in whom recurrence occurred three years after an initial open curettage and resection. The patient was eventually treated definitively with surgical excision.

CASE REPORT

A 39-year-old female initially presented to our outpatient

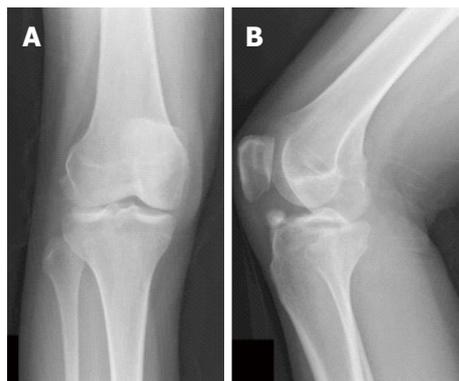


Figure 1 Initial radiographs of the right knee in the anteroposterior (A) and lateral (B) views.

office with a several month history of right knee pain, swelling, and instability, particularly with walking down stairs. Non-steroidal anti-inflammatory medications only mildly relieved her discomfort. She denied night pain, constitutional symptoms, or a recent history of trauma or injury. Medical history was significant for a history of congenital hip dysplasia and family history was negative for any inflammatory diseases, bone disorders, or dysplasia.

On physical exam, a mild antalgic gait was noted. A right knee effusion was present as well as lateral joint line tenderness. A firm, palpable mass protruding from the anterolateral proximal tibia was easily appreciated. No erythema or skin ulceration was presented at the site of the mass. Her remaining physical exam was otherwise grossly normal.

Radiographs (Figure 1) of the right knee revealed an unusual calcific density measuring 2.0 cm × 1.0 cm above the anterolateral tibial plateau. Computed tomography (CT) (Figure 2) of the right knee revealed an exophytic, lobulated, sclerotic mass measuring 2.4 cm × 0.9 cm × 0.8 cm involving the anterolateral margin of the anterior lip of the lateral tibial plateau. An MRI showed a 1.2 cm well-margined lesion abutting the anterolateral cortical surface of the lateral tibial plateau following bone marrow on all sequences, most likely due to an osteochondroma or loose body. Whole body bone scan also revealed mild to moderate uptake at the site of the lesion.

The patient underwent an open curettage and debulking of the right lateral proximal tibial lesion given its periarticular location, which prevented it from being amenable to marginal excision. Pathology revealed fragments of benign and reactive bone and cartilage consistent with a diagnosis of periosteal chondroma. The patient's symptoms fully resolved post-operatively with no signs of recurrence at 1-year and 2-year follow-up.

Two and a half years later, the patient presented with a two and a half month history of recurrent pain and swelling of her right knee. Furthermore, under her well-healed scar was a firm, palpable mass that was larger

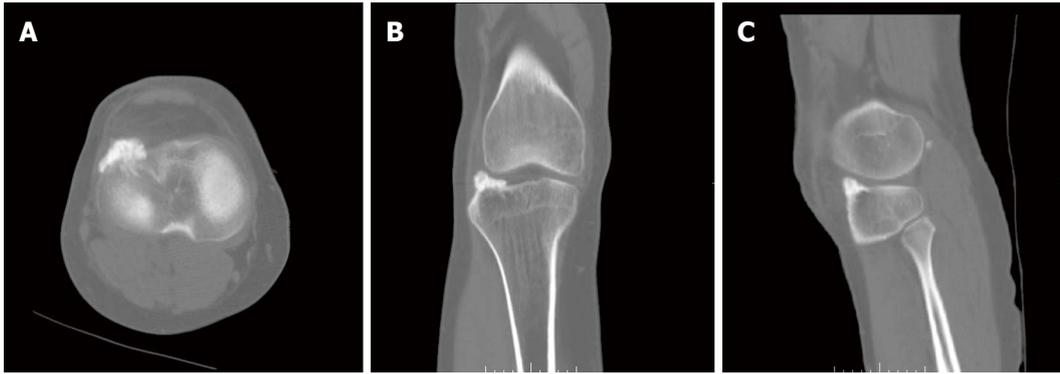


Figure 2 Initial computed tomography images of the right knee in the axial (A), coronal (B), and sagittal (C) planes.



Figure 3 Computed tomography images of the right knee after lesion recurrence in the axial (A), coronal (B), and sagittal (C) planes.

than her original mass. CT (Figure 3) scan revealed a recurrent, sclerotic mass measuring 0.8 cm × 2.3 cm × 1.6 cm arising from the lateral tibial plateau consistent with recurrent intra-articular dysplasia epiphysealis hemimelica. A complete excision was performed and pathology showed sclerotic bone with overlying cartilage consistent with exostosis. At her one-year and two-year follow-up, the patient remains symptom-free with no appreciable mass recurrence.

DISCUSSION

Dysplasia Epiphysealis Hemimelica is a rare, oftentimes aggressive outgrowth of bone and cartilage occurring most frequently in the epiphyseal region of long bones. Mouchet first described the lesion in 1926, referring to the entity as *tarsomegalie* to describe the pathology as a lesion about the ankle^[10]. In 1950, Trevor described 8 cases involving epiphyseal lesions about the knee and ankle, terming them tarso-epiphysal aclasis^[11]. He postulated that a congenital error in lower limb bud formation ultimately resulted in cartilaginous hyperplasia. Fairbank eventually coined the term dysplasia epiphysialis hemimelica in 1956 after publishing a case series on 14 children with the lesion^[12]. DEH can resemble an osteochondroma due to its predilection towards children and developing bones and similar histologic appearance. However, osteochondromas are generally found in the meta-diaphyseal region, unlike DEH, which is typically an epiphyseal lesion^[13].

Most lesions are discovered before 8 years of age^[14]. The most common location for DEH is the talus, where it was originally described, followed by the distal femur and the distal tibia^[14,15]. To our knowledge, only six reported adult-onset cases have been previously described in the literature, comprising less than 1% of known cases. As of a recent systematic review by Gökkuş *et al*^[7], six adult cases have been described in the proximal femur, distal radius, carpus, distal tibia, proximal tibia, and talus^[4-8,11]. The re-appearance of an adult lesion in the proximal tibia is a novel finding.

The recurrence rate of this osteocartilaginous overgrowth is unknown after surgical intervention. It is agreed upon that the gold standard for treatment of extra-articular lesions is surgical excision in the setting of pain or decreased range of motion, yielding more favorable outcomes^[13,16]. The treatment for intra-articular lesions is less clear and determined on a case-by-case basis, with excision only indicated in the presence of symptomatic loose bodies, because of the detrimental effects of excision to the articular cartilage. Currently, only 1 recurrent case has been described in the literature; this patient was a child and had 3 operations all before the age of 5 years. In this case, a new-onset proximal tibial DEH in an adult patient recurred approximately 3 years after initial open excision. There were no known factors affecting recurrence in this one case. However, the presence of pain two a half months prior to the patient's subsequent presentation may be explained by inadequate initial management, despite

debulking and curettage that was deemed sufficient at the first attempt. We recommend that clinicians considering operative treatment for these lesions should note the potential for recurrence and should contemplate a more aggressive excision as a preventative measure. We also recommend that a post-operative follow-up period of several years may be warranted to identify lesions in the initial stages of recurrence.

In conclusion, DEH, although rare, does often require surgical resection once diagnosed based on symptoms and relevant imaging. Although more commonly occurring in children, it should remain in the differential diagnosis for adults with bony lesions in the epiphyseal region. Surgical resection is a viable option in the setting of pain and decreasing range of motion and must be balanced with the sequelae of destroying articular cartilage, however adequate follow-up is advised for potential recurrent lesions.

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COMMENTS

Case characteristics

A 39-year-old female presented with a history of right knee pain, swelling, and instability.

Clinical diagnosis

A right knee effusion was present as well as lateral joint line tenderness, and a firm, palpable mass protruding from the anterolateral proximal tibia was easily appreciated.

Differential diagnosis

Dysplasia epiphysealis hemimelica, osteochondroma, periosteal chondroma, osteofibrous dysplasia, adamantinoma, osteosarcoma, synovial chondromatosis.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

CT scan revealed a recurrent, sclerotic mass measuring 0.8 cm × 2.3 cm × 1.6 cm arising from the lateral tibial plateau.

Pathological diagnosis

Intra-articular dysplasia epiphysealis hemimelica.

Treatment

Complete surgical excision of lesion.

Related reports

Dysplasia epiphysealis hemimelica (DEH) is a rare, oftentimes aggressive outgrowth of bone and cartilage occurring most frequently in the epiphyseal region of long bones. DEH can resemble an osteochondroma due to its predilection towards children and developing bones and similar histologic appearance.

Term explanation

DEH is a rare, frequently aggressive outgrowth of bone and cartilage occurring most frequently in the epiphyseal region of long bones. The most common location for DEH is the talus, where it was originally described, followed by the distal femur and the distal tibia.

Experiences and lessons

This entity is commonly mistaken for a neoplastic process due to its location and behavior. Clinicians considering operative treatment for these lesions should note the potential for recurrence and should contemplate a more aggressive excision as a preventative measure.

Peer-review

This paper is well written.

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Teriparatide anabolic therapy as potential treatment of type II dens non-union fractures

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Abstract

Odontoid fractures account for 5% to 15% of all cervical spine injuries and 1% to 2% of all spine fractures. Type II fractures are the most common fracture pattern in elderly patients. Treatment (rigid and non-rigid immobilization, anterior screw fixation of the odontoid and posterior C1-C2 fusion) remains controversial and represents a unique challenge for the treating surgeon. The aims of treatment in the elderly is to quickly restore pre-injury function while decreasing morbidity and mortality associated with inactivity, immobilization with rigid collar and prolonged hospitalization. Conservative treatment of type II odontoid fractures is associated with relatively high rates of non-union and in a few cases delayed instability. Options for treatment of symptomatic non-unions include surgical fixation or prolonged rigid immobilization. In this report we present the case of a 73-year-old woman with post-traumatic odontoid non-union successfully treated with Teriparatide systemic anabolic therapy. Complete fusion and resolution of the symptoms was achieved 12 wk after the onset of the treatment. Several animal and clinical studies have confirmed the potential role of Teriparatide in enhancing fracture healing. Our case suggests that Teriparatide may have a role in improving fusion rates of C2 fractures in elderly patients.

Key words: Type II odontoid fractures; Non-union; Anabolic therapy; Teriparatide; Fracture healing

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Core tip: Odontoid fractures are common in elderly patients and treatment of these injuries remains challenging. Conservative management consists of rigid immobilization with collar or Halo vest. Delayed union or non-union is a common outcome in patients treated conservatively. For a symptomatic non-union, surgery may be the only option. In this case report we discuss the case of a patient with an odontoid fracture non-union successfully treated with systemic anabolic Teriparatide therapy. A complete fusion was achieved after 12 wk of treatment. Teriparatide therapy may have a role in fostering fusion of C2 fractures in elderly patients.

Pola E, Pambianco V, Colangelo D, Formica VM, Autore G, Nasto LA. Teriparatide anabolic therapy as potential treatment of type II dens non-union fractures. *World J Orthop* 2017; 8(1): 82-86 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i1/82.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i1.82>

INTRODUCTION

Odontoid fractures comprise 5% to 15% of all cervical spine fractures and represent the most common cervical spine injury in elderly patients (> 65-year-old)^[1,2]. Type II fractures (*i.e.*, a fracture through the base of the dens, below the transverse ligament) account for the majority of cases (67%). Odontoid fractures in the elderly are a potentially life threatening injury. Acute respiratory arrest and spinal cord injury have been described following fracture displacement. More commonly, patients present with acute neck pain and occasional occipital neuropathic pain. Reduced mobility, chronic pain, and the presence of multiple medical comorbidities often lead to a progressive decline of the health status and excess mortality in elderly patients. In a retrospective review, mortality risk at 1 year following a cervical fracture in patients > 65 years of age was 28%^[3].

There is a lack of agreement regarding the optimal treatment of odontoid fractures in the elderly. The aim of treatment is to stabilize the fracture to prevent neurological damage and allow early and safe mobilization. Treatment options include conservative management (*i.e.*, hard collar and Halo vest immobilization) or surgical fixation. Surgery provides the advantage of early mobilization and higher fusion rates. However, it is also associated with high complication rates and perioperative morbidity^[4]. Conservative management is a safer option but is associated with higher risk of delayed union or non-union (77%) and increased morbidity due to prolonged immobilization^[5].

Factors determining the poor healing potential of odontoid fractures in the elderly are poorly understood.

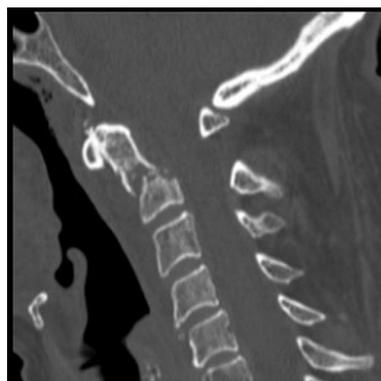


Figure 1 Computed tomography-scan at admission to the hospital showing a transverse fracture line above C2 vertebral body and below transverse ligament of the odontoid process (type II fracture).

Known factors associated with higher risk of nonunion include age > 50, displacement greater than 6 mm, posterior displacement, angulation of the fragments, and smoking^[6,7]. The role of segmental osteoporosis and poor osteoblastic response is less clearly defined but is commonly perceived as a potentially important factor in determining fracture healing potential. Teriparatide (*i.e.*, rhPTH1-34) is the recombinant form of the biologically active component of the human parathyroid hormone. It is a novel anabolic drug therapy for osteoporosis which has also been shown to stimulate osteoblasts and enhance fracture healing *in vivo*. The aim of this study is to report our experience with the use of rhPTH1-34 in the treatment of a non-union type II dens fracture in an elderly patient.

CASE REPORT

A 73-year-old woman was transferred to our emergency department following a road traffic accident. The patient was a restrained passenger of a car, the driver lost the control of the vehicle and the car fell into a ditch at the side of the road. The patient lost consciousness at the time of the impact but was found alert and oriented at the time of the arrival of the ambulance. Patient observations were stable and there were no signs of other bone injuries. Patient had no neurological deficits and cranial nerves were intact. Past medical history of the patient included acute glaucoma and visual impairment.

A routine trauma series CT-scan was performed and showed a type II odontoid fracture with anterior displacement (Figure 1). Patient was referred to our spinal unit and, after appropriate counselling, elected a non-operative treatment. Cervical spine was stabilized with a Philadelphia collar and patient was discharged home 3 d after the injury. The first outpatient clinic appointment was booked at 2 wk after discharge and patient was seen at regular intervals thereafter. Six months following the injury the patient was still complaining of significant axial neck pain requiring regular pain killer. An interval computed tomography

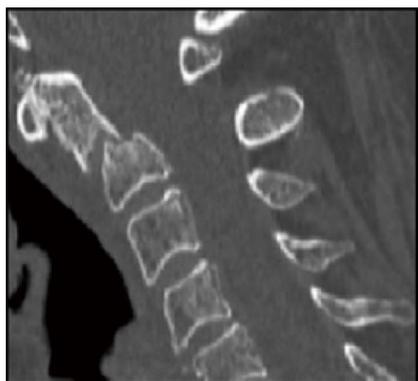


Figure 2 Interval computed tomography-scan 6 mo after the index injury. No healing is demonstrated, sclerotic bone margins are demonstrated at the fracture fragments.



Figure 3 Computed tomography-scan performed at the end of 3 mo of anabolic therapy with Teriparatide confirming a complete fusion of the fracture with acceptable alignment.

(CT) scan at 6 mo after the injury revealed a non-union at the fracture site, distance between fracture fragments was 4 mm and there was evidence of sclerotic bone margins at the level of the fracture (Figure 2). Surgical options were discussed with the patient at this stage, but she again refused any surgical intervention.

Patient was maintained in rigid collar and was offered off-label therapy with daily subcutaneous injections of Teriparatide (rhPTH1-34) 20 µg/d which she accepted. This is the same regime used for treatment of osteoporosis in post-menopausal women. The anabolic treatment with Teriparatide was monitored through periodic examinations and regular measurements of serum levels of calcium, phosphorus, vitamin D, parathyroid hormone and alkaline phosphatase.

Forty-five days after starting Teriparatide treatment, an interval CT scan showed an initial phase of callus formation at the fracture site with partial closure of the fracture gap. Anabolic therapy was continued for 3 mo, at the end of the treatment a final CT scan confirmed a complete consolidation of the fracture (Figure 3). Flexion/extension X-rays of the cervical spine showed no residual instability, and axial neck pain had resolved as well. Mean Visual Analogic Scale score at the end of the treatment was 3 (from a baseline value of 8), whilst SF-12P score was 45.1 and the SF-12M score was 58 (from baseline values of 29.4 for SF-12P and 28.7 for SF-12M). The Neck Disability Index decreased from 70% to 15% at the time of last follow-up. No side effects related to the use of Teriparatide were noted in our patient.

DISCUSSION

The number of elderly patients is growing rapidly in western countries and worldwide. By 2025, one fifth of the world population will be over the age of 65 and the number of osteoporotic and fragility fractures are expected to rise accordingly. Odontoid fractures are common in elderly patients, and treatment remains controversial. Although modern surgical techniques (*i.e.*, C1-C2 transarticular and C1-C2 polyaxial

screw fixation) allow significantly higher fusion rates (83%-100%) than traditional techniques, they remain technically demanding and are associated with a sizable perioperative complication rate^[8-10]. Reported fusion rate for conservative management varies from 23% to 46%^[7,11]. It is safer than surgery in the short term, but associated with prolonged immobilization and reduced mobility. Cranial, pulmonary and cardiac complications have all been reported in patients treated with rigid immobilization. Furthermore, the development of a fibrous non-union is a common finding in patients treated conservatively. Although achievement of a stable fibrous non-union is regarded as an acceptable outcome in elderly patients by some authors, there are cases described of late onset cervical myelopathy in patients with non-union of the odontoid process^[12].

Teriparatide (rhPTH1-34) is a novel Food and Drug Administration (FDA) approved drug for treatment of post-menopausal osteoporosis. Teriparatide is a recombinant form of the N-terminal 1-34 fragment of the human parathyroid hormone (PTH). In humans, PTH regulates blood calcium levels by controlling renal calcium reabsorption and release of calcium from the skeleton. As such, continuous high levels of PTH determine progressive bone demineralization and systemic osteoporosis. Interestingly, the intermittent administration of PTH has opposite effects on bone metabolism and stimulates new bone formation (*i.e.*, anabolic action)^[13]. Teriparatide is the only currently available drug with anabolic effect on bone metabolisms. It is FDA approved for use in patients with severe post-menopausal osteoporosis (*i.e.*, in women with a history of osteoporotic fractures or who are not responsive to other osteoporosis therapies) and can be administered for a maximum of 24 mo.

Several studies have investigated the role of Teriparatide in accelerating fracture healing and non-unions. In 1999 and 2001, Andreassen *et al*^[14,15] reported the effects of systemic intermittent PTH treatment in a rat model of fracture healing. Treated animals showed increased fracture strength and callus volume at 8 wk after treatment. In 2010, similar findings were

published by Moggetti *et al*^[16] in a mouse model of tibial fracture. The authors noted a stimulation of callus formation with Teriparatide dosage of 40 µg/kg per day; 15 d after treatment callus mechanical strength approximated normal bone. The anabolic effect of Teriparatide administration is not limited to the period of treatment as shown by Alkhiary *et al*^[17] in a rat model. The authors showed that 49 d after discontinuing anabolic treatment, treated animals were still showing a continuous increase of bone mineral density and torsional strength^[17]. The anabolic effect of Teriparatide administration has also been confirmed in animal models of delayed bone healing^[18].

The effects of Teriparatide on human fracture healing have been investigated by several authors with contrasting results. In the only Level I study on this topic, Aspenberg *et al*^[19] have studied a cohort of 102 post-menopausal patients with distal radius fractures treated conservatively. Median time to radiographic healing was 9.1 wk in the control group, and 7.4 and 8.8 wk in the groups treated with 20 µg and 40 µg of Teriparatide, respectively. The differences between the groups were not statistically significant^[19]. Opposite results have been reported by Peichl *et al*^[20] in a series of 65 post-menopausal women with pubic bone fracture treated with the 1-84 form of PTH. The median healing time was 7.8 wk for the treatment group vs 12.6 wk for the control group^[20]. The only available data on the effects of anabolic treatment on spinal fractures healing have been reported by Bukata *et al*^[21] in 2010. The authors studied a cohort of 145 patients with spinal or appendicular skeleton fractures. Fracture healing rate was 93% at 12 wk after treatment with Teriparatide.

To the best of our knowledge, no study has systematically investigated the role of Teriparatide in cervical spine fractures. The only available study on this topic is a case report by Rubery *et al*^[22] published in 2010. The authors reported on 3 patients with painful delayed unions of type III odontoid fractures. All 3 patients were started on therapeutic doses of Teriparatide and experienced complete resolution of their symptoms and complete union^[22]. In this study, we report the case of a painful delayed union of a type II odontoid fracture. Our patient presented with persistent pain and failed conservative treatment of the fracture. Teriparatide treatment was started 6 mo after the index injury and a complete fusion with resolution of the symptoms was observed 12 wk after the onset of the therapy.

The nature of our study does not allow a generalization of our results. It is impossible to know whether our patient would have developed a non-painful fibrous non-union at a later follow-up. Also, complete bone union can be observed as long as 9-12 mo after the index injury. Nevertheless, we think our case report raises an important point in the management of this very common injury in elderly patients. Teriparatide may represent a useful adjunct to the armamentarium of the clinician for treatment of painful cervical non-unions in frail elderly patients. We believe that a

prospective study on the effects of anabolic therapy in type II odontoid fractures could have a profound impact on the management and outcomes of frail elderly patients.

We described a case of a painful non-union of type II odontoid fracture in an elderly patient treated conservatively. Due to no improvement in her symptoms and no progress of radiological union we offered our patient systemic treatment with rhPTH1-34 (Teriparatide) for 3 mo. At the end of the treatment a stable union of the fracture was achieved with complete resolution of the pain. Our report suggests that Teriparatide may have a role in enhancement of fracture healing in elderly patients with odontoid fractures.

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COMMENTS

Case characteristics

A 73-year-old woman with type II odontoid fracture. Treated conservatively with Philadelphia collar. Patient presented at 6 mo with ongoing mechanical neck pain with no neurological deficits.

Clinical diagnosis

Painful non-union of type II odontoid fracture.

Differential diagnosis

Delayed union of type II odontoid fracture can present with similar symptoms. Displacement of the fragments can also determine delayed compression on the spinal cord with myelopathy symptoms.

Imaging diagnosis

Cervical CT-scan showing a transverse fracture line of the odontoid process below the transverse ligament. There was minimal fracture displacement with fragments osteoporosis and sclerotic bony margins (non-union).

Treatment

Rigid external immobilization with cervical collar (Philadelphia) and systemic anabolic therapy with Teriparatide (20 µg/die) for 12 wk.

Related reports

Painful non-union is common after conservative treatment of type II odontoid fractures in elderly patients. Treatment options involve delayed surgical stabilization and fusion or conservative treatment with analgesia and external rigid immobilization. Stability must be assessed with flexion/extension X-rays to prevent delayed cervical myelopathy.

Experiences and lessons

Systemic Teriparatide therapy can be a valuable alternative approach to surgical fixation and fusion in symptomatic non-unions of the odontoid process. Teriparatide use for fracture healing enhancement is non Food and Drug Administration approved and must be considered "off label".

Peer-review

Authors report the treatment of a relatively common disease (a type II odontoid

fracture) with a widely used therapeutic approach in enhancing fracture healing (teriparatide), that has not been specifically reported as a therapeutic agent in this precise condition.

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Challenges of bone tissue engineering in orthopaedic patients

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Abstract

Bone defects may impede normal biomechanics and the structural stability of bone as an organ. In many cases, the correction of bone defects requires extensive surgical intervention involving the use of bone-grafting techniques and other procedures in which healing is slow, there is a high risk of infection and considerable pain is provoked - with no guarantee of complete correction of the defect. Therefore, the search for surgical alternatives continues to present a major challenge in orthopaedic traumatology. The reamer-irrigator-aspirator (RIA) system, which was devised to avoid the problems that can arise with autograft harvesting from the iliac crest, consists of collecting the product of the femoral canal after reaming. The RIA technique improves osteogenic differentiation of mesenchymal stem cells, compared to bone marrow aspiration or cancellous bone harvesting from the iliac crest using a spoon. Another approach, the Masquelet technique, consists of reconstructing a long bone defect by means of an induced membrane grown onto an acrylic cement rod inserted to fill the defect; in a second surgical step, once the membrane is constituted, the cement rod is removed and cancellous autograft is used to fill the defect. Both in RIA and in the Masquelet technique, osteosynthesis is usually needed. Bone transportation by compression-distraction lengthening principles is commonly implemented for the treatment of large bone loss. However, complications are frequently encountered with these techniques. Among new techniques that have been proposed to address the problem of large bone loss, the application of stem cells in conjunction with tissue engineering techniques is very promising, as is the creation of personalised medicine (or precision medicine), in which molecular profiling technologies are used to tailor the therapeutic strategy, to ensure the right method is applied for the right person at the right time, after determining the predisposition to disease among the general population. All of the above techniques for addressing bone defects are discussed in this paper.

Key words: Bone loss; Mesenchymal stem cells; Reamer-irrigator-aspirator; Autograft; Personalised medicine; Bone transportation; Precision medicine; Masquelet technique

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Core tip: This paper discusses the problems created by large bone loss, especially after major trauma, and considers current alternatives to autograft or allograft, such as the reamer-irrigator-aspirator system, the Masquelet technique, bone transportation, or the combination of stem cell therapy and tissue engineering. Future Directions addressed mainly concern the new concepts of personalised medicine and precise medicine.

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INTRODUCTION

High-speed traffic accidents and injuries in the workplace continue to present major orthopaedic trauma challenges, often requiring tissue reconstruction. Worldwide, more than 4.5 million reconstructive surgical procedures are performed annually, in response to accidents, cancer surgery or cosmetic needs. In many countries, too, victims of war or civil conflict must receive complex reconstructive surgery to overcome large tissue losses^[1]. Although progress has been made to reduce the incidence of such events (for example, through legislation and improved road safety), orthopaedic procedures for the treatment of large bone loss have not achieved such tangible improvements.

Bone defects can be classified into two different groups: Cavity defects, when the loss does not affect limb biomechanics but nevertheless interferes with osteosynthesis or arthroplasty implantation; and segmental defects, when normal biomechanics are impeded and the structural stability of the bone as an organ may be endangered^[2,3]. Reparative surgery is still the treatment of choice for these lesions, and autologous bone grafting is considered the gold standard approach in the clinical setting, in order to harness bone's natural regenerative capacity when a bone defect occurs. Large bone losses, however, are best treated by allograft, despite its less osteogenic nature. In many cases, the correction of bone defects requires extensive surgical intervention using bone-grafting techniques. Numerous surgical procedures may be needed, involving long healing times. These fairly aggressive surgical techniques can produce a high risk of infection; moreover, they provoke substantial pain and do not guarantee complete correction of the defect. The emotional impact on the

patient and financial burdens on the healthcare system are further problematic issues. Moreover, substantial donor-site morbidity and limitations on the quantity of bone that can be harvested proscribe its application when large bone loss occurs. In view of these considerations, alternatives to autograft for reconstructive surgery in large bone defects continue to be sought in orthopaedic traumatology.

Cavity defects can be resolved by the application of bone autograft, morselized allograft or bone substitutes. When cavity defects are not too large, they can be treated relatively straightforwardly, and alternative approaches such as combining cavity filling with implants are usually possible. On the other hand, cavity defects - and segmental bone defects in particular - can present major problems. This kind of lesion is often provoked by high-energy trauma, as a result of which the soft tissues are severely affected. Segmental defects may provoke major functional disability and even require amputation. The pelvis is often affected in patients with long-term arthroplasty loosening and also after bone tumour resection, whereas the femur and the tibia are commonly injured by severe trauma. In addition, the long bones of the upper limbs are frequently affected in serious accidents.

In this respect, many surgical techniques have been proposed, and some success has been obtained in treating relatively minor injuries. However, they have proved less effectiveness against large tissue lesions following high-energy trauma. When a large bone defect is experienced, the treatment challenge is twofold. On the one hand, since bone cannot remain uncovered, by skin or muscle, the absence of soft tissue cover will provoke necrosis and the non-viability of any therapeutic attempt; this is very commonly the case with injuries affecting the tibia, when anterior muscle cover is absent or insufficient. Furthermore, even well-covered bone will also need suitable vascularisation of an appropriately-sized, strong graft; otherwise, bone healing will never take place. Apart from these soft tissue and bone problems, function can be severely affected by lesions to tendons and nerves. Therefore, graft size and the vascularisation of bone implantation are of crucial importance for tissue viability, tendon function and nerve physiology.

Current therapies in this field have been developed over many years. The reimplantation of extruded bone segments is uncommon, due to worries about infection and unclear guidelines regarding timing, stabilisation and sterilisation techniques, which have led this procedure to be rejected by the majority of surgeons. The few papers that have been published in this respect have encountered great difficulties in reaching useful conclusions^[4]. Another approach is that of autograft harvested from the iliac crest, followed by vascularised autograft - however, the thin shape of this autograft makes it less useful in cases of large bone loss. Bone transportation procedures have also been suggested, together with the induced membrane Masquelet technique, with the creation of an artificial in-situ chamber, after inserting a temporary cement spacer

which will eventually be surrounded by a periosteum-like layer. These therapies have been complemented by growth factors - including platelet-derived growth factors and bone morphogenetic proteins (BMPs) - and cell therapies. Synthetic bone has also been included in compound approaches, in a quasi-random combination involving chance as much as science^[5].

All of these research lines have sought to focus on the keystone of bone synthesis: Matrix-forming cells. However, although the results of these new therapies are always said to be "promising", they still cannot be managed precisely or combined appropriately with osteosynthesis fixation.

At present, achieving a biomechanically strong, well-vascularised and physiologically-functional bone from the treatment of segmental bone defects continues to pose a major challenge.

Tissue engineering (TE) is a promising technology for secondary reconstruction after severe trauma. TE is an interdisciplinary science combining cellular, engineering, biochemical and physicochemical factors to improve or replace biological functions^[6-8], either in combination with, or independently of, an osteosynthesis technique. Different types of cells and bioactive factors have been shown to play an important role during this regeneration. The ideal biomaterial is currently believed to comprise a porous three-dimensional scaffold with patterned substrates, offering vascularisation and regeneration properties^[9]. However, the biochemical mediators of this process are imperfectly understood, and their biochemical properties and the sequence in which they act remain to be clarified.

In any case, creating tissue is an unavoidable necessity, as large bone loss cannot be repaired by an *in vivo* physiological mechanism. Whether TE will eventually be capable of replacing normal biological mechanisms has yet to be determined.

BMPs are known to promote cell multiplication and differentiation, but not sufficiently as to provide an alternative to currently-available therapies. Moreover, the sequence pathways of the different molecules remain unknown. Cell therapy, as currently applied, involves three sequential steps: *In vivo* extraction, *ex vivo* manipulation and *in vivo* implantation. After this long and complex procedure, the outcome is still uncertain, especially for large bone defects.

In view of these considerations, the following techniques have been proposed, incorporating the knowledge accumulated from cell therapy principles.

REAMER-IRRIGATOR-ASPIRATOR

The reamer-irrigator-aspirator (RIA) technique is designed to avoid the problems that arise with autograft harvesting from the iliac crest, and consists of collecting the product of the femoral canal after reaming^[10-13]. The cells thus collected and cultured present the same properties as those from the iliac crest^[14-17]. Studies have shown there are no phenotypical differences between

mesenchymal stem cells (MSCs) collected from the pelvic bone and RIA, and that the gene expression alteration found in RIA can be owned to the isolation technique employed^[18]. Cell characterisation is similar for adipose-MSCs, bone marrow-MSCs and RIA-MSCs, and the osteogenic potential is similar with *in vitro* and *in vivo* approaches^[19,20].

The RIA technique enhances the osteogenic differentiation of MSCs, in comparison with bone marrow aspiration or cancellous bone harvesting with a spoon from the iliac crest^[17,18]. A recent study^[18] compared harvesting by RIA with iliac crest aspiration and collection with a spoon, and reported that a greater concentration of colony-forming unit-fibroblasts of MSCs was obtained by RIA. Better results were also obtained by RIA for calcium tissue fixation as well as the gene expression of BMP2, SMAD5, runt-related transcription factor 2, osteocalcin and collagen type I alpha 1. Calcium fixation and osteogenic gene expression diminished considerably with higher passage numbers, in every specimen. The authors concluded that the harvesting procedure is critical for MSC differentiation *in vitro*. On the other hand, the CD271 selection of MSCs in RIA also produces a significant rise in MSC pureness and an increase expression of the transcripts implicated in bone synthesis, vessels formation and chemical attraction^[20].

Revascularisation takes place within three months of reaming, and bone thickness restoration of the cortex appears normal after 14 mo, allowing the opportunity for further reaming^[21].

Although RIA has achieved very promising results with respect to cavity defects, this technique is less useful for segmental ones, for which osteosynthesis supplementation is required. Furthermore, complications can arise in relation to the learning curve, to over-reaming and, in some patients, to cardiac problems produced by rapid blood loss; the latter complication is closely related to previous cardiopathy^[22,23].

RIA produces less pressure than intramedullary reaming and nailing, and a lower incidence of micro-embolism, according to studies of animals^[24,25] and of humans^[26]. However, one clinical study reported different findings from those obtained in animal experimentation, observing no differences in healing complications between intramedullary reaming and RIA, although there was a statistically non-significant tendency for the RIA group to present more complications^[27].

Both in conventional reaming for intramedullary nailing and in RIA, the coagulation and fibrinolytic response consists of higher cytokine levels, together with increased IL-6 levels, particularly in intramedullary reaming^[28]. However, other authors found no differences between these groups in relation to complications and IL-6 levels^[29]. In a biomechanical study of cadavers, under ideal conditions, it was found that RIA did not greatly reduce femoral cortical strength but that careful attention was needed to avoid the catastrophic failure that can occur using this eccentric reamer^[30]. In fact, femoral fracture can occur^[31], and complications have been reported to affect

31% of cases, including postoperative pain, bone defects, lung embolism, myocardial infarction and iatrogenic fracture^[32].

RIA has similar outcomes among all human races^[13], and can be performed either antegradely or retrogradely^[33,34].

MASQUELET TECHNIQUE

In the original Masquelet technique, a long bone defect is reconstructed by an induced membrane grown onto an acrylic cement rod inserted to fill the defect; in a second surgical step, once the membrane is constituted, the cement rod is withdrawn and the gap is filled with cancellous autograft^[35]. In a modification of this technique for tibial fractures, new surgical steps were added, such as the transfer of the soleus muscle island flap, vascularised with retrograde flow on the posterior tibial artery^[36]. Further research, on large animals, has shown that the membrane compartmentalises the bone defect, protecting it from the humoral and cellular environment of the muscular layer^[37]. The Masquelet technique has become increasingly popular in recent years for the treatment of large bone defects^[38]. Good results have been achieved in a large-scale study of bone defects in which autograft harvesting from the iliac crest was replaced by RIA^[39], with reduced morbidity in the second step of graft collection.

New research into the Masquelet technique has been conducted in animal studies, but the cell biology of animals is radically different from that of humans^[40-43]. In this respect, the paper by Aho *et al.*^[44] is particularly significant because these authors histologically characterised the induced membrane in humans, finding that greatest vascularisation took place in 30 d old specimens, and that levels diminished by sixty per cent during the following ninety days. Thirty day-old membranes presented the highest expression of vascular endothelial growth factor, interleukin 6 and collagen 1, while sixty day-old membranes expressed less than 40% of these levels. Specific alkaline phosphatase activity, the production of aminoterminal propeptide of type- I procollagen and calcium concentration all increased in co-cultures in the presence of a membrane sample. Furthermore, in thirty day-old cultures membranes, the formation of aminoterminal propeptide of type- I procollagen was more than twice as high, and calcium fixation was four hundred per cent greater, than in cultures of sixty day-old membranes. The authors concluded that induced membranes present osteogenesis-improving competences but that outcomes gradually worsen, and that the ideal period for carrying out the second step operation is before the second month following the implantation of foreign material^[44].

Although many studies have been conducted since the Masquelet technique was first presented in 2000, it is still difficult to predict the outcome of this approach to bone defect reconstruction, as complications are likely among most patients; at the outset, the surgical field is not optimal and the course of reconstruction is long and

difficult^[45].

Refinements of the Masquelet technique have recently been published by the original authors^[46], and further research has been carried out on the basic science for human patients, with multicentre recruitment^[47]. It has been shown that effective osseous formation *via* the Masquelet technique only incompletely emulates the cytokine expression of normal biological bone regeneration^[47]. Abundant expressions of insulin-like growth factor 1 are associated with successful Masquelet therapy, whereas transforming growth factor β appears to have low contribution. Consequently, the appropriate examination of a successful non-union treatment and of cytokine expression can be made even with a lesser number of cases. Therefore, further research in this field should be aimed at finding a method, based on a small population of patients, for predicting the success or otherwise of treatments for bone loss defects, including the Masquelet technique.

BONE TRANSPORTATION

In 1969, a paper appeared in MEDLINE on the Ilizarov technique aimed to treat "long tubular bones defects by means of one of their fragments"^[48]. However, it was published only in Russian and had little impact in Western orthopaedic science. Four years later, an Australian nursing journal published a paper by another Russian author on the Ilizarov technique^[49], and during the 1970s more papers appeared on the biomechanics of the Ilizarov apparatus^[50]. However, it did not become known worldwide until the 1980s, when Italian authors gave it major prominence^[51,52]. The approach described by Ilizarov was more than a single apparatus or technique; it became a new paradigm of the cell biology of bone regeneration, and was amply referred to as such in Russian publications during this decade^[53]. By creating a fracture only in the bone cortex ("bone corticotomy"), thus minimising surgical trauma, a callus consolidation process is triggered, and then maintained by means of immobilisation for 7-10 d. Thereafter, continuous slight distraction of less than 1 mm/d is exerted, and over time the gap becomes filled in.

Since its introduction, the Ilizarov technique, with its associated compression-distraction lengthening principles for the treatment of large bone loss, has been applied worldwide, and is now known as bone transportation. It has been shown that during this bone lengthening, the soft tissues also undergo stretching and subsequent physiological metaplasia^[54].

However, from the outset it has been apparent that the results obtained with the Ilizarov technique are excellent in some cases, good in others, and only fair in many. Consequences such as persistent infection, deformity, limb shortening, resultant limping, impacts on other joints (for example, equinus), dystrophy and severe pain have led some patients to request amputation. The duration of this treatment and its many negative consequences discourage many therapists from considering bone

transportation in patients with severe osseous loss, and these complex cases are often referred to specialised centres^[55]. Outcomes are also compromised by variables such as age older than 20 years, a larger gap magnitude, and diaphyseal rather than metaphyseal loss location^[56].

More is now known about the biology underlying Ilizarov bone transportation, and greater experience and better fixators have enabled surgeons to better apply this technique. In addition, new approaches have been tested, mainly in animal experimentation, combining Ilizarov's principles with TE^[57-63]. Nevertheless, the technique is still subject to complications and cannot systematically ensure a satisfactory outcome following large bone loss.

COMBINED STEM CELL THERAPY AND TE

Along the last decade, the combined treatment with immature MSCs and growth factors has been considered another promising therapy for bone synthesis. Nonetheless several terminally-differentiated cell lines (keratinocytes, osteoblasts, fibroblasts, osteocytes, chondrocytes and hepatocytes) cannot be used for artificial tissue constructs. Stem cell candidates to build artificial tissues comprise embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and postnatal adult stem cells^[64,65]. There are still some limitations to the practical use of ESCs and iPSCs, including the cytogenetic regulation of teratoma development, ethical issues, immune uncertainties in relation to ESCs, and the requirements for genetic manipulation of iPSCs. Multipotent MSCs derived from postnatal adult stem cells (Wharton's jelly cells, adipose tissue, bone marrow and dental pulp) are potentially useful because of their immunocompatibility and the absence of ethical concerns. Bone marrow (BM) and adipose tissue are also good sources of stem cells for clinical use^[66,67]. MSCs are cells of mesodermal derivation - different from the hematopoietic lineage- existing in various infant and adult organs and conjunctive tissues. Pluripotent MSCs in the BM stromal tissue are capable of differentiating to multiple mesenchymal lines, including osseous and chondral cells. Therefore, it follows that these MSCs could be employed in the restoration of large bone loss caused by traumatism, surgical procedures or maladies. MSCs from tissue sources such as human dental pulp, exfoliated deciduous teeth (SHED) and periodontal ligaments have similar characteristics to BM-MSCs but are commonly liable to problems such as a short collection of cells and a reduced quantity of collected tissues^[68,69]. Other significant drawbacks to the use of MSC in tissue repair include, firstly, the ache and problems associated with BM collection and, secondly, the low income (1 MSC/10⁴-10⁵ stromal cells), which makes *ex vivo* amplification a necessity^[70-72].

The adipose compartment appears to have a rich population of stem cells and, like BM, has a large cellular stroma, constituted of fibroblastic-like cells (the stromal vascular fraction - SVF). This cell segment, obtained from

human aspiration of fat, in turn has cells with multiline capabilities, called adipose stem cells (ASCs), which experience adipogenesis, osteogenesis, chondrogenesis and myogenesis *in vitro*. Some experiments have started to study the osteogenic potential of ASCs *in vivo*, in amalgamation with a great diversity of scaffolding materials^[73]. The use of human ASCs (hASCs) in scaffolds for osseous TE has been indicated as the alternative approach of the current century to substitute or repair the normal physiology of traumatised, injured or lost bone. The biological relationship between osteoblasts and adipocytes is reflected in their common MSC origin. The accumulation of marrow adipocytes in bone loss may be caused by a shift in the commitment of MSCs from the osteogenic to the adipogenic pathway. hASCs have several characteristics that make them compatible with currently-available strategies for creating new tissue, including cell transfer, induction and the generation of tissue constructs. The MSCs located within adipose tissue are effortlessly harvested in wide amounts, with slight donor site injury or general alterations. Furthermore, human adipose tissue is ubiquitous. Subcutaneous fat tissue fragments can commonly be obtained without general or regional anaesthesia. Present techniques for extracting ASCs are based on collagenase proteolysis after which centrifugal isolation of the SVF from primary adipocytes^[74] is performed. Among other features, ASCs present a fibroblast-like phenotype and lack the intercellular lipid precipitations observed in adipocytes^[75].

The proliferation capability of ASCs appears to be superior than that of BM-derived MSCs. Studies have revealed that the doubling times of ASCs along the logarithmic phase of growth range between 40 to 120 h, and it changes according to donor age, the nature of fat tissue (white or brown), its placement (subcutaneous or visceral), the harvesting procedure employed, the culture circumstances, the plating concentration and media preparations^[76]. Younger donors, have superior proliferation and cell adhesiveness of the ASCs. Cells progressively miss their multiplication capability with passaging. According to the β -galactosidase action, senescence in ASCs is comparable to that seen in BM-derived MSCs. The multiplication of ASCs can be encouraged by a solitary growth factor such as fibroblast growth factors (FGF)-2, EGF, insulin-like growth factor (IGF)-1 or tumor necrosis factor (TNF)- α . FGF-2, in particular, is an effective growth-stimulating factor that is needed for the long-term proliferation and self-renewal of ASCs *via* the extracellular signal-related kinase (ERK) 1/2 signalling pathway^[77]. The multiplication of ASCs can likewise be activated by platelet-derived growth factor *via* c-Jun amino-terminal kinase (JNK) activation and by oncostatin M *via* activation of the microtubule-associated protein kinase/ERK and the JAK3/STAT1 pathways. ASC multiplication has also been published to be enhanced by numerous growth factors, which can contain any of the particular growth factors formerly mentioned, complemented by thrombin-activated platelet-rich

plasma, human platelet lysate and human thrombin^[78].

ASCs have the capability to differentiate toward a diversity of cell lines, both *in vitro* and *in vivo*. Though ASCs are of mesodermal origin, it is now well known that they can commit themselves into ectoderm and endoderm, as well as mesoderm, lineage cells^[79]. Concerning differentiation into cells of the mesodermal line and the regeneration of mesodermal tissues, ASCs may differentiate into adipogenic, osteogenic, chondrogenic, myogenic, cardiomyogenic, angiogenic, tenogenic and periodontogenic lineages. Very little is known about how cell differentiation is affected by aging.

When used combined with a carrying scaffold, the directed osteogenesis of hASCs confirms that adipose tissue is a hopeful autologous font of osteoblastic cells for bone production. This approach provides support for hASC colonisation, migration, growth and differentiation. Few descriptions have been made of purified hASCs in bone engineering, and varying degrees of success have been reported^[80-87]. It has not been reported whether cellular free scaffold controls immersed in an osteogenic medium are also capable of achieving bone healing, to any degree^[88,89]. Nevertheless, the use of autologous hASCs, managed in the absence of animal-derived materials, following appropriate work in standard unpolluted places, has shown that these cells can be considered safe for uses in tissue engineering, according to European Union standards for clinical cell therapy safety.

Current limitations of hASC for bone TE include the following issues: (1) transitioning from preclinical *in vivo* models to the clinical setting signifies a foremost stride; (2) appropriate serum-free media for these cells must be developed, as foetal bovine serum (FBS) is not suggested for clinical treatments, ought to contamination and infection risk; (3) the *ex vivo* multiplication of cells for two or three weeks renders them vulnerable to possible genomic unpredictability in culture; and (4) appliances that would allow sole-step recruitment, manipulation and grafting are consequently required, to avoid the necessity for cell culture and the associated hazards of utilizing FBS.

Among the challenges to be addressed in hASC bone tissue-engineering for clinical applications, it should be emphasised that the main aim of the ASC TE strategy is to define the real osteogenic capability of ASCs independently of their association with growth factors. Further key challenges to be addressed include the standardising of techniques for recruitment, separating, cultivating and managing hASCs and the publication of procedures for the correct utilisation of carrier materials. Moreover, prospective randomised clinical trials should be conducted to categorize appropriate suggestions for hASC therapies and to validate the clinical results thereby achieved. Finally, ethical and security worries must be determined previous to human use, as the first step in new scaffold usage^[90].

As yet, there is little consensus regarding the efficacy of cell-based therapies in skeletal regeneration, or the

most effective cell origin type, number, combination or method of delivery^[91]. However, better regeneration results have been observed when cells are administered intravenously, subcutaneously or directly to the defect^[92-96]. Bone cell progenitors provide bone with its distinctive capacity for repair and regeneration^[97], and so their inclusion within a carrier is favoured by most surgeons. Nevertheless, the results obtained in this respect during the last 20 years have been only "promising". Experimental delayed-injection models utilising BM stromal cells have been shown to enhance the repair of injured tissue in relation to "time-of-trauma" cell uses. Time is allowed to elapse between the lesion/bone loss and the injection in order to avoid the early stages of tissue lesions, when the release of cytomodulatory peptides - including TNF- α , interleukins and interferons - and increased concentrations of acute-phase protein in serum appear to diminish the efficacy of stem and precursor populations. Although studies based on experimental spatiotemporal manipulation of cell delivery after the acute inflammatory response have achieved promising results in the field of segmental osseous tissue production^[92], it remains apparent that the media and moment of cell delivery significantly influence therapy effectiveness^[98].

FUTURE DIRECTIONS

The following main principles of tissue-engineering application in humans are generally accepted: (1) The manipulation of human stem cells for clinical treatment has to be carried out rendering upright laboratory techniques and the guidelines of the Food and Drugs Administration (in United States) or the European Medicines Agency^[99]. In this respect, the standardisation of separation and culture processes might raise quality regulations; (2) TE constructs must be considered as medicinal products and their intended use for clinical investigation purposes are subject to European regulations for clinical trials of medical devices and advanced therapies^[100]; and (3) Engineered tissue must be structurally and functionally comparable to natural tissue, be of the required size and shape, be able to continue developing after implantation into the body and be able to achieve full integration with the host.

Three components are usually necessary in TE: Cells, extracellular matrices and growth factors to provide molecular signals. The extracellular matrix-scaffold construction is a crucial aspect of bone defect repairing. Recent advances in TE have made available a large number of materials suitable for healing of bone defects and lost bone. Both *in vitro* and *in vivo* formation of bone tissue, using MSCs and 3D scaffolds has been shown^[101]. Several scaffolds such as HA/chitosan composites, chitosan or gelatin/TCP constructs, electrospun collagen nanofibres, honeycomb collagen scaffolds and titanium meshes have been used with MSCs. Newly designed scaffolds, resembling the effect of growth factors on adhesion-based mechanisms, need to be further implemented by analyses of the specific "pro-osteogenic" signal

transduction pathways. Osteogenic differentiation relies on cell adhesion and the substrate interaction, which are under the control of integrin complexes interactions. Integrin-matrix interactions can induce numerous signalling pathways, including the MAPK cascade. Although few studies with hASCs have been published, their results show that alternative methods for growth factor stimulation may be fostered to induce hASCs to make and heal bone^[102,103].

Regarding signalling systems, it has been suggested that soluble factors produced by ASCs (secretome) are the responsible for the potential clinical impact on different organs/tissues instead of the differentiation capability of hASCs^[104]. Analyses from primary hASCs cultures have shown the release of a large series of soluble factors including growth factors such as HGF, VEGF, β -TGF, IGF-1, bFGF, GM-CSF, TNF- α , interleukins (6, 7, 8 and 11), adiponectin, angiotensin, cathepsin D, pentraxin, pregnancy zone protein, retinol-binding protein and CXCL12^[105]. Indeed, HGF expression is increased after the cells have been exposed to bFGF, EGF or ascorbic acid, reinforcing the idea that soluble factors secreted by ASCs can be modulated by exposure to different agents. Thus, transplanted hASCs into inflammatory or ischaemic regions, actively secrete these growth factors, becomes a relevant strategy to promote wound healing and tissue repair. As mentioned previously, the increased bone formation attributed to BMP2-treated ASCs is derived from the osteoconductive and osteoinductive effects of BMP2 or from the ASCs themselves, although this remains to be demonstrated by means of appropriate controls.

Improving the ability of hASCs to generate large quantities of bone to repair bone defect without growth factors represents a major challenge. For that reason signal transduction pathways in adult ASCs need to be explored. Osteogenesis induced by hASCs might employ an alternate signalling pathway for adipogenic and osteogenic fates. Moreover, directed manipulation of downstream signalling paths rather upstream growth factors might be also responsible for stem cell-directed bone regeneration. In this respect, ERK pathways and MAPK signalling in ASC proliferation, migration and apoptosis have been analysed. Bone regeneration has been observed in rabbits with implants of MSCs transduced with Sonic Hedgehog (Shh)-a key protein involved in bone morphogenesis. Furthermore, BMP signalling in ASCs can be modulated by downregulating noggin, using rat ASCs transduced with noggin shRNA, and thus to enhance the differentiation of cells to a osteogenic terminal lineage. This noggin suppression + BMP-2 strategy has been confirmed in 3D *in vitro* experiments using complex scaffolds (consisting of chitosan, chondroitin sulphate and an apatite layer) designed to slowly release BMP-2. Wnt signalling pathways are involved in regulation of embryologic patterning, mesenchymal differentiation and stem cell fate^[106]. The association of LRP5 gene mutation and the osteoporosis-pseudoglioma syndrome strongly suggests the participation of Wnt signalling in bone formation.

Wnt3a induced signalling has been associated with the *in vitro* and *in vivo* inhibition of bone formation^[107]. In contrast, increased bone regeneration in bone defects has been observed in MSCs from bone tissues overexpressing Wnt4. This effect may be due to a specific increase in p38 MAPK phosphorylation, which mediates the promotion of bone formation.

TE is considered an advanced therapy medicine product (ATMP), the characterisation of which requires its characteristics (identity, potency, purity and safety) to be defined and measured during product development. ATMP manufacturing activities are mainly focused on the following areas; Pre-Production Activities (patient and donor selection, biopsy procurement, cell/tissue extraction, testing, storage and distribution to Good Manufacturing Practice-GMP-laboratories for production); Production Activities (manufacturing, packaging, labelling, testing, storage and distribution); and Post-Production Activities (testing, storage and administration/implantation of the manufactured product). In the European Union, these activities are mainly regulated by Directive 2004/23EC of the European Parliament^[108] which sets quality and safety standards for the main process involved in TE intended for human use (donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells). Other applicable legislation includes Directive 2006/17/EC, Directive 2006/86/EC, Directive 2012/39/EU, Commission Directives (EU) 2015/566 and 2015/565, Regulation (EC) 1394/2007, Directive 2009/120/EC and Directive 95/46/EC^[109-116], in addition to EuroGTP guidelines^[117].

In ATMPs, preclinical safety/toxicology assays are mandatory for sterility, mycoplasma contamination, endotoxins, aerobic/anaerobic micro-organisms, tumorigenicity and genetic stability. Their design requires specific pre-GMP laboratory activities for the selection and recruitment of stem cell donors and patients. In addition, there are specific regulations for stem cell donors^[117]. The clinical problem to be solved with ATMP has two related aspects: On the one hand is the question of individual genetic susceptibility to DNA single nucleotide variants (SNV) related to several pathological conditions, especially tumorigenesis, neoangiogenesis, lymphangiogenesis and cell capacities such as cell adhesion and migration. On the other hand, account must be taken of the gene instability of the cultured and manipulated MSCs used in manufacturing ATMP products.

Among other current limitations to this technique, the potential risk of genomic instability of cells is clearly a main limitation for clinical purposes. This risk appears to increase when *ex vivo* expansion of cells are maintained for more than three weeks. Therefore, much remains to be done to standardise methods and techniques for preparing hASCs for clinical applications and this also must be carried out following GMP, FDA and EMA regulations^[118,119]. Indeed, procedures for cells expansion in culture must be according to GMP guidelines for cell manipulation, and their standardisation will facilitate the quality controls, comparative studies,

maximising the reliability and reproducibility of results. In fact, discrepancies have been observed from different studies and from different laboratories, due to variability of the methods and quality of hASC isolation and of the composition of the initial cell culture. hASCs are generally stable (normal diploid karyotype) in long-term cultures, even when they have undergone more than 100 population doublings^[120]. However a single report suggests malignant transformation of hASCs cultured for more than four months^[121]. Yet, this spontaneous transformation of MSCs may also be due to cross-contamination with malignant cell lines (fibrosarcoma and osteosarcoma)^[122]. This controversy on spontaneous hASC transformation requires further experiments and discussion, bearing in mind the needs for a careful manipulation of hASCs, together with long-term follow-up of patients.

As most cells intended for engineering tissues have been subjected to mechanical or enzymatic dissociation, and to rapid proliferation in culture with growth factors and media, among other operations, there is always the possibility that some kind of alteration might be generated within the genetic burden of the cell. Any alteration of these genes could result in tissue dysfunction and a loss of function of the affected tissue.

In this context, the quality control of cell/tissue-engineering should be focused on histomorphology patterns, 3D perfusion seeding, cellular assessments of cell sterility and endotoxins, *in vitro* cellular toxicity, proliferation, adhesion in constructs, genetic quality control for DNA and gene expression and the rheological analysis of scaffolds and new cell/TE. At present, the analysis of tumorigenicity and genetic stability, with respect to chromosomal integrity and mutations of tumour-related genes, is mainly achieved by means of genetic and epigenetic quality controls, to verify at DNA level the absence of any alteration that could lead to malignant transformation, and to ensure that gene expression levels correspond to the functions of native tissues, *via* gene expression analysis of mRNA and proteins.

TE is a novel, complex and specific technology with unexpected risks to public health and to patients. There are three main types of risks to be considered.

Risks to patients arising from the quality of the ATMP product, in particular its components, stability, activity and purity (regarding non-physiological proteins). In the characterisation of a final ATMP product, genetic stability testing is of crucial importance to avoid the risk of clinical side effects due to tumorigenicity, inadequate cell adhesion and/or the increased cell migration capability of expanded/differentiated MSCs seeded onto scaffolds.

Risks derived from the interaction between the ATMP product and the effects on molecular systems of the patient. In this sense it is important to know the immunogenicity, the risks related to genetic modification of cells driving the apoptosis, any change of function, modification of growth and/or differentiation and malignancy. Early and late consequences of homing, grafting, differentiation, migration and proliferation need

also to be explored.

Risks related to persistence of the ATMP product in the patient responsible for late complications, such as cancer and autoimmune disorders.

EU legislation requires the genetic analysis of cells to ensure the absence of chromosomal instability and mutations, deletions or translocations in all tissues generated by TE and intended for clinical use.

Personalised medicine/precision medicine (PM) uses molecular profiling technologies to tailor therapeutic strategies, ensuring the right one is delivered to the right person at the right time, and determining the predisposition to disease among the population. Now days, next-generation sequencing (NGS) technologies are more accessible by cost, analytic validity and rapidity. Whole exome sequencing (WES) together with bioinformatics allows the analysis of single nucleotide variants of 85% of coding protein genes (20000 genes, 180000 exons, 1% of the whole genome)^[123]. WES sensitivity for known mutations and benign variants reach up to 98.3% and its main clinical use is for the diagnosis of genetic disorders, however, WES also allows phenotype expansion and makes it possible to identify newly mutated genes, undetectable by other techniques.

Taking into account the genetic instability risk of the *ex vivo* expansion of MSCs, we suggest that the standardisation of pre-implant testing of tumorigenic burden, neoangiogenesis and cell adhesion and migration capacities, by means of NGS analysis throughout the differentiation culturing of hASCs, would improve the quality control of artificial bone tissues used for bone repair and help achieve a valid prognosis of full integration within the host of *ex vivo* differentiated hASCs.

Joint exome and transcriptome analysis will help identify a panel of genes involved in hASC proliferation, differentiation, adhesion, migration, and also telomere length control, among other questions, thus constituting a standard genetic stability cell analysis for tissue-engineered bone. This analysis will reinforce the clinical criteria applied in selecting participants for clinical trials with TE, and hence reduce the risk of adverse effects arising from an accumulation of tumour-related gene mutations.

In summary, the clinical reconstruction of large bone defects is a highly challenging procedure, and will probably remain so for the foreseeable future.

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Tips to avoid nerve injury in elbow arthroscopy

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Abstract

Elbow arthroscopy is a technical challenging surgical procedure because of close proximity of neurovascular structures and the limited articular working space. With the rising number of elbow arthroscopies being performed nowadays due to an increasing number of surgeons performing this procedure and a broader range of indications, a rise in complications is foreseen. With this editorial we hope to create awareness of possible complications of elbow arthroscopy, particularly nerve injuries, and provide a guideline to avoid complications during elbow arthroscopy.

Key words: Elbow; Arthroscopy; Complications; Nerve injury; Education; Preventive strategies

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Core tip: Elbow arthroscopy is a technical challenging surgical procedure because of close proximity of neurovascular structures and the limited articular working space. With the rising number of elbow arthroscopies being performed nowadays due to an increasing number of surgeons performing this procedure and a broader range of indications, a rise in complications is foreseen. With this editorial we hope to create awareness of possible complications of elbow arthroscopy, particularly nerve injuries, and provide a guideline to avoid complications during elbow arthroscopy.

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INTRODUCTION

A small working space and close by neurovascular structures are the main reasons elbow arthroscopy is a technical challenging surgical procedure^[1-12]. Advantages over open surgery may be less scar tissue, decreased risk of infection, less postoperative pain, fast return to work and sports and better visualization of intra-articular pathology^[13-17]. Nowadays arthroscopy of the elbow is performed more frequently for an increasing range of indications; loose bodies, primary degenerative and rheumatoid arthritis, posttraumatic contractures, lateral/medial epicondylitis, osteochondral defects, posteromedial impingement, synovial disorders, fractures of the radial head, capitellum and coronoid, and debridement of osteophytes^[2,18-22]. With the rising number of elbow arthroscopies being performed nowadays due to an increasing number of surgeons performing this procedure and a broader range of indications, a rise in complications is foreseen.

A range of complications has been described after elbow arthroscopy, such as: Transient neuropraxia^[3,6,13,23-45], permanent nerve injury^[28,41,46-55], complex regional pain syndrome^[31], delayed wound healing^[31], superficial wound infection^[28,32,37,42,43,56-58], deep wound infection^[32], limited range of motion^[28,44,59], synovial fistula^[28,37], ganglion cyst at portal site^[32], granuloma of portal scar^[39], heterotopic ossifications^[23,32,43] and triceps tendon ossification^[32]. One of the most devastating complications is nerve injury^[19,60] of which the majority is fortunately transient^[13,32].

Recently Desai *et al.*^[60] conducted a survey among the member of the American Society for Surgery of the Hand to determine which nerves and what kind of nerve injuries were treated after elbow arthroscopy over a five-year period; 222 nerve injuries were identified, an estimated 1.2% occurrence rate. In half of the patients additional surgical intervention was needed; 77%-80% had either partial or no recovery. This seems contradictory with the only 13 cases on permanent nerve injury after elbow arthroscopy published in current literature^[28,41,46-55]. Desai *et al.*^[60] stated that in view of the high number of elbow arthroscopies performed these days permanent nerve injury is probably under-reported. In current literature the ulnar nerve seems most susceptible for nerve injury during elbow arthroscopy^[60-62].

The goal of this current concepts review is to raise awareness of possible complications of elbow arthroscopy, in particular nerve injuries, and provide a practical guideline that can help to avoid nerve complications during elbow arthroscopy.

HOW TO AVOID NERVE COMPLICATIONS IN ELBOW ARTHROSCOPY?

A general necessity is thorough knowledge of the

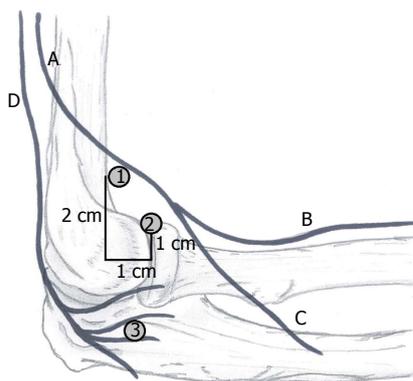


Figure 1 Proximity of nerves and portals: Lateral side view. A: Radial nerve; B: Superficial branch; C: Deep branch; D: Posterior antebrachial cutaneous nerve; 1: Proximal lateral portal; 2: Anterolateral portal; 3: Midlateral portal.

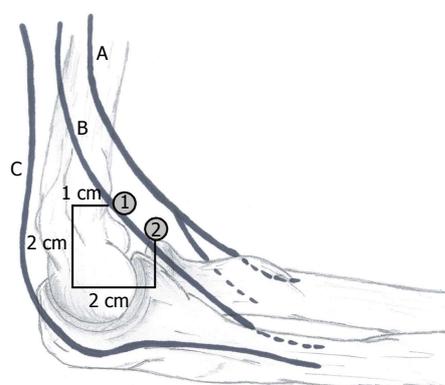


Figure 2 Proximity of nerves and portals: Medial side view. A: Median nerve; B: Medial antebrachial cutaneous nerve; C: Ulnar nerve; 1: Proximal medial portal; 2: Anteromedial portal.

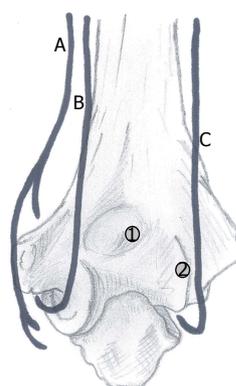


Figure 3 Proximity of nerves and portals: Posterior side view. A: Medial antebrachial cutaneous nerve; B: Ulnar nerve; C: Posterior antebrachial cutaneous nerve; 1: Transtricipital portal; 2: Posterolateral portal.

anatomy of the elbow in order to comprehend the spatial relation among neurovascular structures and portals and be able to safely perform elbow arthroscopy (Figures 1-3).

Work up

Avoiding peri-operative complications starts with a proper work-up. Firstly, there has to be a valid indication for surgery, which starts with patient complaints, history



Figure 4 Osteophytes can cause changed anatomy, for example posteromedial osteophytes could push the ulnar nerve out of its groove.

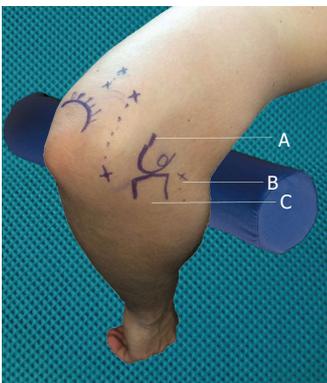


Figure 5 Marking of anatomical structures and portals: Lateral side view. A: Lateral epicondyle; B: Anterolateral portal; C: Radial head.

taking and physical examination. Setting a valid indication prevents unnecessary surgery and subsequently prevents neurological complications. A history of trauma, previous elbow surgery or rheumatoid arthritis, or burns, skin grafts, a subluxing ulnar nerve or congenital deformity of the elbow on physical examination can be complicating factors for surgery due to alteration of the anatomy; for example nerves can be adhered to the capsule^[63], the capsule may have less distension capacity and scar tissue may make identifying nerves and vessels difficult. Additional imaging studies (CT, MRI or ultrasound) might be needed to confirm the diagnosis or for careful planning of surgery when expecting changed or difficult anatomy (Figure 4)^[25]. For example, a subluxing or previously transposed ulnar nerve. The incidence of a subluxing ulnar nerve is reported to be 11%-21%^[64,65] and not recognizing its presence preoperatively may lead to iatrogenic ulnar nerve injury. Dodson *et al.*^[19] suggested that arthroscopic surgery should be avoided if the patient had undergone previous ulnar nerve transposition. In order to prevent missing a not physiological ulnar nerve course it is recommended to routinely report if patients had a ulnar nerve transposition or are diagnosed with a subluxing ulnar nerve during physical examination in the outpatient setting.

Preoperative preventive measures

Prior to incision and distension of the joint, preoperative

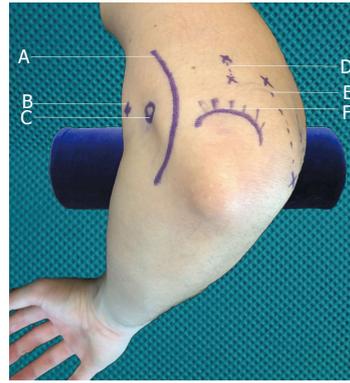


Figure 6 Marking of anatomical structures and portals: Medial side view. A: Ulnar nerve; B: Proximal medial portal; C: Medial epicondyle; D: Transtricipetal portals; E: Posterolateral portals; F: Olecranon.

examination under anesthesia, marking of anatomic landmarks and portal sites, and palpation of the course of the ulnar nerve are of great importance to obtain good orientation and avoid complications^[3,18,28,66] (Figures 5 and 6). In cases with changed ulnar nerve anatomy a possible safe anteromedial approach depending on with what certainty the course of the ulnar nerve can be determined is described by Sahajpal *et al.*^[66]. If the course is unequivocal a safe anteromedial approach is possible by placing the portal 1cm from the nerve, if the course is equivocal portal placement should be 1 cm from the nerve by mini-incision, or by open approach *via* an incision of 2- to 4-cm in order to identify the nerve and subsequently place the portal if localization of the nerve is impossible. However, in the opinion of the authors the safest approach of an elbow with a subluxing or transposed ulnar nerve is an immediate open approach and starting elbow arthroscopy after identifying the ulnar nerve. Whenever establishing or re-entering the portal the ulnar nerve should be fixated posteriorly of the medial epicondyle.

Anesthesia

Most surgeons prefer general anesthesia with total muscle relaxation because of patient comfort and the disabling of unexpected patient movement, and it allows for supine positioning^[2,18]. Some surgeons prefer to add regional anesthesia, for optimal reduction of postoperative pain. However, in a randomized controlled trial performed by Wada *et al.*^[67] no additional pain relief was observed using a supplemental axillary nerve block over general anesthesia alone. In addition, regional anesthesia has a small risk for nerve injury with an incidence of 3:10000 based on two large prospective studies^[68-70].

Patient positioning

Several alternatives are available in positioning of the patient: The most common are the lateral decubitus position and the supine-suspended position with the use of a limb positioner (Figure 7). An advantage of the lateral decubitus position over the supine-suspended position

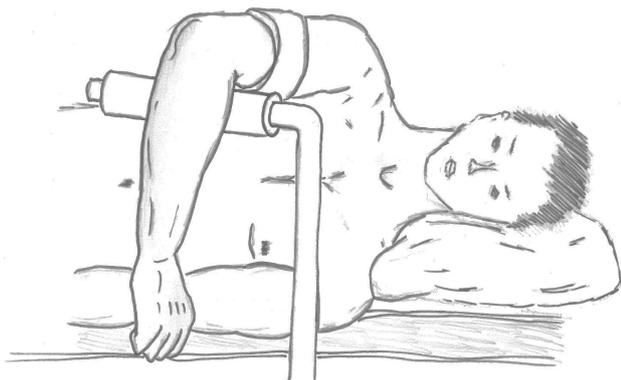


Figure 7 Lateral decubitus position.

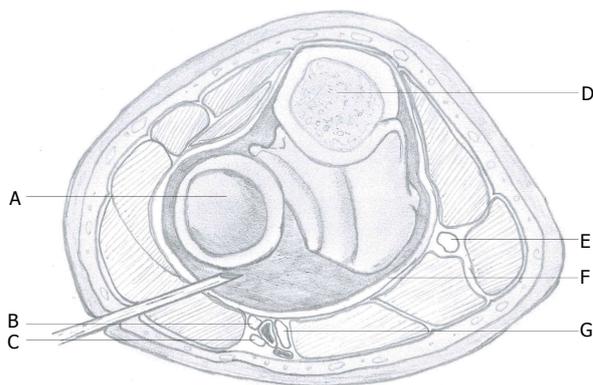


Figure 9 Distended joint. A: Head of radius; B: Radial nerve; C: Lateral antebrachial nerve; D: Cross-section of olecranon; E: Ulnar nerve; F: Capsule; G: Median nerve.

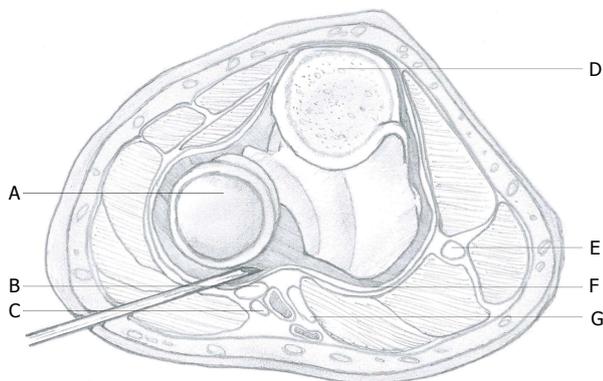


Figure 8 Non-distended joint. A: Head of radius; B: Radial nerve; C: Lateral antebrachial nerve; D: Cross-section of olecranon; E: Ulnar nerve; F: Capsule; G: Median nerve.

is that gravity assists in displacing the neurovascular structures away from the anterior capsule and from the anterior working field. Furthermore, the lateral decubitus position facilitates easy access to all compartments. A stable and comfortable patient position can be achieved by use of vacuum beanbag immobilizer.

Joint distension

When proper orientation of the surgical landmarks and patient positioning has been acquired, the next step is fluid distension (20-30 mL) of the joint *via* the midlateral soft spot or *via* a posterior approach. The latter approach is preferred by the authors because of the absence of cartilage in addition to the absence of nerves. Fluid distension of the elbow joint space moves the neurovascular structures away from the surgical field by expanding the joint capsule^[3-5,10,45,71-75] (Figures 8 and 9). It is very important to realize that the nerve-to-capsule distance does not increase with joint distension, but only nerve-to-portal distance and the nerve to osseous structures distance^[3,5,75,76]. Therefore, joint distension probably reduces the chance of nerve injury during joint entry *via* the portals and during intra-articular surgical procedures, but not during performance of capsular procedures. Since the capsule may rupture at pressures below 50 mmHg, it is advised to use gravitational force

only, and avoid pressurized infusion, to keep the joint distended. Higher pressures occurring in fluid pumps cause fluid to flow extra-articular decreasing joint visibility^[76,77]. Saline-infusion of 5 mL or less indicates a decreased displacement of neurovascular structures and less working space, for example in elbow contractures, making surgery more complicated^[1]. Successful joint insufflation of the elbow with fluid will cause an extension movement.

Elbow positioning

It is advised to flex the elbow to 90 degrees as it displaces the brachial artery and the anterior nerves anteriorly^[4,9], maximizing the distance between the joint capsule and the brachial artery, and the nerve-to-capsule distance^[3,73]. The distance between the portals and the medial and radial nerves is doubled solely by elbow flexion, in combination with the aforementioned joint distension this distance even triples^[72]. Furthermore, capsular capacity is maximized by flexion, increasing arthroscopic working space and minimizing the chance of neurovascular complications^[1,3-5,73,78]. Disorders as rheumatoid arthritis, stiff and posttraumatic elbows may compromise the distension capacity of the capsule, thus raising the risk of neurovascular complications^[1,3,5,13,38,52]. For maximal range of flexion, compression of the flexion crease due to supportive arm holders should be avoided.

Portal placement

Portal placing can cause nerve injury^[13,18,46,62]. The above-mentioned preventive measures are meant to minimize the risk of neurovascular injury during the placing of portals. Mini-incision of the skin, avoiding incision of subcutaneous tissue, and the use of a blunt trocar or clamp are the first two preventive measures to avoid injury to the antebrachial nerves^[9,75]. Furthermore, recognize that portals placed proximally of the joint have the tendency of being safer^[9,79]. Pronation (in addition to flexion) of the elbow protects the posterior interosseous nerve when placing lateral portals. The elbow should be in midpronation at least. This way the nerve is brought

Table 1 Recommendations in short

Step	Phase	Recommendations
1	Work-up	Determine a valid indication. Identify possible complicating factors. If needed obtain additional imaging studies for careful planning of surgery Routinely report a subluxing or previously transposed ulnar nerve for all patients in the outpatient clinic setting previous of elbow arthroscopy
2	Preoperative preventive measures	Critical assessment of CT-studies to determine if osteophytes compress or mobilize the nerves (Figure 4) Examination under anesthesia (ROM) Marking of anatomic landmarks and portal sites (Figures 5 and 6) Palpation of the ulnar nerve course
3	Anesthesia	General anesthesia is recommended because of patient comfort and disabling unexpected patient movement
4	Patient positioning	Lateral decubitus position is recommended because of additional gravitational displacement of nerves away from the anterior capsule and easy access to all compartments (Figure 7) Use a bean bag for stable patient positioning
5	Joint insufflation	Increases nerve-to-portal distance by expanding the joint space en pushing the neurovascular structures away from the surgical field. Recognize that joint insufflation does not increase nerve-to-capsule distance (Figures 8 and 9)
6	Elbow positioning	Elbow flexion increases distension capacity of the joint and increases nerve-to-portal distance Supportive arm holders should not compress the flexion crease
7	Portal placement	Portals proximal to the joint tend to be safer Mini-incision of the skin only and the use of a blunt trocar or clamp prevents injury to the antebrachial nerves Pronation and flexion of the elbow protects the posterior interosseous nerve when placing lateral portals Avoid use of the posteromedial portal as the posterolateral and midposterior portals are good alternatives when inspecting the posterior compartment
8	Use of instruments	Always visualize the tip of the instrument Avoid suction when in the vicinity of a nerve or against the capsule Use a retractor to lift the capsule away from the debriding instrument, particularly in compartments at risk The use of hooded burrs instead of unhooded burrs is recommended as it help prevent the burr tangling up in the soft tissues No suction while shaving Availability of different shaver sizes during surgery

more anteromedial and the portal-to-nerve distance has increased^[4,78,80]. When assessing the anterior compartment of the elbow it is advised to start with an anteromedial portal subsequently placing a lateral portal using the camera because this possibly reduces the risk of radial nerve, *i.e.*, posterior interosseous nerve (PIN), injury^[7,9,10,12]. The proximal medial portal might even be a superior alternative compared to the anteromedial portal due to greater distance to the medial antebrachial nerve and no difference in arthroscopic view^[9,81]. When placing the proximal medial portal stay anterior of the medial intermuscular septum to keep the ulnar nerve posterior of the portal and avoid ulnar nerve injury^[9,82]. A method to reduce neurovascular injury when placing the proximal medial portal is by using a blunt hemostat or clamp after the usual mini-incision of the skin and place it on the anterior aspect of the humerus and aim it at the coronoid. By sliding downward over the humerus the capsule will be reached with small chance of injuring the median nerve, medial antebrachial nerve or brachial artery^[81]. When assessing the posterior compartment of the elbow avoid using the posteromedial portal as it brings risk for ulnar nerve injury; posterolateral and midposterior portal are good alternatives^[81].

Use of instruments

Once safe entry to the joint has been established it is

important to always keep your instrument tips within sight even under hard conditions and keep clear of using suction when working in the proximity of a nerve or the capsule to prevent within-out- injury^[75]. Never use suction while shaving. Another way of preventing within-out injury is using a retractor, *via* a separate portal, to keep the capsule away from a debriding instrument^[75]. This particularly applies to the posteromedial and the anterolateral compartment because of limited distance to the ulnar nerve and radial nerve respectively. Other advantages of using a retractor, aside from preventing within-out injury, are better visualization and exposure of the elbow joint. Lastly, to prevent a burr from getting entangled in the surrounding soft tissues and causing damage to an adjacent nerve hooded burrs are advised. Availability of different sizes of shavers during surgery is obligatory, so you can adjust the shaver size to the specific circumstances and avoid within-out-injury due to usage of a too large shaver.

All aforementioned recommendations are summarized in Table 1.

DISCUSSION

Thorough knowledge of the anatomy of the elbow in health and various diseases, handling of arthroscopic instruments and number of performed elbow arthroscopies

are of influence on one's arthroscopic expertise^[13,20,31,83,84]. There still is no consensus on the minimal number of elbow arthroscopies that has to be performed to become an experienced arthroscopist. However it is apparent that elbow arthroscopy has a long(er) learning curve. Savoie^[20] states that a minimal number of 100 performed elbow arthroscopies is necessary to become an experienced elbow arthroscopist. After the first 15 arthroscopies Kim *et al*^[84] observed a significant decrease in surgical time in elbow arthroscopy.

It is common sense that with more experience comes a decreased complication rate. This seems to be confirmed when comparing the study of Claessen *et al*^[83] with the studies of Marti *et al*^[31] and Elfeddali *et al*^[28]. Claessen *et al*^[83], observed a 30% complication rate in portal placement by novice surgeons whom were trained by a single didactic lecture and a single cadaveric training and found the complication rate significantly higher when compared to studies in current literature by experienced elbow arthroscopists. Marti *et al*^[31] found 6 minor complications (5%) in a series of 100 elbow arthroscopies done by 1 fellowship trained surgeon with only previous cadaveric experience, however no correlation could be found between the complication rate and the learning curve. Elfeddali *et al*^[28], found a 7.5% complication rate in 200 elbow arthroscopies over 8 years all performed by a single surgeon; due to the sample size it was not possible to detect any significant learning effect.

Following out of the aforementioned studies is that inexperienced surgeons are more likely to cause iatrogenic complications during elbow arthroscopy. A "young" surgeon should undergo extensive training with as much hands-on exposure as possible, comprehending guidance by an experienced elbow arthroscopist, computer-simulated hands-on courses, pre-clinical hands-on cadaveric courses preferably yearly and in line with the current opinion of arthroscopy experts and Claessen *et al*^[83] fellowship training.

In current literature the prevalence of neurologic injury after elbow arthroscopy, transient and permanent, is reported to range between 0% and 14%^[8,13,14,32,34,42,45,63,85-88]. As stated by Desai *et al*^[60] the reported prevalence is probably underreported. Possible causes of nerve injury underreporting after elbow arthroscopy are; the lack of a national registration for nerve injuries like there is for orthopedic implants, loss-to-follow-up due to the diagnosis and treatment of nerve injury by another specialty, and the possible reluctance or fear of the consequences when reporting iatrogenic nerve injury.

The goal of this editorial is to make one aware of the complications that can occur when performing elbow arthroscopy and more importantly stress the difficulty of performing elbow arthroscopy. The abovementioned instructions are to be a general guideline in order to help avoid complications during elbow arthroscopy. We believe a proper and thorough work-up and awareness of the possible severe complications throughout all steps of the procedure is the key for a successful elbow arthroscopy.

No matter the experience of an elbow arthroscopist, for

every indication a surgeon should assess if he is capable to perform the procedure as a surgeon's experience is directly related to the incidence of complications^[20].

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Total knee arthroplasty and fractures of the tibial plateau

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Abstract

Tibial plateau fractures are common injuries that occur in a bimodal age distribution. While there are various

treatment options for displaced tibial plateau fractures, the standard of care is open reduction and internal fixation (ORIF). In physiologically young patients with higher demand and better bone quality, ORIF is the preferred method of treating these fractures. However, future total knee arthroplasty (TKA) is a consideration in these patients as post-traumatic osteoarthritis is a common long-term complication of tibial plateau fractures. In older, lower demand patients, ORIF is potentially less favorable for a variety of reasons, namely fixation failure and the need for delayed weight bearing. In some of these patients, TKA can be considered as primary mode of treatment. This paper will review the literature surrounding TKA as both primary treatment and as a salvage measure in patients with fractures of the tibial plateau. The outcomes, complications, techniques and surgical challenges are also discussed.

Key words: Arthroplasty; Knee; Tibia; Intra-articular fractures; Fracture fixation

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Core tip: It is well known that patients undergoing open reduction and internal fixation (ORIF) following tibial plateau fracture have a high rate of post-traumatic arthritis (PTOA) requiring total knee arthroplasty (TKA) in the future. Currently, ORIF is the standard of care for all patients requiring operative management. Small groups of select patients have shown good results with TKA as primary treatment of tibial plateau fracture. This group includes elderly patients with poor bone stock who are shown to have high rates of post-traumatic arthritis and fixation failure. In younger and more active patients, the options for salvage TKA in the case of PTOA is discussed, as this procedure is more complex than primary TKA.

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INTRODUCTION

Tibial plateau fracture is a common injury of the lower extremity that is seen in the population with a bimodal age distribution. These injuries are often categorized using the Schatzker classification, which can be used to classify the fracture pattern and oftentimes dictate treatment. Type I, II and III fractures involve the lateral plateau. Type IV fractures involve the medial plateau, while type V describes bicondylar involvement. In type VI fractures, there is complete metadiaphyseal dissociation. In younger patients with more robust bone stock, tibial plateau fractures are generally the result of high energy mechanisms, whereas low energy mechanisms are usually observed in the elderly, osteoporotic population. Due to the mechanical axis of the lower extremity, with the lateral plateau higher and in 3 degrees of varus, the medial tibial plateau receives 60% of the load placed on the knee, creating stronger subchondral bone. As a result, lower energy injuries more commonly injure the lateral plateau. Therefore, medial injuries are not simply the counterpart to lateral injuries, but rather represent a much higher energy impact, and therefore associated injuries (*i.e.*, ACL and MCL) are more common with this pattern^[1]. Approach to the patient should commence with evaluation of the soft-tissue envelope and neurovascular exam. In Schatzker IV-VI fractures, clinicians should be especially sensitive to the possibility of vascular injuries and compartment syndrome^[1]. Computed tomography imaging in addition to standard radiographs are important in both fracture classification and operative planning.

Options for the management of these fractures range from conservative methods including bracing and limited weight bearing to surgical management, most commonly open reduction and internal fixation. The decision to pursue surgery is based upon the characteristics of the fracture. Regardless of patient age and bone quality, fractures with significant displacement or fragment depression require surgical management for a successful outcome. Instability and fracture displacement usually require an operative approach to restore joint surface congruity. A major factor when considering surgical management in the acute period following the injury is concomitant damage to the soft tissue structures surrounding the knee. If there is significant soft tissue damage or swelling precluding acute open reduction and internal fixation (ORIF), external fixation using a spanning frame with delayed surgical management of 2-3 wk is usually pursued. Goals of articular fracture management include restoration of the articular surface, normalization of the mechanical axis, stable fixation, early range of motion and delayed weight bearing in most cases. Lansinger *et al.*^[2] determined that long-term outcomes correlate better with restoration of joint axis

in the sagittal and coronal planes than exact articular reduction. Achieving these goals gives patients the best chance of restoring their pre-injury level of function and avoiding the complications associated with these types of injuries^[1,3].

Complications of tibial plateau fractures may require arthroplasty as a salvage procedure. Complications of operative management of tibial plateau fractures include infection, knee stiffness, non-union, fixation failure, and most relevant to this discussion, post-traumatic osteoarthritis (PTOA). Infections may be a frequent complication of ORIF of tibial plateau fractures with rates ranging from 2%-11%^[4]. With optimal handling of the soft tissue envelope and appropriate decision-making by the surgeon, rates of infectious complication can be kept to a minimum. Infection should be avoided at all costs because patients who suffer infection following ORIF incur on average an additional five surgeries^[5]. Factors associated with infection after tibial plateau fracture include smoking, compartment syndrome requiring fasciotomy and fractures requiring dual incisions with dual plating^[6]. Knee stiffness is thought to be the result of post-operative immobilization. Patients with higher-energy fracture patterns are noted to be more likely to experience unsatisfactory knee motion following ORIF of the tibial plateau. This is also the case in patients with longer periods of immobilization. Three to four weeks of immobilization vs immediate ROM is associated with higher rates of stiffness and flexion contracture^[4]. Fixation failure can be loosely defined as loss of reduction resulting in either step off of > 3 mm or malalignment of the extremity of greater than 5 degrees, loosening or breaking of implants. The rates of fixation failure range from between 1%-31%^[7].

PTOA is caused mainly by articular incongruity and joint instability, although direct damage to the articular surface at the time of injury may play a role. PTOA is seen in 23%-44% of patients following tibial plateau fracture, even in those with stable knees. In one study, the rate of secondary OA was seen in 44% of patients who suffered PTOA and were followed up at an average of 7.6 years. An important point was that after 7 years, the rate of OA development did not increase significantly^[8,9]. Weigel *et al.*^[10]'s 20-year follow-up of patients with high energy tibial plateau fractures found that after 2-4 years of follow-up, there was not a significant change in the rate or grade of arthrosis. There is a higher rate of PTOA in patients who undergo meniscectomy during fracture repair, and therefore preservation of menisci should be a priority during surgical management of these patients. Ligamentous injury also correlates with the development of secondary arthritis, as does residual tilt of the tibial plateau. Seventy-five percent of patients with ligamentous injury at the time of surgery developed secondary osteoarthritis vs 27% of those with no evidence of ligamentous injury or instability at the time of repair^[8]. Not surprisingly, age is also a predictor of development of PTOA, with older patients being more likely to suffer secondary OA following trauma. Risk of degenerative change increases significantly with greater age at time of

injury^[4,9,10]. It should be noted that there does not seem to be a difference in the rate of PTOA between those managed operatively vs non-operatively^[8].

For patients who develop post-traumatic arthrosis of the knee, total knee arthroplasty (TKA) is a widely accepted treatment option, just as prosthetic replacement is considered for patients who develop primary osteoarthritis of the knee. In fact, the risk of TKA in patients with previous fracture of the tibial plateau is 5-times higher than matched controls from the general population, at 7.3% in the 10-year period following injury^[11]. Age of the patient, activity level and the status of bone mineralization are some of the major factors that are involved in treatment of PTOA. Non arthroplasty options for physiologically younger patients generally include osteotomy and arthrodesis, however in most patients, especially older patients, TKA should be considered the optimal treatment for end stage PTOA^[12].

In contrast to TKA for salvage in patients who suffered complications of tibial plateau fractures, TKA is potentially a primary treatment option for elderly patients with lower demands along with fracture patterns and bone quality that make ORIF a less desirable option. Elderly, osteopenic patients present several unique issues in the management of tibial plateau fractures. Fractures in this patient population are generally lower-energy injuries than seen in younger patients. Due to poor bone quality, fracture patterns are often complex with significant displacement and damage to the articular surface. As such, there is an association between patient age and failure of fracture fixation. Patients older than 60 have an increased risk of fixation failure and radiographic evidence of osteoporosis is a major predictor of failed fixation. One study reported a 79% rate of radiographic fixation failure in elderly patients vs 7% in the younger group of patients^[7]. Second, fracture fixation in elderly patients will often times prevent early weight-bearing following surgical intervention. Delayed weight bearing in elderly patients is associated with higher morbidity and mortality than in younger populations. The earlier you can get an elderly patient mobile following surgery, the better the outcome and more likely the return to preoperative functional status, which should be the ultimate goal in management of these injuries. Therefore, investigators selecting patients to undergo TKA acutely following tibial plateau fracture used evidence of osteopenia or osteoarthritis as indications for TKA. This allows the identification of patients who are at risk for either failed fixation or later requirement of TKA. Some groups specified an age range, for instance, Vermeire *et al*^[13] limited participants to over 70 years of age with evidence of poor bone stock or over 55 with severe, debilitating pre injury osteoarthritis.

Finally, as some studies have indicated, delayed TKA presents a greater challenge both in the operating room and during recovery than primary TKA, and complications can often be more dramatic in elderly patients. Considering these ideas, several papers are presented here that have examined groups of patients with tibial plateau fractures

treated primarily with TKA and examined the outcomes and complications experienced by these patients.

APPROACH TO TKA IN TIBIAL PLATEAU FRACTURES

Total knee arthroplasty for PTOA

Arthroplasty in patients with prior fixation about the knee can present major challenges. It is more technically demanding and is associated with higher rates of complication than arthroplasties performed in patients with primary OA^[14]. When planning TKA for patients with prior fixation of tibial plateau fracture, surgeons must consider several factors. First of all, patients should undergo a standard and thorough preoperative evaluation. This includes a medical evaluation, full length alignment radiographs along with an infectious and nutrition workup. Next the surgeon should take into consideration the previous repair and hardware present in the knee. Prior hardware may be removed intraoperatively or the removal can be staged if it will require extensive incisions or dissection, which can predispose to infection if performed simultaneously with TKA^[15]. Additionally, not all hardware requires removal. Some authors suggest removing only the hardware that is going to directly interfere with the prosthesis^[12].

In addition to challenges posed by the fracture, alterations to the soft tissue environment imposed by previous surgeries can complicate wound healing. Prior incisions should be approached carefully by using the most lateral incision and taking care not to create acute angles across prior transverse incisions. Careful attention should be taken to preserve the medial skin flap, as this is where the perforators arise. Other issues that can be encountered in this population is surgically constructed flaps and grafts which have a tenuous blood supply of their own. Surgeons should have a low threshold for consulting a plastic surgeon for management of the soft tissues in patients with prior soft tissue reconstruction. Careful consideration in this regard is necessary to preventing skin necrosis and wound healing complications.

Exposure of the knee can be difficult, as PTOA patients often have stiff knees. Certain maneuvers can be employed in different scenarios to provide excellent exposure as well as to manage injury to extensor mechanism and collateral ligaments. These include quadriceps snip, VY turndown, tibial tubercle osteotomy and lateral retinacular release. Weiss *et al*^[16] performed lateral release in 28% of their patients to facilitate their approach while Saleh *et al*^[17] performed the same maneuver in 33% of their patients. Civinini *et al*^[18] performed quadriceps snip and tibial tubercle osteotomy to facilitate exposure in 12% and 16% of their patients, respectively. It must be pointed out that these maneuvers are not without morbidity. Lateral release is generally benign and doesn't require any additional post-operative rehabilitation. Tubercle osteotomy can be more problematic, and mechanical

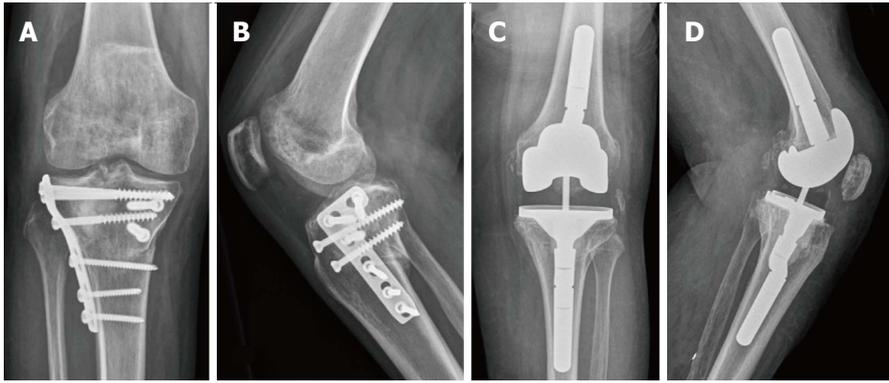


Figure 1 Total knee arthroplasty following open reduction and internal fixation of the tibial plateau. A and B: Radiographs of a 61-year-old woman made 3 years after ORIF for tibial plateau fracture; C and D: Radiographs at 7-year follow-up after constrained PS prosthesis with offset and stem in both components. ORIF: Open reduction and internal fixation.

complications relation to the procedure include disruption of the extensor mechanism or resultant fracture, with rates around 15%^[19]. Quadriceps snip and VY turndown are soft tissue techniques that evolved as an alternative to tibial tubercle osteotomy, however they also pose a minor threat to the extensor function^[20]. One study identified factors in their patient population that predicted patellar tendon rupture and these includes diabetes mellitus, steroids, trauma and patella baja^[17]. Managing bony loss in these patients involves techniques similar to those for revision TKA including cement filling, morselized bone grafting and metal wedge augmentation, among others^[12] (Figure 1).

Device selection should take into account ligament integrity and bone quality. A general rule is to use the least amount of prosthesis constraint necessary while allowing symmetric and balanced flexion and extension of the knee^[12]. The high rate of constrained implant use in these patients makes this procedure more similar to revision TKA than primary standard TKA. The choice of implant should take into account the stability of the knee and existing bony defects. The most common implants types were varus/valgus constrained, hinged and PCL-retaining prostheses. Most but not all groups performed patellar resurfacing and required long-stems in certain patients to bypass fracture areas.

There is a well-known benefit to using computer assistance (CAS) in total knee arthroplasty. Kini *et al.*^[21] examined the use of CAS in acute TKA for a group of elderly patients with proximal tibial fractures, 6 of which were Schatzker type II. Mean time to walking was 2 d and all patients returned to preoperative functional status. There were no major complications or revisions. Successful TKA relies on restoration of mechanical axis, which is improved with CAS. All patients in this sample had mechanical axis restored to within 3 degrees, which prevents off-axis loading and can lead to greater implant survivability. This study, while small, suggests that navigation systems for TKA can play a role in delivering acceptable outcomes to patients undergoing primary TKA for tibial plateau fracture. While CAS is an option for TKA in tibial plateau fractures, it is certainly not the standard

of care^[21].

TKA AS PRIMARY TREATMENT

Most authors evaluating this approach comment on the technical aspects of arthroplasty as the primary treatment for tibial plateau fracture. Preoperative planning as always is the first major step in ensuring an optimal outcome. Implant type and level of constraint should be determined based on pre-operative radiographs, assessing whether or not the fracture line likely compromises the medial or lateral collateral ligaments. In this case, a rotating hinge prosthesis should be selected. In terms of timing of surgery, all authors discussed the immediate post-injury period as ideal for surgery, as the primary goal of arthroplasty was early mobilization to prevent the sequelae of prolonged non-weightbearing. One study reported a mean surgical delay of 7.5 d, while another reported 4 d of mean surgical delay^[22]. While it makes sense to allow a modest period of time for soft-tissue healing to prevent infection, we recommend allowing no more than three weeks before definitive repair. In most cases, unless prevented by the fracture site, medial parapatellar approach to the joint was used. Some authors utilized tibial tubercle osteotomies in all patients as a protocol^[13], while other authors managed to avoid it entirely. For the bony cuts, the distal femoral cut should be 2.5 cm distal to the epicondyles and the tibial cut should allow joint line positioning 1 cm above the fibular head^[19]. In terms of selecting prostheses, the choice between a hinged system and posterior-stabilized is made based on the integrity of the ligaments. In the studies evaluated, constrained, PS, rotating hinge and super stabilized prostheses were all used. If the fracture line is compromising the stability of the medial or lateral collateral ligaments, a rotating hinge prosthesis is best option^[22]. Vermeire *et al.*^[13] has noted equally satisfactory results in using PS modular prostheses and cemented rotating hinge implants. This group also used stemmed cemented components, which allowed early weight bearing in these elderly patients. In series published on this topic, more attention should be paid



Figure 2 Primary total knee arthroplasty following tibial plateau fracture. Proximal tibial fracture with poor bone stock and post-operative radiograph showing rotating hinge prosthesis.

in the future to discussing the reasoning behind implant selection. As most studies were retrospective in nature, surgeon preference was often cited as the reasoning behind surgical decisions. Patellar resurfacing was variable between studies, with some groups performing this step systemically in all patients, others in select patients, and other groups not at all. In terms of managing bony loss, usually in osteoporotic or comminuted fractures most authors made use of wedges, augments and bone grafts to deal with osseous defects in these patients. One paper expanded on this and recommended wedges or cone shaped metallic augments or the patient's own bone for fixing defects^[22]. Fracture reduction and joint alignment to determine pre-injury joint congruity and rotation, making use of diaphyseal landmarks is one approach used by Boureau *et al*^[23]. If this cannot be performed accurately, surgeons should elect to approach the case as a revision TKA with major bone loss^[22]. Simultaneous bony stabilization was used by all authors in this review (Figure 2).

RESEARCH RESULTS

TKA for ptoa following tibial plateau fracture

A number of studies exist in the literature that identified patients who underwent TKA following tibial plateau fractures that were managed operatively and nonoperatively. Most of these series have looked at outcomes in terms of function and pain scores, patient satisfaction as well as stability, survivability of prosthesis, and incidence of common complications of TKA, such as infection, component loosening or periprosthetic fracture. Weiss *et al*^[16] found improvements in KSS for pain and function in a group of 62 patients, with excellent or good results in 48 of those patients. Optimal component positioning had a positive impact on outcome. Civinini *et al*^[18] had a good result in 18 of 25 patients undergoing TKA for this indication. Alternatively, poor outcome was related to complications in this group of patients. Range of motion and stability was significantly improved in this group. Saleh *et al*^[17] reported HSS knee scores that improved from 51 pre-operatively to 80 post-operatively. Twelve/fifteen outcomes were considered good or excellent in their paper. Scott *et al*^[14] matched the patients undergoing TKA for prior tibial plateau fracture with controls undergoing TKA for primary OA. Absolute OKS scores

did not differ significantly between the two groups at five years. This is in sharp contrast to other studies of this nature which highlight poorer knee outcomes based on KSS and HSS knee scores. The authors here suggest that OKS is a more-patient centered scale that is based on the experience of the patient, while the HSS and KSS scales may be reporting more physician-centered data that might ignore the fact that patients are actually satisfied with their implants despite clinically discouraging measures such as range of motion, contracture and instability^[14]. Lizaur-Utrilla *et al*^[15] performed a similar comparison. The authors of this study challenged the notion that the outcomes between TKA for PTOA and routine TKA are significantly different. This study had a homogenous surgical and postoperative protocol not seen in most of its contemporaries. Functional outcomes including WOMAC pain score, KSS knee and function scores, ROM, SF12 physical and mental scores did not differ significantly between the two groups. The authors posited that a protocolized surgical scheme, which involved separate removal of hardware and standardized exposure strategy, can improve outcomes for patients undergoing TKA for PTOA secondary to tibial plateau fracture^[15]. Abdel *et al*^[24] followed 46 patients over 15 years and found that KSS and ROM both improved significantly from pre-operative values.

TKA as primary treatment

More recently in the literature is a group of studies analyzing the success of TKA as a primary treatment of tibial plateau fractures in elderly patients. Considering that TKA for PTOA is a more established concept than primary TKA for tibial plateau fracture, the series presented in this section are also smaller. The first small series performed primary TKA on four elderly patients with tibial plateau fractures. Excellent results were obtained in three cases and a fair result in one. No reoperations were required, and radiographic follow up showed optimal alignment with no evidence of loosening^[25]. Vermeire *et al*^[13] selected 12 patients who underwent primary TKA within 3 wk of tibial plateau fracture. Seven patients had outcomes rated as excellent and median final knee score was 78 and function score was 58. The authors concluded that primary TKA for tibial plateau fracture is an acceptable alternative to fracture fixation in patients with difficult fractures or poor

bone quality who would likely end up requiring a TKA^[22]. Malviya *et al.*^[26] studied a group of elderly patients who underwent primary TKA for either tibial plateau or distal femoral fractures. Eighty-one percent of elderly patients with fractures about the knee returned to preoperative functional status. Patient satisfaction was similarly excellent although KSS were not overall excellent (90.2 knee and 35.5 for function). The authors remind us to consider that this patient population likely did not have excellent knee function to begin with^[26]. Haufe *et al.*^[27] limited their series to only patients with fractures of the tibial plateau. They found improved mean knee scores for patients undergoing the procedure. Their paper contended that in the elderly population, tibial plateau fractures represent a great technical challenge in primary repair and primary TKA can avoid this challenge while presenting the patient an opportunity for full weight-bearing in the early postoperative period, which is likely to reduce some of the morbidity associated with delayed weight-bearing following ORIF. An interesting finding in this paper was that the subgroup of patients treated in the later part of the series (2013-2014) showed better functional results than the overall group, potentially indicating that we can expect improved results for this procedure as experience and technology progress^[27]. Another group examining the outcomes of TKA as primary treatment of periarticular fractures about the knee in elderly patients did not find evidence to support the idea that primary TKA in these patients preserves patient autonomy as widely suggested. Patient autonomy was measured using the Parker Score of mobility, and found a significant decline following surgery (7.2 pre op to 4.6 post op). Moreover, autonomy decline was evidenced by only 7/15 patients returning to pre-operative level of independence and only 11/15 patients returning home following surgery. While this group did stratify proximal tibial from distal femoral fractures, the knee scores did not differ significantly between the groups, allowing us to generalize these results to our specific discussion of tibial plateau fractures^[23]. Parratte *et al.*^[22] highlighted 16 cases of tibial plateau fractures treated primarily with TKA in a multicenter retrospective trial in France from 1990-2010. While functional results of the knee were considered good, there was a significant loss of autonomy in this group of patients, as seen in other studies of its nature^[22].

COMPLICATIONS

TKA for PTOA

Despite an acceptable functional outcome, Weiss *et al.*^[16] showed a great deal of complications. Twenty-six percent of patients encountered post-operative complications, most commonly stiffness and wound breakdown. Of note, there were 5 intraoperative patellar tendon ruptures in this sample, all of which were repaired successfully during surgery. For Civinini *et al.*^[18] 8 of 25 knees encountered complication, including patellar tendon rupture and two implant failures. Saleh *et al.*^[17] also reported a high rate of

postoperative complications, 11/15 patients experienced some sort of complication. There were two early patellar tendon ruptures and three patients requiring treatment for early wound complications with prolonged drainage and oral antibiotics. For the controlled trial conducted by Scott *et al.*^[14], rates of intraoperative complication were higher in the PTOA cohort although the incidence of early and late complications failed to differ significantly. In the trial conducted by Lizaur-Utrilla *et al.*^[15], the PTOA group did have significantly more complications than the primary patients, including patellar tendon rupture and wound infection, however they weren't serious enough to affect the functional outcomes. Shearer *et al.*^[28] determined that in patients with soft tissue graft coverage, more common in this population, outcomes were poorer.

In all series reviewed, a number of patients experienced post-operative stiffness, some requiring manipulation under anesthesia. In the papers reviewed, the rates of manipulation under anesthesia for persistent stiffness ranged from 3.44%-20%^[14-18]. Several papers reported repeat manipulations. Stiffness is therefore a major complication associated with arthroplasty following previous ORIF of the tibial plateau. Another common complication experienced throughout the literature is intraoperative avulsion of the patellar tendon and/or the MCL, owing to exposure difficulty in knees with significant scar tissue from previous surgery.

Overall, the type of complications encountered were similar and reflected the complex nature in performing TKA in knees with prior injury. Methods to avoid patellar tendon rupture and to preserve the delicate soft tissue are recommended to avoiding some of the common problems encountered by these authors. In Abdel *et al.*^[24]'s 15-year follow-up, they found that from the 5 to 15 year follow-up, there were only 2 additional complications (periprosthetic fracture and periprosthetic infection), leading the authors to conclude that if the early complications of TKA can be avoided, long-term survivorship free from aseptic loosening and revision (96% and 82%, respectively) can be achieved in pts undergoing TKA for this indication^[24].

Primary TKA

The overall complication rate for primary TKA following tibial plateau fracture is higher than that for primary TKA in the general population but lower than that for TKA following operative repair of the tibial plateau by ORIF^[23]. Overall complication rates of the studies included ranged from 9.5%-33%. The most commonly reported complications were infectious and wound complications, stiffness and flexion contracture, as well as periprosthetic fracture. All authors reported at least one case of wound complications, with many patients requiring re-operation for debridement or revision. Parratte *et al.*^[22] and Boureau *et al.*^[23] both reported problems with knee stiffness with 8% and 19% requiring closed manipulation under anesthesia, respectively. Component loosening was seen radiographically in one patient who required reoperation. Vermeire *et al.*^[13] discussed the case of a patient with a

periprosthetic fracture which was repaired using plates and screws. Other less common complications, which were not unique to this procedure, included hematoma formation and DVT/PE, reported in several papers. In the 12-patient analysis by Vermeire *et al*^[13], three developed spontaneously resolving hematomas and one developed a lower extremity DVT treated with low-molecular weight heparin.

DISCUSSION

The discussion of TKA in patients with fractures of the tibial plateau is two-fold. First, patients who develop complications of fracture management, most commonly post-traumatic osteoarthritis of the knee, can be managed with arthroplasty. It is most commonly considered in older patients with less demand, as arthroplasty is usually not preferred in younger patients who may require several revisions throughout their lifetime. Our review shows that while good results may be achieved, complication rates are high and the procedure requires thoughtful decision making and careful attention to avoid complications. Avoiding the early complications can result in acceptable function and survivability. The body of literature regarding this topic is well-rounded, and will benefit in future years from longer-term data on patients and evolving technology in total joint replacement. While recognizing that there is no argument to be made for primary TKA replacing ORIF for primary treatment of tibial plateau fractures, there is a certain group of patients for whom a primary TKA may be indicated. It has been demonstrated in this literature review that fixation failure is more common in elderly patients with poor bone stock. In patients with low demand, poor bone stock in whom we can predict a high rate of TKA, primary arthroplasty should be considered as a primary treatment for fractures of the tibial plateau.

With that in mind, the second discussion is that of TKA as primary treatment for tibial plateau fractures, which is usually carried out in these older, osteoporotic patients. Most series on this topic are small in number and carried out in Europe. While theoretically well-understood to avoid complications of delayed weight-bearing and poor outcomes of fracture fixation, the overall body of literature for this indication is lacking. Currently, the literature which has discussed the use of acute TKA for this injury has been limited to series of elderly patients with poor bone quality. Perhaps expanding the indications for primary TKA in tibial plateau fracture to outside of the group with obviously poor bone may prove to be beneficial for a wider group of patients. However, at this time there is no reason to consider expanding in the indications for primary TKA following a fracture to the tibial plateau. At the same time, it should also be recognized that a high percentage of patients who undergo successful ORIF will need prosthetic knee replacement down the road. This is well established and accepted in the world of orthopaedic trauma. Refining the indications and technique for performing a primary TKA after tibial plateau fracture is an important task. Future effort should be placed in identifying patients with

high risk of poor outcome (either failed fixation or PTOA) and evaluating TKA as an alternative to fixation in this group. Our paper shows clearly that for the elderly patients selected, primary TKA is a potentially valuable option to address their injury. Slowly expanding the indications with future series will possibly show that younger patients with healthier bone can benefit as well. For now, ORIF remains the standard of care for these patients. Large cohort, multi-center data, as well as head-to-head comparison of the two methods is going to be required to determine the true benefit of primary TKA for patients with fractures of the tibial plateau.

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Failed medial patellofemoral ligament reconstruction: Causes and surgical strategies

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Abstract

Patellar instability is a common clinical problem encountered by orthopedic surgeons specializing in the knee. For patients with chronic lateral patellar instability, the standard surgical approach is to stabilize the patella through a medial patellofemoral ligament (MPFL) reconstruction. Foreseeably, an increasing number of revision surgeries of the reconstructed MPFL will be seen in upcoming years. In this paper, the causes of failed MPFL reconstruction are analyzed: (1) incorrect surgical indication or inappropriate surgical technique/patient selection; (2) a technical error; and (3) an incorrect assessment of the concomitant risk factors for instability. An understanding of the anatomy and biomechanics of the MPFL and cautiousness with the imaging techniques while favoring clinical over radiological findings and the use of common sense to determine the adequate surgical technique for each particular case, are critical to minimizing MPFL surgery failure. Additionally, our approach to dealing with failure after primary MPFL reconstruction is also presented.

Key words: Medial patellofemoral ligament; Failed medial patellofemoral ligament reconstruction; Trochleoplasty; 3D-CT in patellofemoral surgery

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Core tip: An increasing number of revision surgeries of the reconstructed medial patellofemoral ligament (MPFL) will be seen in the foreseeable future. There are several reasons for this trend: (1) The increasing number of primary MPFL reconstructions; (2) The fact that more and more orthopedic surgeons perform this surgical technique; and (3) The high percentage of patients returning to sport after this type of surgery and thereby put the reconstructed ligament at risk. Our paper tries to answer a crucial question: What must we do to reduce the number of failed MPFL reconstructions? Furthermore, we analyze our approach to dealing with failure after MPFL reconstruction.

Sanchis-Alfonso V, Montesinos-Berry E, Ramirez-Fuentes C, Leal-Blanquet J, Gelber PE, Monllau JC. Failed medial patellofemoral ligament reconstruction: Causes and surgical strategies. *World J Orthop* 2017; 8(2): 115-129 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/115.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.115>

INTRODUCTION

What is a failure of a medial patellofemoral ligament (MPFL) reconstruction? A MPFL reconstruction in patients with chronic lateral patellar instability (CLPI) fails when there is either recurrence of the instability, disabling anterior knee pain (AKP) or a combination of both. While this usually demands a revision surgery, there are some more questionable cases. It ultimately depends on the activity level and how much this instability or AKP affects a patient with the same ligament deficiency. The higher the physical requirements are the greater the disability caused by the malfunctioning MPFL. Patients with low physical requirements will tolerate instability much better and will have less instability and/or pain. In addition, standard scales (Kujala, IKDC) used to measure results in "normal" people are not practical for athletes due to their low sensitivity. Instead, functional tests that includes specific sporting gestures (cutting, pivoting, stopping, etc.)^[1] should be used in this specific group of patients.

Shah *et al.*^[2], in a systematic review (meta-analysis-level of evidence II) of complications and failures associated with the MPFL reconstruction in patients with a CLPI, found that the complication rate associated with this procedure (26%) is not at all insignificant even though MPFL has a high success rate. Therefore, it is important to inform the patient of the potential risks of this surgery before the surgery. These authors also showed that instability represents 32% of all the complications (52/164) found in MPFL reconstruction^[2]. This recurrence of instability may be secondary to a ruptured or elongated MPFL graft, or secondary to the failure to recognize other risk factors for instability. However, Parikh *et al.*^[3] found a slightly smaller rate of complications (16%) in a

case series (level of evidence IV). Surprisingly enough, almost half of those complications resulted from technical problems or surgical errors. Ultimately, most failed MPFL reconstructions result from surgeon-dependent factors. Schneider *et al.*^[4] reported a low rate of reoperations after an isolated MPFL reconstruction, specifically 3.1% (95%CI: 1.1%-5.0%), in a systematic review and meta-analysis published in 2016. However, this study only reported on short term results. Similarly, the recurrence of instability and the persistence of apprehension was 1.2% (95%CI: 0.3%-2.1%) and 3.6%, respectively (95%CI: 0%-7.2%).

The increasing number of primary surgeries will lead to a higher number of MPFL revision surgeries in upcoming years. Schneider *et al.*^[4] showed that 84.1% (95%CI: 71.1%-97.1%) of patients return to sports after an isolated MPFL reconstruction. Thus, the return to sports puts the reconstructed ligament at risk and so its break again due to an indirect trauma to the knee.

This paper tries to answer a crucial question: What must we do to reduce the number of failed MPFL reconstruction? An approach to dealing with failure after primary MPFL reconstruction is also presented.

MPFL RECONSTRUCTION FAILURE DUE TO AN INCORRECT SURGICAL INDICATION - INAPPROPRIATE SURGICAL TECHNIQUE/PATIENT SELECTION

The first requirement for a successful MPFL reconstruction is, logically, to properly select the patient. The ideal indication of an isolated MPFL reconstruction would be a CLPI with at least two documented episodes of dislocation, and confirmation of dislocation with examination under anesthesia, in a patient with a TT-TG distance of less than 20 mm, a positive apprehension test up to 30° of knee flexion, a patellar Caton-Deschamps index of less than 1.2 and trochlear dysplasia grade A^[5]. A double-bundle MPFL reconstruction is recommended given that it is associated with a lower failure rate than single bundle reconstruction^[6].

On the other hand, an MPFL reconstruction is not indicated in patients with AKP without patellar instability. Neither is it indicated for excessive lateral patellar tilt and/or lateral patellar subluxation on imaging without a history and a physical examination for CLPI. Lateral patellofemoral instability, with at least 2 documented episodes of patellar dislocations and a physical examination demonstrating patellar dislocation, is the primary indication for an MPFL reconstruction^[5]. Pain and "giving out" episodes are not sufficient criteria for establishing this diagnosis. Examination under anesthesia may be necessary to confirm lateral patellar instability objectively (Figure 1). A MPFL reconstruction should not be performed if the patella cannot be laterally dislocated.

An MPFL reconstruction is not aimed at "pulling"



Figure 1 With the patient under anesthesia, we verify that the patella can be dislocated laterally.

the patella into position, but rather at stabilizing it once the patellofemoral tracking has been corrected. That is so once the patella is in an adequate position within the trochlear groove. Therefore, an isolated MPFL reconstruction is not indicated to eliminate patella J-tracking.

Finally, an isolated MPFL reconstruction should not be performed with fixed lateral patellar dislocation in knee flexion (Figure 2). In this situation, the main problem is the retraction of the extensor mechanism of the knee and a flat lateral condyle, factors that contribute to secondary MPFL insufficiency^[7]. Therefore, the correct treatment for these cases would be a lateral retinaculum lengthening, lengthening of the rectus lateralis tendon and quadriceps tendon lengthening^[7]. If needed, the lateral condyle may be raised. Then, an MPFL reconstruction may be performed as the final surgical step^[7].

MPFL RECONSTRUCTION FAILURE DUE TO A TECHNICAL ERROR

According to Parikh *et al.*^[3], 47% of the complications that occur after MPFL reconstructive surgery are related to technical errors.

The most frequent and significant technical mistake that can lead to MPFL reconstruction failure is to position the femoral tunnel incorrectly although we can see both an incorrect femoral fixation point associated with an incorrect patellar fixation point in some cases (Figure 3). Femoral fixation point is crucial as it determines the length change behavior of the graft and therefore the graft tension at different angles of knee flexion, that is, it determines the kinematic behavior of the graft^[8]. A normal MPFL is tighter in extension than in flexion. If the graft tightens when the knee is flexed, stiffness, pain and patellar overload will occur^[8]. This situation typically occurs when the femoral fixation point is placed excessively anterior. In the mid-term, it may produce a severe patellar chondropathy (Figure 4) and patellofemoral osteoarthritis in the long-term (Figure 5). Therefore, it is essential to accurately check the femoral tunnel placement intra-operatively.

An incorrect femoral fixation point can lead to excessive obliquity of the graft, making it ineffective in preventing an excessive lateral patellar displacement in the first 40 degrees of knee flexion. This would explain a persistent lateral dislocation of the patella with a healthy graft. In this case, correction of the instability can be accomplished simply by modifying the fixation points despite the presence of additional anatomical factors predisposing to lateral instability such as severe trochlear dysplasia (Figure 6).

Schöttle *et al.*^[9] have recommended the use of intraoperative fluoroscopy to more accurately placed the femoral tunnel. Obtaining a true lateral image intra-operatively is imperative when using this radiographic method. Unfortunately, this is not always easily accomplished. In addition, several authors have observed that Schoettle's radiological method, universally accepted as the gold standard, does not guarantee a true anatomical fixation point in many cases^[10] even with the use of a true lateral radiograph^[11]. The radiological method is only an approximation and should not be the sole basis for femoral attachment location. The most accurate method for pinpointing anatomic placements is to perform a large enough incision to identify the most relevant anatomic landmarks. In this case, it is the adductor magnus tendon (AMT). The AMT is readily identified and leads right to the MPFL origin on the femur, situated 10.6 ± 2.5 mm distal to the apex of the adductor tubercle and parallel to the long axis of the femur^[12]. The great variability in the location of the adductor tubercle (Figure 7) explains the variability in the location of the femoral insertion of the MPFL. This explains the large number of errors when using Schoettle's method to identify the femoral anatomic fixation point of the MPFL.

Relative to the MPFL patellar insertion site, Kikuchi *et al.*^[13] have recently shown that it is largely consistent. Most of its fibers insert more into the vastus medialis obliquus (VMO) and vastus intermedius than into the patella. Unlike the femoral fixation point, accuracy in placing the patellar fixation has been shown to be less important^[8]. In fact, the MPFL length changes depend on the femoral attachment site more than on the patellar attachment site^[8].

Another technical error that can lead to surgical failure is excessive graft tension. The concept of "tensioning" the MPFL graft is not correct from a conceptual point of view given that in its native state the MPFL is not under constant tension^[5]. It only comes under tension when a lateral force acts on the patella displacing it laterally. Philip Schoettle makes a very intelligent simile, comparing the MPFL to a dog leash. The leash is loose most of the time, except when the dog (the patella) wants to run away (dislocate), and then it becomes tight. If the leash (the MPFL) were tight all the time, it would choke the dog. Continuing with our simile, it would create a high patellofemoral pressure that would lead to osteoarthritis. *In vivo*, MPFL kinematic studies have shown that MPFL length was longest from 0° to 60° of knee flexion and decreased significantly during flexion from 60° to 120°,

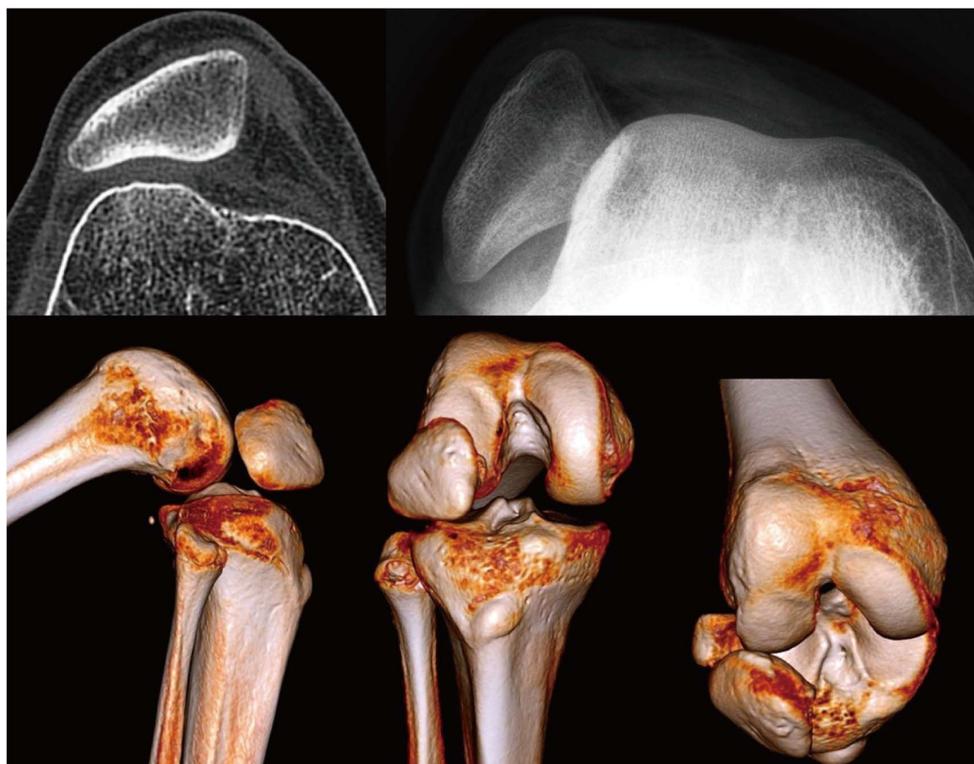


Figure 2 Lateral patellar instability in flexion. The patella dislocates laterally beyond 40° of knee flexion.



Figure 3 The femoral tunnel is non-anatomic. A very serious mistake when performing patellar tunnels. We can see that the patellar tunnels are drilled through the medial facet articular surface and exit through the central dorsal aspect of the patella.

thereby checking excessive patellofemoral compression force during high degrees of knee flexion^[8]. Additionally,

the MPFL is not tight when the patella is not subject to a lateral displacing force^[5].

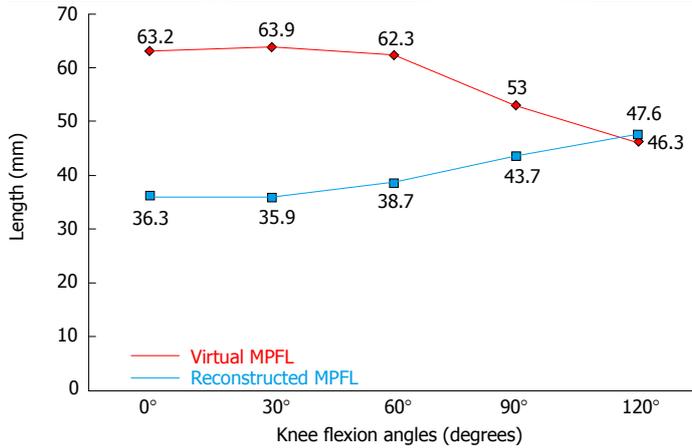


Figure 4 Patient of 19 years of age with severe anterior knee pain and lateral patellar instability. Three years ago, he had a MPFL reconstruction with a single bundle semitendinosus tendon graft. During the physical examination, there was no disorder in patellofemoral tracking. With the patient under general anesthesia, the patella could not be dislocated beyond 40° of knee flexion. We note that the femoral tunnel of the MPFL reconstruction is too anterior, which is a serious mistake. There is also severe chondropathy of the articular surface of the patella. We can see that the distance between the patellar fixation point and the femoral fixation point increases with knee flexion. Clinically, this causes an increase in patellofemoral pressure during knee flexion that could justify the severe patellar chondropathy the patient has. The anatomic MPFL reconstruction, using the contralateral semitendinosus tendon with a double bundle technique, led to the resolution of all the patient's symptoms. MPFL: Medial patellofemoral ligament.

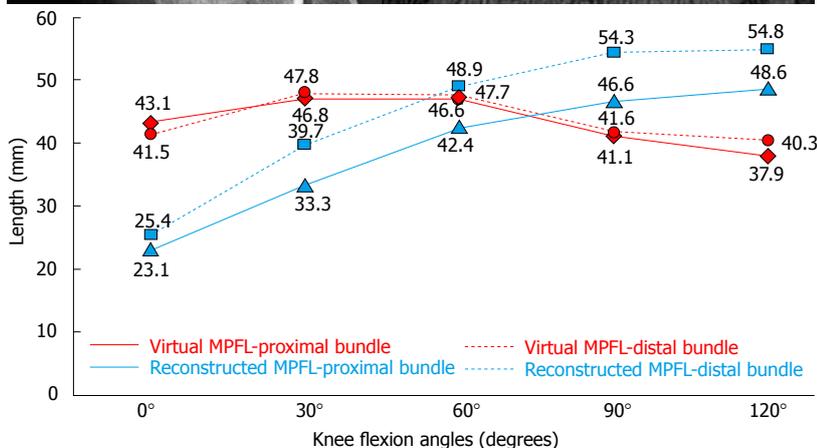
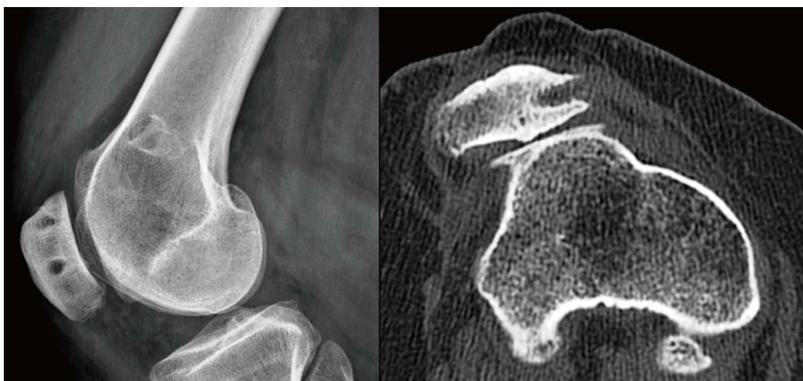


Figure 5 Patient 28-year-old, with very severe anterior knee pain and lateral patellar instability. During the physical examination, we saw a clear patellofemoral mal-tracking and we were able to dislocate the patella laterally beyond 60° of knee flexion. She has been operated on several times over the last 8 years: A lateral retinacular release, proximal realignment, an osteotomy for medialization of the tibial tubercle and MPFL reconstruction. We note that the femoral tunnel is too proximal and anterior. The distance between the patellar fixation point and the femoral fixation point increases significantly with knee flexion. Clinically, this increases patellofemoral pressure significantly during knee flexion, which could explain the severe patellofemoral osteoarthritis the patient has. In this specific case the pain disappeared after a sulcus deepening trochleoplasty. We performed an anatomic double bundle MPFL reconstruction with a semitendinosus tendon graft and the lateral patellar instability also disappeared completely. MPFL: Medial patellofemoral ligament.

How to avoid excessive tension on the graft?

Use the trochlea to reduce the patella when the graft is fixed by having the patella fully engaged in the trochlea at this point - 30° of knee flexion is generally sufficient

to accomplish it^[8]. Do not pull the graft tight at the time of fixation. If the other knee is asymptomatic, the aim is to reproduce the degree of patellar mobility of the contralateral healthy knee. We must note that tighter is

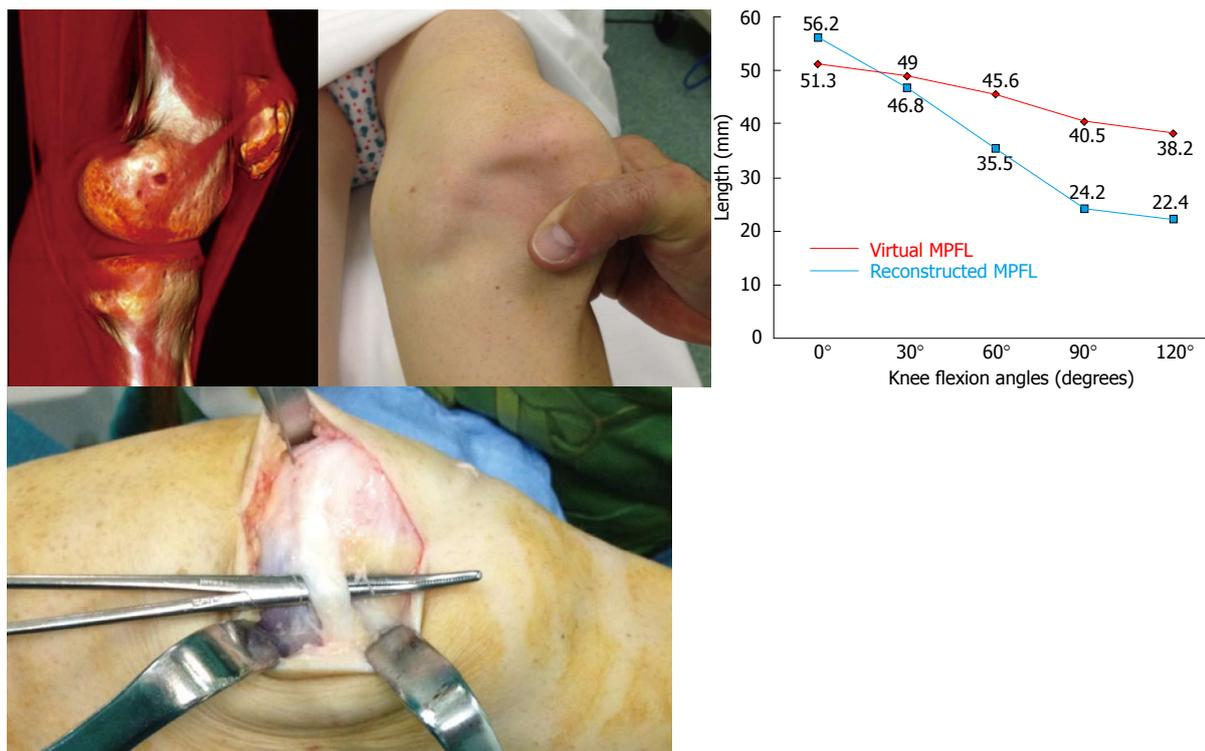


Figure 6 Very severe left anterior knee pain in a female patient of 30 years of age who had a medial patellofemoral ligament reconstruction using partial thickness quadriceps tendon. Clinically, no patellofemoral tracking disorders were found. With the patient under general anesthesia, the patella could be dislocated laterally despite an intact MPFL. In this specific case, the instability is due to an inadequate graft length change pattern during knee flexion and extension. After an anatomic double bundle MPFL reconstruction, using a semitendinosus tendon graft, the lateral patellar instability as well as the pain were completely resolved. MPFL: Medial patellofemoral ligament.



Figure 7 The anatomic variability of the adductor tubercle may explain the anatomic variability of the medial patellofemoral ligament femoral fixation point.

never better in this operation.

Case example

In Figure 8, you can see a failed MPFL reconstruction due to poor positioning of the femoral fixation point. The value of this particular clinical case is threefold. First, there are no confusion variables that can influence the result as the most important factors predisposing to instability were normal (no patellar tilt, no patella alta, normal TT-TG distance, and no trochlear dysplasia). Secondly, the contralateral knee was operated on with an

excellent result, and therefore we were able to compare the femoral fixation point of the failed operated knee with the successfully treated contralateral knee. In the third place, the patient was a professional athlete with high demand on her knees and therefore the surgical precision had even a greater role. While minor surgical malpositioning of the femoral tunnel might be well tolerated in non-athlete patients, it is not the case in an athlete. The only differentiating factor between both knees was the position of the femoral fixation point, with maximum physical demand of both knees.

Figure 8 shows the case of a 20-year-old female, a professional classical and contemporary ballet dancer, operated on for lateral patellar instability in both knees, secondary to an obvious trauma during sport practice. She had had two clear dislocation episodes in each knee, one of which required a reduction in the emergency department. A double bundle semitendinosus reconstruction was performed in her left knee with an excellent result at 10 years after surgery. A single bundle partial thickness quadriceps tendon reconstruction was performed in the right knee. One year and a half after surgery, she complained of severe disability while practicing sports with pain and instability. She had AKP that caused her to develop defense mechanisms during physical activities to mitigate the pain. They included avoiding full knee extension while doing splits, avoiding performing full squats and squatting with the upper

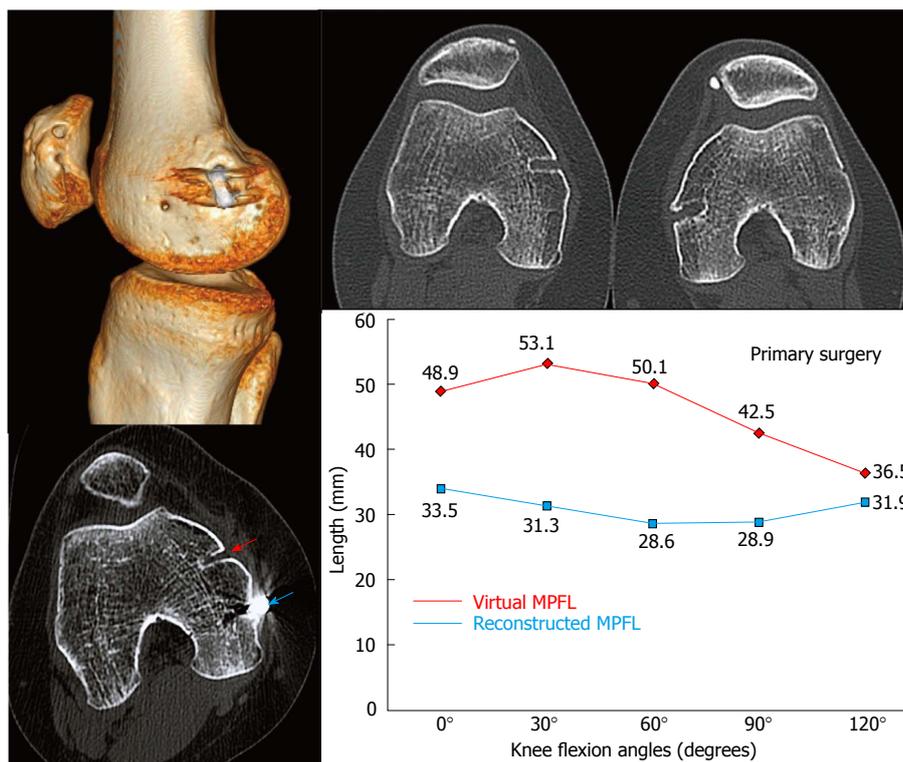


Figure 8 This patient had a bilateral medial patellofemoral ligament reconstruction for lateral patellar instability with no anatomical predisposing factors. The left knee has an anatomic femoral tunnel with an excellent clinical result. However, the right knee has a femoral tunnel that is too anterior and this fact is responsible for the non-physiological behavior of the graft. It is isometric from 0° to 120° of knee flexion. After anatomic MPFL reconstruction, the symptoms disappeared completely (Reproduced with permission from Springer). MPFL: Medial patellofemoral ligament.

body flexed forward in order to reduce patellofemoral compression force and therefore the pain. She also showed a very severe patellofemoral crepitus and pain with knee flexion. She also had instability and apprehension. To perform "spiral twists" in her classical ballet activity, she avoided knee flexion from 0 to 30 degrees because of the fear that the patella "would slip laterally". So, she also developed a defense mechanism against instability. She was then operated on again on the right knee. A semitendinosus double bundle graft was performed with an anatomic femoral fixation point. Four years after surgery, the clinical outcome was excellent. She was pain- and instability-free and was involved in high-level competitive sports with no limitations. Additionally, the previous severe painful crepitus completely disappeared.

How should we plan a revision surgery?

When we consider a revision surgery in a patient with a failed MPFL reconstruction, a dynamic 3D - Computed Tomography (CT) study at 0°, 30°, 60°, 90° and 120° of knee flexion to evaluate the kinematic behavior of the graft *in vivo*^[5,8] should be performed. In the left knee of the patient in Figure 8, the length change behavior of the graft, although non-anatomic, was similar to that of a graft fixed anatomically in the femur, which is isometric from 0° to 30° of knee flexion. However, the first surgery performed on the right knee with a non-anatomic technique showed an isometric behavior between 0° to 120° of knee flexion, clearly different to the native anatomic MPFL. Therefore, a non-anatomic femoral fixation point is not necessarily associated with a failed reconstruction. In other words, if a patient with

a reconstruction with a non-anatomic femoral fixation point which behaves physiologically has pain and instability, we must rule out other causes than the MPFL femoral fixation point as responsible for the pain and/or instability^[8].

After performing an anatomic femoral fixation point during the revision surgery in the right knee the result was excellent, with the resolution of pain, crepitus, and instability. Therefore, we can conclude that the technical error in placing the femoral tunnel too anteriorly was the cause of the failed surgery in the right knee. On the other side, the left knee operated on with a non-anatomic femoral fixation point showed excellent outcome at ten years of follow-up. This gives rise the following question: Is the anatomic femoral tunnel position so relevant in MPFL reconstruction?

Femoral tunnel malposition does not always lead to a poor outcome^[8,14]. In our experience, those ligaments with a non-anatomic femoral fixation point that behave kinematically as an anatomic MPFL, as occurs in the left knee of our "case example", are those with an excellent clinical outcome at long-term follow-up^[8,14,15]. However those non-anatomic grafts that do not have a physiologic kinematic behavior, as in the right knee, are those that have a poor clinical outcome^[8]. Therefore, what should we do? We believe every MPFL graft should be placed anatomically, because an anatomic femoral tunnel position maximizes outcomes and provides the best chance of excellent short-term and long-term success. In summary, an anatomic MPFL reconstruction of the MPFL is a fast and reproducible way to achieve an MPFL that is long enough to act as an isometric "leash" from 0° to 30° and becoming loose after 30° of knee flexion. In

conclusion, to avoid complications, the relevant anatomy and biomechanics must be identified and restored.

FAILED MPFL RECONSTRUCTION DUE TO AN INCORRECT ASSESSMENT OF THE CONCOMITANT RISK FACTORS FOR INSTABILITY

Instability occurs between 0° and 30° range of knee flexion in about 85% of the cases of CLPI. In these degrees of range of motion, patellar stability against the lateral displacing forces of the patella relies mainly on the MPFL^[5]. Beyond 30° of knee flexion, the stability of the patella mainly depends on the bony anatomy of the femoral trochlea. While an isolated MPFL reconstruction it is sufficient in most cases in the former group of patients, this might fail to control the instability in the second group. Surgical failure in MPFL reconstructions are due to incorrect diagnosis where non-treatment of additional lateral patellar instability risk factors such as trochlear dysplasia are not addressed. Apprehension that is relieved at 30° of knee flexion suggests a good clinical result with an isolated MPFL reconstruction. An apprehension beyond 60° of knee flexion suggests a severe trochlear dysplasia, or a significant patella alta or both.

The surgical treatment of a patient with lateral patellar instability should be an individualized treatment as the Lyon School advocates. Awareness of the major risk factors for the development of CLPI (trochlear dysplasia, patella alta, TT-TG distance greater than 20 mm and patellar tilt greater than 20°) is required^[16]. Among all these factors, the most relevant is trochlear dysplasia. Interestingly, Nelitz *et al.*^[17] observed that severe trochlear dysplasia (Dejour type B-D) was significantly more frequent in the surgical failure group (89%) than in the non-surgical failure group (21%) in an analysis of failed surgery for patellar instability. However, they did not find differences relative to the patellar height ratio (Insall-Salvati index) and the TT-TG distance between the two groups. Considering that trochlear dysplasia seems to be a major risk factor for failure of operative stabilization of CLPI, reconstruction of the MPFL as well as trochleoplasty should be considered in such cases. Wagner *et al.*^[18] also found that high degrees of trochlear dysplasia correlate with poor clinical outcome because the MPFL graft might be overloaded given that there is more instability in dysplastic situations. They conclude that trochleoplasty must be considered in cases with high degrees of trochlear dysplasia. However, this conclusion was only based on one case series study (level of evidence IV). Similarly, Kita *et al.*^[19] reported that severe trochlear dysplasia is the most important predictor of residual patellofemoral instability after isolated MPFL reconstruction. They have shown that a combination of severe trochlear dysplasia with an increased TT-TG distance was more likely to affect the outcomes of MPFL reconstruction^[19]. They also suggested that additional stabilization procedures should

be performed in the surgical treatment of such patients. Matsushita *et al.*^[20] demonstrated that isolated MPFL reconstructions performed in CLPI with a TT-TG distance greater than 20 yielded similar clinical outcomes to those performed with a TT-TG under 20. Moreover, there were no re-dislocations in either group. They concluded that a TT-TG distance greater than 20 mm may not be an absolute indication for medialization of the tibial tubercle.

Surgical pearl

The trochleoplasty procedure not only corrects the trochlear dysplasia, but also the increased TT-TG distance.

Dejour *et al.*^[21] have shown that the sulcus-deepening trochleoplasty is an acceptable revision option for the surgical treatment of patients with persisting patellar dislocation and high-grade trochlear dysplasia. According to Fucentese *et al.*^[22] trochleoplasty is a useful and reliable surgical technique to improve patellofemoral instability in patients with a dysplastic trochlea. However, while improved stability is predictable, pain is less predictable and may even increase following surgery. Interestingly, Schöttle *et al.*^[23] have shown that the risk for cartilage damage after trochleoplasty is low. Be that as it may, overall results are directly dependent on the type of the dysplasia, with a significantly better clinical outcome in type B and D^[22]. In conclusion, severe trochlear dysplasia can be successfully treated with a trochleoplasty.

Case example

In Figure 9, a 25-year-old male patient complained of persistent instability after 2 surgical procedures for CLPI of his left knee. After the first procedure performed 2 years earlier with a single-bundle semitendinosus MPFL reconstruction, he had countless episodes of lateral patellar dislocation. In one of them, he had a patellar osteochondral fracture that was not diagnosed initially, and that brought on locking episodes. A second surgeon had recommended an arthroscopy to remove the intraarticular loose body and to perform an Insall proximal realignment surgery (overlapping of the VMO and a lateral retinaculum release). The patient did not accept this later technique. An isolated arthroscopic loose body removal and a lateral retinaculum release (LRR) were finally performed. Logically, while the locking symptoms were resolved, the instability got even worse. During physical examination, the patella could be dislocated laterally within the whole range of motion of the knee. Imaging studies showed a grade D trochlear dysplasia, a patella alta (Caton-Deschamps of 1.24), a TT-TG distance of 26 mm, and a patellar tilt of 38°. Thus, all the four major risk factors were concomitantly present.

The 3D-CT study revealed a non-anatomical femoral fixation point. However, the *in vivo* kinematic study of the MPFL using 3D-CT showed a graft similar in length to a native virtual ligament and an isometry from 0° to 30° similar to the native healthy ligament. We must note again that a non-anatomic MPFL reconstruction

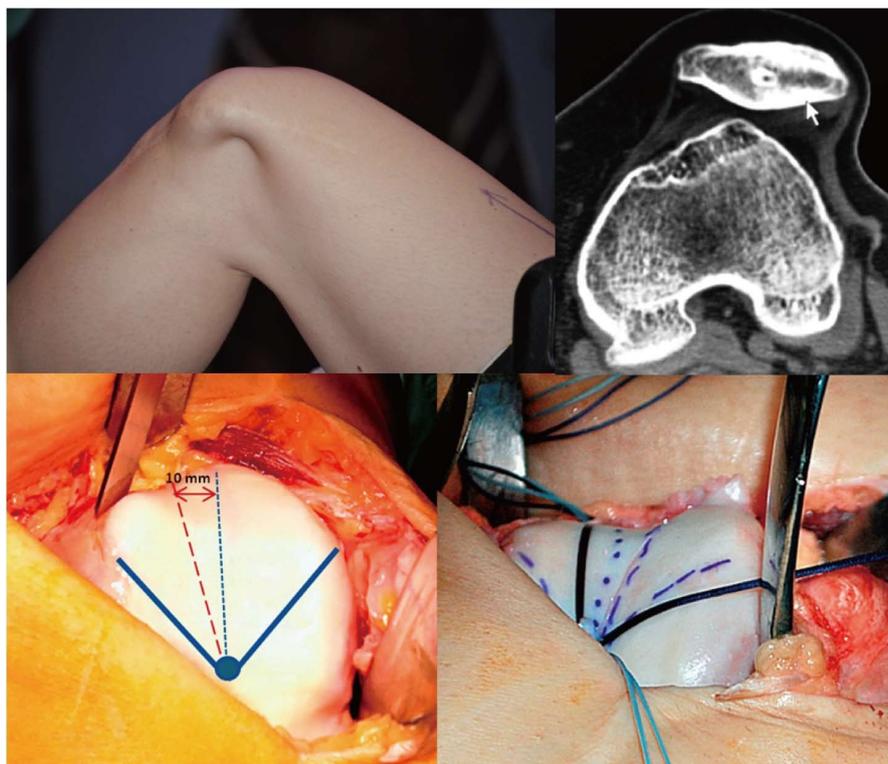


Figure 9 Chronic lateral patellar instability in a patient with grade D trochlear dysplasia. We note that the patella dislocates beyond 40° of knee flexion. Lateral patellar instability resolved after a MPFL reconstruction associated with a sulcus deepening trochleoplasty. MPFL: Medial patellofemoral ligament.

may be able to achieve an adequate change of length pattern of the graft and an optimal isometry from 0° to 30° that leads to excellent long-term clinical result^[8]. Hence, the persistent pain and instability could not be attributed to this non-anatomic femoral fixation point. Thus, causes of graft failure other than the choice of the femoral fixation point should be highlighted. Type D trochlear dysplasia justified the instability at high degrees of knee flexion and might also explain the failure of the MPFL reconstruction.

Since a LRR was performed in the second surgery, medial patellar stability was also tested during the dynamic CT study. This study showed no pathological findings. Extensive LRR might lead to iatrogenic medial patellar instability or a patellar multidirectional instability that would require a reconstruction of the lateral patellar retinaculum^[24-26].

Surgical pearl

Reconstruction of the deep bundle of the lateral patellar retinaculum in cases where the LRR performed in a previous surgery was too extensive should be considered.

A double bundle semitendinosus MPFL anatomic reconstruction associated with a sulcus deepening trochleoplasty was finally performed. After 4 years of follow up, the outcome was excellent.

Trochleoplasty should be only performed when the patella dislocates at high degrees of knee flexion, mostly in revision surgeries.

In this type of trochleoplasty, TT-TG distance and patellar tilt are secondarily corrected to normal physiological values. No tibial tubercle medialization or lengthening of the lateral retinaculum is needed. The remaining major

instability factor, patella alta, is not addressed. However, the threshold from where the patella must be lowered remains unclear^[7]. Moreover, we must note that isolated MPFL reconstruction can decrease patellar height^[27]. Therefore, an isolated MPFL reconstruction may normalize patellar height in patients with CLPI and a borderline patella alta. Furthermore, we must be cautious when performing a distalization of the tibial tubercle because it always implies a certain degree of medialization (a decrease in the TT-TG distance)^[28].

As to the timing of the surgical techniques, patellofemoral mal-tracking correction is needed initially. The trochleoplasty procedure fulfills the goal of neutralizing the lateral displacing forces.

Selective epidural analgesia in selected cases can help to evaluate the active patellar excursion after realignment surgery.

Once the patellofemoral joint is realigned, the second step is to stabilize the joint, which means restoring the passive restraining structures. In this second step, we perform an MPFL reconstruction.

In some infrequent cases and once the MPFL has been reconstructed, patellar tilt may still show an abnormal condition. In this scenario, a third surgical step in the lateral patellar retinaculum may be necessary to achieve a good patellofemoral balance. The decision to operate or not on the lateral patellar retinaculum is an intraoperative decision, based on the patella tilt test^[29].

The patella tilt test is crucial to determine the necessity for surgery on the lateral retinaculum. To do this test, a transverse K wire is placed on the proximal patella, from medial to lateral. With the knee in full extension and at 20° of flexion, the K wire should be parallel to the surgery

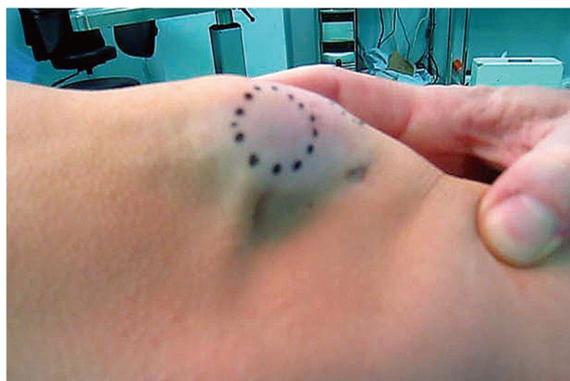


Figure 10 Notice how the medial patellofemoral ligament tightens with the patella's passive medial displacement. In this case, the MPFL can be visualized very well because the patient is slender and has subcutaneous tissue atrophy due to multiple cortisone injections. This finding confirms the fact that the MPFL is not only a stabilizer for patellar lateral displacement but also for medial displacement. MPFL: Medial patellofemoral ligament.

table. If the K wire is tilted (positive test) within this range of motion, a lateral patellar retinaculum lengthening is needed. Lateral retinaculum release is only performed when lengthening is not feasibly.

Also in cases where an extensive LRR had been performed, a reconstruction of this lateral retinaculum would be necessary^[26]. This surgery should only be performed after a detailed radiological assessment of medial patellar instability. Always this technique is performed after the MPFL reconstruction, since this sometimes also stabilize the patella medially (Figure 10).

To guide the patella towards the trochlear sulcus during the first degrees of knee flexion, the MPFL and the lateral retinaculum must interact in a harmonious way. Both ligaments behave similarly to a horse's reins. The rider must hold the reins loosely, without too much tension. If not, the bit (equivalent to the patella) would press into the tongue (equivalent to the femoral trochlea), hurting the horse. However, both reins must have some degree of tension. Otherwise, it would not be possible to lead the horse to the right path.

IS RADIOLOGICAL ASSESSMENT HELPFUL IN DECISION MAKING WHEN OTHER INSTABILITY RISK FACTORS ARE PRESENT? WHAT ARE ITS LIMITATIONS?

In this section, the three anatomical factors most closely related to CLPI from an imaging point of view are analyzed.

Trochlear dysplasia

Although lateral conventional radiography allows the evaluation of the typical signs of trochlear dysplasia^[16,30], it tends to underestimate the degree of dysplasia in comparison to CT and magnetic resonance imaging

(MRI)^[31]. It also requires a true lateral view of the knee to avoid misinterpretation^[32].

CT and MRI also provide a more accurate assessment of trochlear dysplasia. The qualitative analysis is crucial and determines the severity of the dysplasia using the classification described by D. Dejour. In addition, different quantitative measurements have been proposed to determine the depth and inclination of the trochlea in CT and MRI^[33-35]. However, diagnosis of the degree of trochlear dysplasia with CT and MRI is still a challenge. Firstly, a recent study has shown that only low-grade (type A) or high-grade trochlear dysplasia (types B-D) can be reliably distinguished using Dejour's classification, whereas the four-grade classification shows fair intraobserver and interobserver agreements^[31]. Secondly, quantitative measurements of the femoral trochlea are not correlated with the Dejour's classification of trochlear dysplasia and there are no reproducible methods for quantifying types B, C and D severe dysplasia^[36]. And finally, some studies have revealed differences in the surface geometry of the cartilage and subchondral osseous contours with an exacerbated dysplasia due to the overlying cartilaginous morphology^[37-39]. This highlights the importance of evaluating the femoral trochlea with MRI, which provides direct visualization of the cartilage and functional information of articular congruence.

Patellar height

Patellar height has classically been evaluated in standard radiography with the use of different indexes, such as the Caton-Deschamps, the Insall-Salvati, the modified Insall-Salvati and the Blackburne-Peel. However, these methods have many limitations. They have poor agreement and the patellar height classification relies heavily on the chosen ratio^[40]. In addition, they refer to the position of the patella relative to the tibia and are based on bone contours and not on cartilaginous landmarks. Patellar height may be normal when measured on one index and abnormal when measured on another index.

Some authors have studied the "functional engagement" between the articular surfaces of the femur and tibia in sagittal MRI, which is more clinically relevant in patellofemoral disorders. Biedert and Albrecht introduced the patellotrochlear index^[41]. Dejour described the sagittal patellofemoral engagement index in two distinctive sagittal slices, allowing measurements in patients with patellar dislocation who have different positions of the patella in the axial plane^[42]. Some studies have demonstrated the absence of correlation between these functional engagement indexes and the other ratios for patella alta^[42-44]. Nowadays, the evaluation of the functional engagement of the patella with MRI is recommended as a supplementary tool to the existing radiographic methods^[42,44].

TT-TG distance

The TT-TG distance is the distance between the deepest aspect of the trochlear groove (TG) and the most anterior

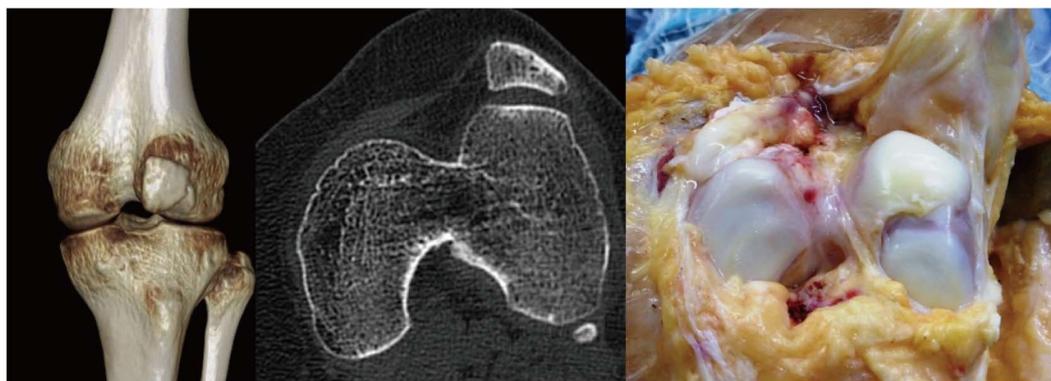


Figure 11 The TT-TG distance is not measurable in this particular case because of the severe and peculiar trochlear dysplasia. On the 3D model, the TT looks quite lateralized in comparison with the TT-TG distance calculated by the radiologist: 15 mm. We suggest a TT-PCL measurement when the TT-TG is not measurable.



Figure 12 When we consider a surgical procedure to correct patellofemoral maltracking, we have to take not only the TT-TG distance (abnormal if > 20 mm) into consideration but also the existence of chondral lesions and their location in the patella. In this case, a possible candidate for a Fulkerson osteotomy, the location of the chondral lesion would worsen the prognosis.

aspect of the proximal tibial tubercle (TT) in the center of the patellar tendon insertion, measured on axial CT and MRI views. They are routinely measured with the patient in the supine position, knees at 0° of flexion, feet at 15° of external rotation and the quadriceps muscle relaxed. A threshold of 20 mm is widely considered pathological.

Some factors significantly influence this measurement. The TT-TG distance is sensitive to knee rotation, small changes in femoral alignment and axial CT or MRI scan orientation^[45,46]. In addition, low reproducibility of the measurement has been described, with an error of about 3-4 mm depending on the slices selected and the landmarks chosen by the radiologist^[47]. Therefore, it should be interpreted with caution if the examination procedure and the measurement method have not been standardized.

The tibial tubercle-posterior cruciate ligament (TT-PCL) distance has been recently introduced as a measurement not influenced by the rotation of the knee or the shape of the trochlea (Figure 11)^[45]. Similarly, the new TT-TG index allows for correlation of the distance with individual joint size, which is especially important in cases of marginal TT-TG distance^[48]. These additional methods for determining the position of the tibial tubercle are currently recommended to facilitate

the therapeutic approach.

High quality clinical studies are needed to determine the specific role of the TT-TG measurement in surgical decision-making for the treatment of CLPI.

A pathologic index, as an isolated number, is insufficient to consider an associated surgical technique to the MPFL reconstruction. Other factors must be considered, such as maltracking, chondropathy location (Figure 12), type of dislocation (traumatic vs atraumatic), bilaterality, activity level, and patient expectations. Much more controversies exist about osteotomy indications. According to Robert Teitge (personal communication) we may consider an osteotomy in cases with torsion greater than 20° above normal (femoral anteversion > 35° and tibial external torsion > 45°) that have failed after a MPFL reconstruction while pain, instead of instability, is the main symptom, and there is no osteoarthritis.

MPFL RECONSTRUCTION WITHOUT BONE TUNNELS IN COMPLEX REVISION CASES

In patients who have been operated on several times, multiple tunnels and implants both in the patellar inser-

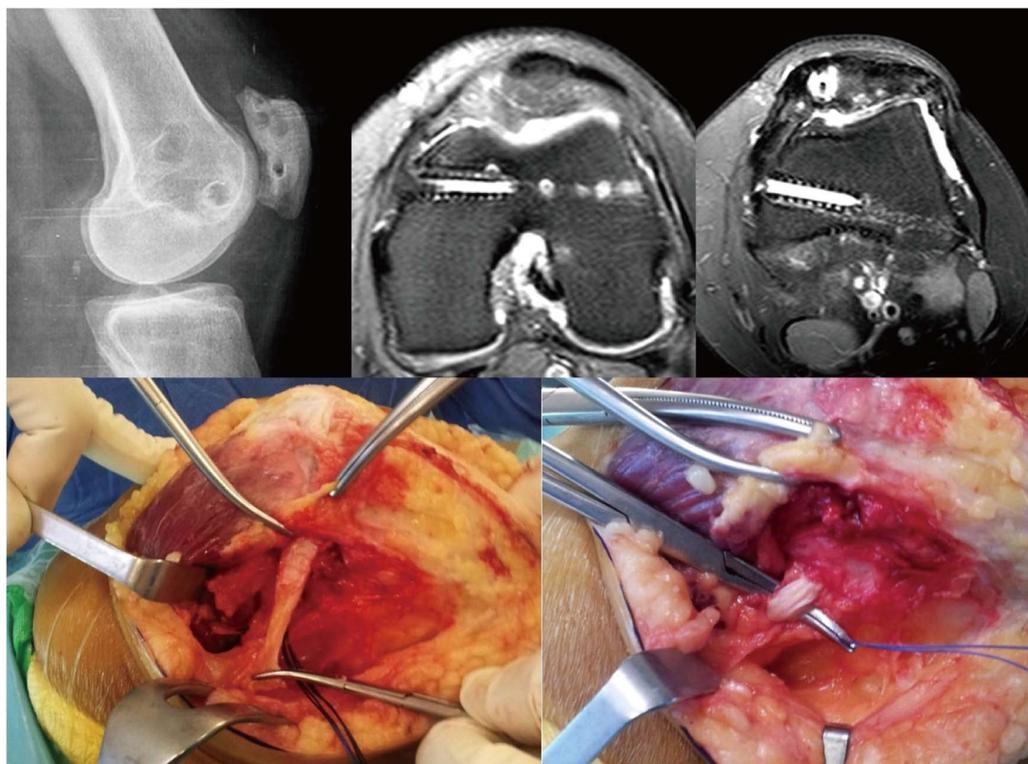


Figure 13 This patient has had two operations on his medial patellofemoral ligament. We can observe the different tunnels in the patella and distal femur. In this case, a MPFL reconstruction was performed without bone tunnels using the adductor magnus tendon as a post and a partial thickness medial quadriceps tendon as a graft (reproduced with permission from AOTT Journal, The Turkish Society of Orthopaedics and Traumatology). MPFL: Medial patellofemoral ligament.

tion area as well as in the femoral insertion area are usually seen. This situation makes revision surgery a real challenge (Figure 13), increasing the risk of patellar fractures either during or after surgery. Moreover, if we drill another tunnel in the patella or in the femur we can cause tunnel collisions that might compromise the implant fixation. This may sometimes call for a two-stage surgery as occasionally occurs in ACL revision surgery. Alternatively, we could consider a ligament reconstruction using methods that do not require anchoring bone tunnels. One option would be the use of an autologous quadriceps tendon graft which is anchored in the proximal 1/3 of the patella, maintaining its native patellar insertion site and using the AMT as a post (Figures 13 and 14). It has been reported that the AMT is a suitable point of insertion for MPFL reconstruction because the kinematic behavior exhibited by the reconstructed MPFL using either the anatomical femoral footprint of the MPFL and the AMT is similar^[15]. In addition, this *quasi*-anatomic reconstruction using the AMT as the femoral fixation point has been shown to be safe and suitable for the treatment of CLPI and has good clinical results^[14]. The advantages of this surgical technique are that there is no need to implants, no need for bone drilling and no need for allografts. These eliminate the necessity of a two-stage procedure.

The quasi-anatomical MPFL reconstruction using the adductor magnus tendon as the femoral fixation point is a good solution to deal with challenging cases in our daily practice.

Surgical technique

The quadriceps tendon graft is harvested in its medial aspect, obtaining 1 cm width and the superficial anterior half in its complete length (Figure 14). However, the most important thing to keep in mind is to make a good estimation of the length of the graft. It should be large enough to allow for the correct isometric properties of the graft. In this regard, an extra 2 cm in the graft length to the distance between the quadriceps tendon insertion and the AMT is recommended. This will allow the graft to flip around the AMT. When the graft is harvested, dissecting the plane between the VMO and the joint capsule is a must (Figure 14). Once the graft is passed on this plane, a loop is created with its end around the AMT. Then, the attachment of the quadriceps tendon graft into the medial rim of the patella (superior third) is fixed with sutures. This prevents the graft rupturing during posterior steps and also places the graft insertion in a more anatomical position. Finally, the quadriceps tendon graft is sutured to itself in an end-to-side fashion at 30 degrees of knee flexion (Figure 14).

CONCLUSION

Complications after MPFL reconstruction can be more disabling than the primary CLPI. Some patients who have experienced more than one patellar dislocation are still highly functional and may not need surgery. Only when patients are significantly limited in their activities of daily

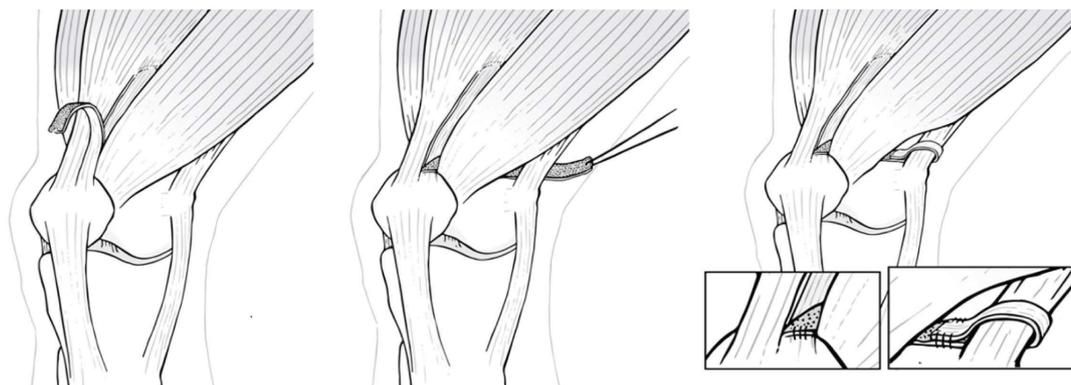


Figure 14 Diagram of a medial patellofemoral ligament reconstruction without bone tunnels using a partial thickness graft of the medial area of the quadriceps tendon (reproduced with permission from AOTT Journal, The Turkish Society of Orthopaedics and Traumatology).

living or with more demanding activities should surgical treatment such as MPFL reconstruction be considered. We, as a professional group, need to be extremely careful recommending this procedure to patients who must be clearly informed about the complications and secondary procedures. Even though, most failed MPFL reconstructions are a result of factors that the surgeon can control. Understanding of the anatomy and biomechanics, cautiousness with the imaging techniques while favoring clinical over radiological findings and common sense to determine the adequate surgical technique for each particular case are critical steps in minimizing potential complications.

Unfortunately, while there are several national registries collecting data on anterior cruciate ligament (ACL) reconstructions, there is a lack of such registries on MPFL reconstructions. Hopefully, the same interest will be given to the MPFL surgery in the future. These registries, along with evidence based medicine promotion, and planning higher levels of evidence studies than those available today, obviously including clinical trials, will provide tools to improve the surgical indications mostly in more the challenging cases of patellofemoral instability. Given the fact that MPFL injuries are much less frequent than ACL injuries and that there are many more factors favoring patellofemoral instability, some of them acting as confounding factors, multicentric studies should be promoted.

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Basic Study

Evaluation of a chitosan-polyethylene glycol paste as a local antibiotic delivery device

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Abstract**AIM**

To investigate the efficacy of a chitosan/polyethylene glycol blended paste as a local antibiotic delivery device, particularly in musculoskeletal wounds.

METHODS

Acidic (A) chitosan sponges and neutralized (N) chitosan/polyethylene glycol (PEG) blended sponges were combined in ratios of 3A:2N, 1A:1N, and 2A:3N; then hydrated with phosphate buffered saline to form a chitosan/PEG paste (CPP). Both *in vitro* and *in vivo* studies were conducted to determine the potential CPP has as a local antibiotic

delivery device. *In vitro* biocompatibility was assessed by the cytotoxic response of fibroblast cells exposed to the experimental groups. Degradation rate was measured as the change in dry mass due to lysozyme based degradation over a 10-d period. The antibiotic elution profiles and eluate activity of CPP were evaluated over a 72-h period. To assess the *in vivo* antimicrobial efficacy of the CPP, antibiotic-loaded paste samples were exposed to subcutaneously implanted murine catheters inoculated with *Staphylococcus aureus*. Material properties of the experimental paste groups were evaluated by testing the ejection force from a syringe, as well as the adhesion to representative musculoskeletal tissue samples.

RESULTS

The highly acidic CPP group, 3A:2N, displayed significantly lower cell viability than the control sponge group. The equally distributed group, 1A:1N, and the highly neutral group, 2A:3N, displayed similar cell viability to the control sponge group and are deemed biocompatible. The degradation studies revealed CPP is more readily degradable than the chitosan sponge control group. The antibiotic activity studies indicated the CPP groups released antibiotics at a constant rate and remained above the minimum inhibitory concentrations of the respective test bacteria for a longer time period than the control chitosan sponges, as well as displaying a minimized burst release. The *in vivo* functional model resulted in complete bacterial infection prevention in all catheters treated with the antibiotic loaded CPP samples. All experimental paste groups exhibited injectability and adhesive qualities that could be advantageous material properties for drug delivery to musculoskeletal injuries.

CONCLUSION

CPP is an injectable, bioadhesive, biodegradable, and biocompatible material with potential to allow variable antibiotic loading and active, local antibiotic release to prevent bacterial contamination.

Key words: Chitosan; Polyethylene glycol; Paste; Local antibiotic delivery; Biofilm; Bacterial infection

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Core tip: The study investigates the efficacy of a chitosan-polyethylene glycol paste as a local antibiotic delivery device to prevent bacterial infection, particularly in high risk, severe musculoskeletal wounds complex in shape and experiencing decreased vascularity. Research focusing on three different paste formulations categorized by the ratio of acidic to neutral components involved *in vitro* evaluation of the paste cytotoxicity, degradation, antibiotic elution, as well as an *in vivo* functional infection model evaluating the antimicrobial efficacy of the paste. Preliminary study outcomes demonstrate the potential of a chitosan-polyethylene glycol paste as a local antibiotic delivery device capable of infection prevention.

Rhodes CS, Alexander CM, Berretta JM, Courtney HS, Beenken KE, Smeltzer MS, Bumgardner JD, Haggard WO, Jennings JA. Evaluation of a chitosan-polyethylene glycol paste as a local antibiotic delivery device. *World J Orthop* 2017; 8(2): 130-141 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/130.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.130>

INTRODUCTION

Musculoskeletal wounds are among the most prevalent types of injuries in the United States, accounting for over 60% of unintentional injuries per year^[1], and are among the leading causes of death in all age groups^[2]. Systemic antibiotic therapy is standard prophylactic treatment^[3], but compromised vasculature in some complex musculoskeletal wounds reduces systemic distribution allowing for proliferation of contaminating bacteria and establishment of infection^[4,5]. A complex musculoskeletal wound has an estimated 20% chance of becoming infected in a civilian^[1,5,6] and 65% chance for soldiers suffering an open fracture in battlefield conditions^[6,7]. Musculoskeletal infections severely impair wound healing^[1] and can be complicated even further when antibiotic resistant and/or biofilm-forming bacterial strains are present, such as *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*)^[6,8,9], resulting in the need for higher concentrations of systemic antibiotics^[10]. Increased systemic antibiotics can help clear infection, but may lead to adverse side effects^[4]. Even with systemic antibiotics delivered in a clinical setting, patients still develop infections, reported by Mlynek *et al.*^[11]. Antibiotics present at levels below the minimum inhibitory concentration (MIC) in a *S. aureus* infection can lead to the development of more biofilm and a resistance to the antibiotic. One could rationally associate the peaks and troughs of antibiotic bioavailability seen in systemic delivery with the development of antibiotic resistant bacterial strains and biofilm. A local antibiotic delivery system could increase antibiotic levels at the musculoskeletal wound without increasing risk to the patient^[10].

Vancomycin and amikacin are both optimal for local delivery to musculoskeletal trauma, and were used for all studies involving antibiotics. Vancomycin is effective against *S. aureus* which can evolve into methicillin resistant *S. aureus*, a difficult to treat strain of bacteria attracted to open and avascular musculoskeletal wounds. Amikacin has a broad spectrum of efficacy including against Gram negative bacteria, such as the biofilm forming *P. aeruginosa*. Both antibiotics are considered reliable because they're capable of sustained activity over an extended elution time, storage time, or variable environmental conditions such as a low pH.

Biomaterials currently used as local antibiotic delivery devices, including polymethylmethacrylate and calcium sulfate, increase the local antibiotic levels within the tissue

surrounding a wound; which could enhance treatment outcome for contaminated wounds. However, the current options present limitations such as surgical removal after a period of time^[12,13], rapid degradation^[14], or a limited choice of antibiotics utilized at the time of application^[15]. These limitations, among others, drive the need for the development of novel local drug delivery devices in order to provide enhanced treatment over current devices; particularly in complex trauma wounds or patients with infection risk factors (*i.e.*, diabetes, positive skin cultures, history of infection)^[16-20]. The study objective is to develop a biocompatible, local drug delivery device capable of being loaded with physician-selected antimicrobials at the time of surgical intervention, presenting extended drug release profiles, and degrading *in vivo*.

Chitosan has been shown to be effective as a drug delivery system in several forms (*i.e.*, films, sponges), capable of releasing antibiotics at a predictable rate with *in vivo* degradation^[16,21-24]. Additionally, when blended with polyethylene glycol (PEG), chitosan sponges have demonstrated improved biocompatibility, biodegradability, and antibiotic release profiles compared to chitosan alone^[17,18]. Chitosan devices have been approved by the Food and Drug Administration to be used clinically as a hemostatic wound dressing. Starting in 2003, HemCon wound dressings were used widespread by the United States military in combat operations in Iraq and Afghanistan to effectively control hemorrhaging injuries^[25]. Results of previous studies investigating the antimicrobial drug delivery characteristics of sponges consisting of a chitosan/PEG blend as well as sponges made from chitosan alone support their use as local antibiotic delivery device^[16-20]. However, chitosan sponges have shortcomings, including incomplete wound coverage and some implant migration^[19,26]. A chitosan paste developed from sponges and modified with PEG was evaluated to address the shortcomings of sponges^[17,18]. For this body of work, acidic chitosan and neutral PEG blended chitosan sponges were fabricated and combined in various ratios to form a chitosan/PEG paste (CPP).

The aim of the current study is to determine the feasibility of the CPP as a local drug delivery device for the prevention of bacterial wound infections by evaluating the following aspects: Biocompatibility, degradation, antibiotic elution, efficacy in preventing a biofilm-based bacterial infection, the ease of injection, and adhesion to musculoskeletal tissue.

MATERIALS AND METHODS

Fabrication

All materials purchased from Fisher Scientific (Pittsburgh, PA) unless otherwise noted. Chitosan and PEG-blended chitosan products were prepared as previously reported using chitosan powder (Chitinor AS, Tromsø, Norway) and 6000g/mol PEG (Sigma Aldrich, St. Louis, MO)^[17,18]. Chitosan and PEG were dissolved in a 1% acetic acid solution (v/v) containing 0.5% chitosan and 0.5% PEG

(w/v), the PEG must first be dissolved then the chitosan added after. Control chitosan only solution was also made using a 1% acetic acid solution, but instead containing 1% chitosan (w/v). Chitosan/PEG and chitosan solutions (333 mL) were cast, frozen overnight (-80 °C), and lyophilized in a LabConco FreeZone 4.5 Liter Benchtop Freeze Dry System (Kansas City, MO) to create slightly acidic, dehydrated sponges. After lyophilization, the control chitosan sponges and the chitosan/PEG sponges were neutralized *via* submersion in NaOH solution. The chitosan/PEG sponges were submerged in 0.25 mol/L NaOH for 15 min and the control chitosan sponges were in 0.6 mol/L NaOH for 20 min, followed by rinsing cycles with distilled water until a neutral pH was reached. Finally, neutralized sponges were again frozen and lyophilized. Neutral chitosan sponges were used as the control for all experiments, excluding paste injectability evaluations. Acidic and neutral chitosan/PEG sponges were ground separately into a powder, with flake sizes ≤ 0.5 mm in diameter, using a blade grinder. Three different combinations of CPP were made by varying the mass ratios of acidic (A) chitosan to neutral (N) chitosan/PEG powder: 3A:2N, 1A:1N, and 2A:3N. Phosphate buffered saline (PBS) solution was used to hydrate the chitosan/PEG powder with a ratio of PBS volume to dry paste mass of 7.5. Dry CPP components used for biological testing and the infection prevention model were sterilized with ethylene oxide gas (EtO) prior to hydration, and PBS was sterile filtered.

Biocompatibility

In vitro cytocompatibility was assessed using a modified protocol^[18] (Figure 1A). Normal human dermal fibroblast (NHDF) cells (Lonza, Walkersville, MD) were seeded at 1.0×10^4 cells/cm² in 12-well tissue culture plates in 1.5 mL of Dulbecco's Modified Eagle's Medium solution supplemented with 10% fetal bovine serum and 1 \times antibiotic-antimycotic solution (100 units/mL Penicillin G, 100 μ g/mL streptomycin sulfate, 0.25 μ g/mL amphotericin B, Coming Inc., Manassas, VA). Twenty-four hours after cell seeding, hydrated paste samples (0.5 mL) and control sponge samples (8 mm diameter) were added to cell culture inserts (8 μ m pore membrane, Coming Inc., Manassas, VA) ($n = 5$ /group at each time point), and placed into wells containing NHDF cells and media. To assess NHDF viability, at 24 and 72 h post-exposure a Cell Titer-Glo[®] assay (Promega, Madison, WI) was used to measure cell viability using a BioTek Synergy H1 plate reader (Winooski, VT). Tissue culture plastic controls from each time point were used to calibrate luminescence values to a cell viability relative to the tissue culture plastic.

Degradation

In vitro degradation was assessed by weight reduction over time based on a previous method^[18] (Figure 1B). Sample weights were recorded before hydration ($n = 5$), and 5 mL paste samples or 22 mm \times 23 mm sponges were placed in metal, hemispherical containers (Norpro,

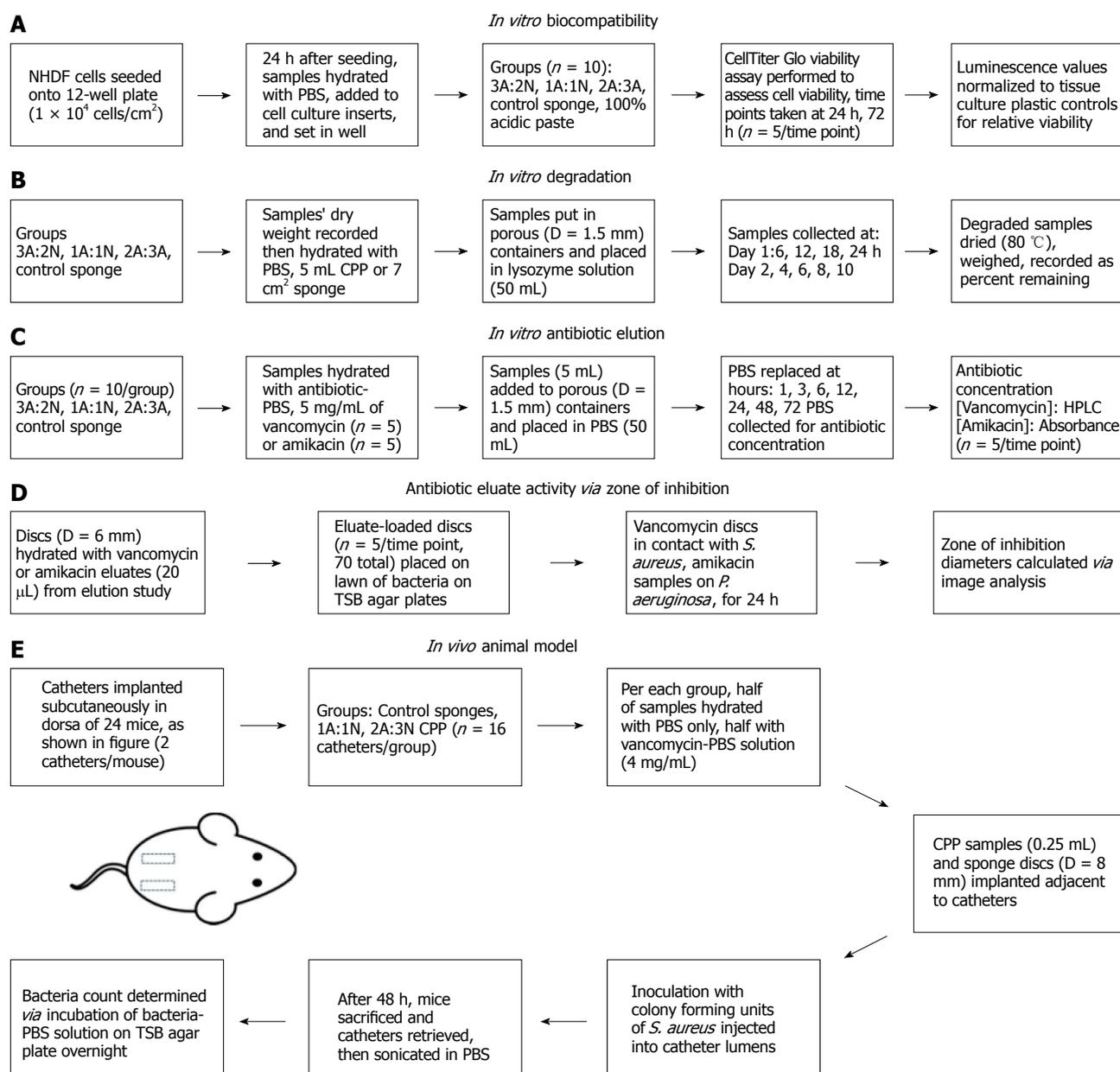


Figure 1 Experimental design flowchart detailing methods for the following studies. A: Biocompatibility; B: Degradation; C: Antibiotic elution; D: Antibiotic eluate activity; E: *In vivo* functional model. NHDF: Normal human dermal fibroblast; PBS: Phosphate buffered saline; CPP: Chitosan/polyethylene glycol paste; TSB: Trypticase soy broth.

Everett, WA) with 1.5 mm diameter holes. Container openings were covered with para-film with appropriate lower holes occluded, in order to prevent leakage of CPP and still allow the transfer of media across the sample surface. The porous vessels containing the samples were placed inside plastic containers, para-film side down, in 50 mL of lysozyme solution (1 mg/mL Lysozyme Type VI, MP Biomedicals, Santa Ana, CA), and placed in an incubator on a shaker. Lysozyme is a naturally occurring enzyme found in human macrophages, among many other tissues and bodily fluid; used for its natural degradation of chitosan, as described by Varum *et al.*^[27]. Samples were gently shaken at 37 °C for the duration of the study. Time points were taken every 6 h through day 1, 24 h later at day 2, and subsequently every 48

h through day 10. Lysozyme solution was completely replaced every 6 h over the entire 10 d degradation period. Degraded samples were dried (80 °C), weighed, and percent CPP remaining was calculated.

Elution

The *in vitro* concentration release profile of vancomycin and amikacin was determined over 72 h by high performance liquid chromatography (HPLC) (Figure 1C). Seventy-two hours was selected as the average period of time between the debridement and irrigation of a complex musculoskeletal wound in a clinical setting^[28]. Contrary to the degradation study, samples were hydrated with an antibiotic loaded PBS (5 mg/mL of amikacin or vancomycin, $n = 5$, separate groups per

antibiotic type), and the porous hemispheres were placed in 50 mL of PBS, instead of a lysozyme solution. Samples were gently shaken at 37 °C for the duration of the study.

Samples used for the HPLC and antibiotic activity from the elution solution, were collected at 1, 3, 6, 12, 24, 48 and 72 h with complete elution solution replacement at each time point with 50 mL of PBS; thereby implementing infinite sink conditions. Using a modified HPLC protocol^[29,30], vancomycin concentrations were measured utilizing a reversed-phase C18 column with mobile phase containing 35% acetonitrile and 65% phosphate buffer at 0.1 mol/L and 3 pH. Vancomycin had a 2.5 min retention time (1.0 mL/min flow rate, 250 nm UV detection). Vancomycin absorbance readings were normalized to corresponding concentration values *via* a standard curve made from serial dilutions of vancomycin.

Concentration of amikacin in eluates was determined *via* a spectrofluorometric method^[31]. Amikacin eluate samples were reacted with acetylacetone and formaldehyde in a buffer solution containing a combination of boric, acetic, and phosphoric acid at a pH of 2.7. Closed sample vials were heated in an oven at 100 °C for 20 min. Absorbance of the reacted product was measured at 450 nm with a BioTek Synergy H1 plate reader (Winooski, VT). Absorbance values were normalized to concentrations *via* a standard curve of known amikacin concentrations.

Antibiotic eluate activity

Antibiotic activity of vancomycin and amikacin eluted from samples obtained in the elution study was determined using zone of inhibition (ZOI) as described by^[32] (Figure 1D). On trypticase soy broth (TSB) agar plates, blank discs (6 mm diameter) hydrated with vancomycin or amikacin eluates (20 µL) were placed on lawns of *S. aureus* (ATCC 12598) or *P. aeruginosa* (ATCC 27317), respectively. *S. aureus* and *P. aeruginosa* were chosen as the representative bacterial strains because they are found in infected musculoskeletal wounds and are known to be capable of forming biofilm^[33]. The sample size for each test group was $n = 5$. TSB agar plates were incubated (37 °C) and removed after 24 h for photography and measurement of ZOI diameters, excluding discs.

Functional animal model

Animal care and use statement: Study protocols were approved by the University of Arkansas for Medical Sciences IACUC and all appropriate measures were taken to minimize pain and discomfort.

Following an established mouse model protocol^[17,34,35] (Figure 1E) approved by the University of Arkansas for Medical Sciences IACUC (protocol #3608), 24 mice were used to assess *in vivo* prevention of biofilm-forming *S. aureus* (ATCC 49230) growth. The functional evaluation was used to determine the *in vivo* infection prevention efficacy of the CPPs. The more acidic CPP group (3A:2N) was not tested due to the results of the cytocompatibility study indicating its cytotoxic qualities.

Incisions 0.3 cm in length were made on the left and right dorsal surface of the hip and two polyte-

trafluoroethylene catheters, 1 cm length, were implanted subcutaneously into each mouse. Simultaneously, control 1% chitosan sponges, 1A:1N CPP, and 2A:3N CPP samples were hydrated with either a PBS-vancomycin solution, containing 4 mg/mL vancomycin, or PBS alone. There were six test groups with four animals (8 catheters) in each group. Paste samples (0.25 mL) were injected adjacent to each catheter using a U-100 insulin syringe (BD, Franklin Lakes, NJ) with needle removed. Control chitosan sponge discs (D = 8 mm) were also placed adjacent to each catheter *via* tweezers. Incisions were closed with surgical glue. *S. aureus* (UAMS-1) was injected into the catheter lumens at a concentration of 1×10^5 colony forming units (CFUs) in 2 µL of solution. Mice were sacrificed after 48 h and catheters were surgically removed and placed in a sterile saline solution and sonicated to remove biofilm. The resultant bacterial PBS solutions were serially diluted, plated on TSB agar, and incubated at 37 °C overnight in order to quantify the CFUs of *S. aureus* attached to each catheter.

Injection

Injectability was assessed by ejecting paste from a standard 25 mL repeater pipette syringe (Eppendorf; Hamburg, Germany) with 3.25 mm diameter tips ($n = 3$). Syringes were loaded with 6 mL of paste and fixed in an Instron 33R Universal Testing Machine model 4465 (Instron, Norwood, MA) with 5kN load cell, automated by Instron's Bluehill 2 (v2.13) software, compressing the plunger 1 mm/s to fully eject paste. Injectability was also visually assessed by ejecting 0.5 mL of paste from modified repeater pipette syringes ($n = 5$).

Adhesion

To determine the quality of adhesion of CPP to a representative musculoskeletal tissue, porcine cervical vertebrae were used (Kroger, Memphis, TN) coated in fetal bovine serum simulating blood-like components. Adhesion was visually assessed by adhering 5 mL of paste or 22 mm × 23 mm sponge to FBS-coated tissue and timing adherence for a minimum of 1 min ($n = 3$). Samples were then doused with 10 mL of PBS, to partially simulate wound fluid exudate from the representative tissues, to determine if samples would dislodge.

Statistical analysis

The statistical methods for this study were reviewed by Dr. Amber Jennings, professor of Biostatistics in the department of Biomedical Engineering at the University of Memphis. For all applicable data, normality was determined *via* the Shapiro-Wilk test. Data from the *in vitro* degradation, biocompatibility, antibiotic elution, and antibiotic activity studies was analyzed using a two-way Analysis of Variance (ANOVA), and further analyzed *via* Holm-Sidak post hoc tests. Injectability and remaining CFUs from the *in vivo* model were analyzed using Kruskal-Wallis one-way ANOVA on ranks followed by Tukey post hoc tests. An *a priori* power analysis was performed using results from previous studies^[35] by assuming

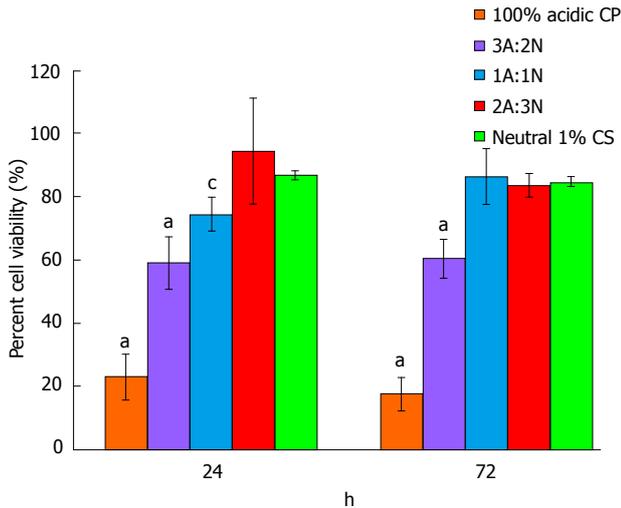


Figure 2 *In vitro* direct contact biocompatibility normalized to tissue culture plastic control reported as the average \pm standard deviation of percent cell viability for 100% acidic chitosan paste, 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations, and neutral 1% chitosan sponges after 24 and 72 h ($n = 5$). (^a $P < 0.05$ vs all at respective time point, ^c $P < 0.05$ vs 2A:3N CPP and neutral 1% CS at respective time point). CPP: Chitosan/polyethylene glycol paste.

standard deviation of 0.9 log-CFUs to determine eight catheters per group were required for 87% power to detect a mean difference of 1.85 log-CFUs between control and experimental groups at significance level $P < 0.05$. All results, excluding percent clearance of bacteria, are presented as average \pm standard deviation (SD). SigmaPlot 12.5 (Systat Software Inc, San Jose, CA) was used for analysis. Statistical significance level was set at $\alpha = 5\%$.

RESULTS

Biocompatibility

Lower cell viability at both time points (approximately 60%) was observed for 3A:2N CPP compared with all other samples ($P \leq 0.006$), excluding 100% acidic paste ($P < 0.001$; negative control) (Figure 2). 1A:1N CPP exhibited lower viability than 2A:3N CPP and neutral sponge (positive control) after 24 h ($P \leq 0.025$). However, after 72 h the groups displayed similar viability ($P \geq 0.800$). From microscopic observations, no evidence was found of cellular malformation, sloughing, or lysis for any samples except the 100% acidic paste.

Degradation

After undergoing lysozyme mass-based degradation, the pastes displayed a greater degradation rate for the first 24 to 48 h than the control sponge group. After approximately 48 h, steady degradation was shown for the 3A:2N and 1A:1N CPP groups at a higher rate than the 2A:3N group (Figure 3). The control group of 1% chitosan sponges remained at a constant mass through day 10. 3A:2N, 1A:1N, and 2A:3N CPP variations displayed significantly greater percentage loss of mass

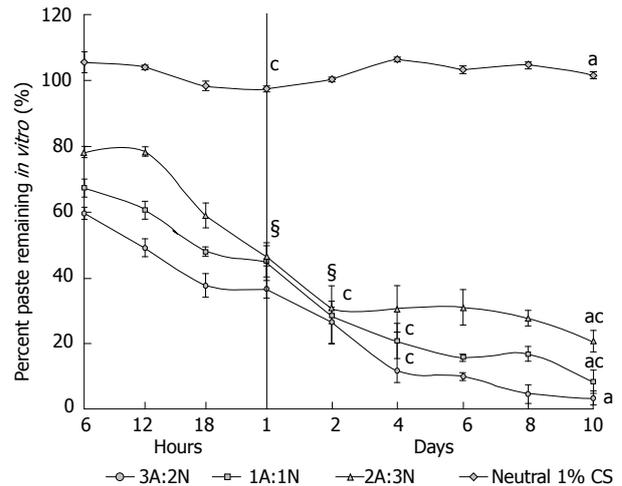


Figure 3 *In vitro* enzymatic degradation reported as the average \pm standard deviation of weight percent remaining of the sample for 3A:2N, 1A:1N, and 2A:3N chitosan/ polyethylene glycol paste variations and neutral 1% chitosan sponges over 10 d ($n = 5$). (^a $P < 0.05$ vs each other at all time points except \S for all pastes at day 2 and 2A:3N and 1A:1N at day 1; ^c $P < 0.05$ showing significant degradation through marked time points).

compared to control sponges ($P \leq 0.001$), 98%, 93% and 81%, respectively.

In vitro antibiotic elution

All paste variations steadily released vancomycin over 72 h. The control chitosan sponges released an initial, high burst with minimal to no release after 6 h. Vancomycin released from the CPP groups remained above the MIC for *S. aureus* of 2 $\mu\text{g}/\text{mL}$ ^[36] through 72 h while sponges released vancomycin concentrations above the MIC through 6 h (Figure 4A). Percent vancomycin released from CPP was lower after 6 h and the initial burst release effect ($P \leq 0.001$), but the vancomycin concentrations increased, in part due to the degradation of the paste, through 48 h and was again significantly lower at 72 h ($P \leq 0.001$). Similarly to the vancomycin elution profile, all CPP groups released amikacin at a concentration above the MIC for *P. aeruginosa* of 4-25 $\mu\text{g}/\text{mL}$ ^[16,37] for 48 h. The control chitosan sponges initially released amikacin at a very high concentration for 3 h then minimal elution after (Figure 4B).

Antibiotic eluate activity

Vancomycin eluates from the paste samples remained active against *S. aureus* through 72 h. The eluates from sponges only remained active through 6 h. Amikacin eluates from the CPP groups were active against *P. aeruginosa* through 24 h, while eluates from the control sponge group were active for 3 h (Table 1). Vancomycin eluates from sponges exhibited similar ZOI diameters to 2A:3N CPP at 1 h ($P = 0.252$) but significantly smaller than CPP at all other time points ($P \leq 0.001$). Although vancomycin eluates from the CPP groups exhibited significantly lower ZOI diameters at 72 h ($P \leq 0.001$), activity of *S. aureus* was still inhibited. Amikacin eluates

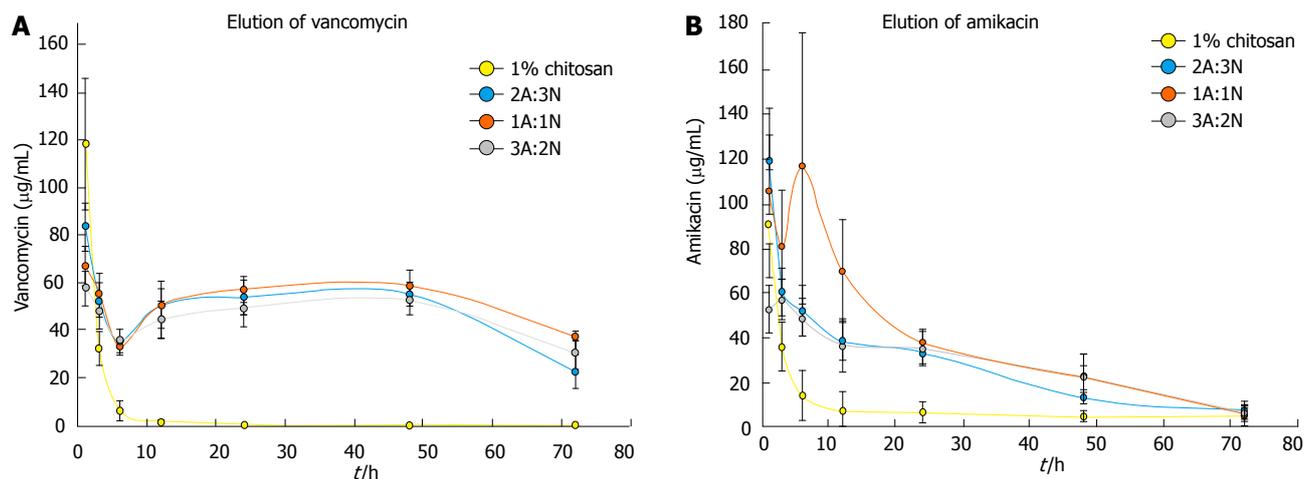


Figure 4 *In vitro* release of antibiotics, vancomycin elution group (A), and Amikacin elution group (B), from 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations and neutral 1% chitosan sponges over 72 h reported as the average \pm standard deviation in concentration of antibiotic in sample retrieved.

Table 1 Zone of inhibition of antibacterial activity results reported as the average \pm standard deviation of the inhibited growth diameter using vancomycin antibiotic eluates against *Staphylococcus aureus* and amikacin antibiotic eluates against *Pseudomonas aeruginosa* from 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations and neutral 1% chitosan sponges after 24 h of direct contact ($n = 5$)

Group	Antibiotic eluate time points (h)						
	1	3	6	12	24	48	72
<i>Staphylococcus aureus</i> zone of inhibition diameter (mm, $n = 5$) of vancomycin eluates							
3A:2N CPP	13 \pm 1.1	11 \pm 0.5 ^a	10 \pm 0.4 ^a	12 \pm 0.4	12 \pm 0.4	12 \pm 0.5	10 \pm 0.8
1A:1N CPP	13 \pm 0.5	13 \pm 1.1	11 \pm 0.0 ^a	12 \pm 0.4	11 \pm 0.4 ^a	13 \pm 0.4	10 \pm 0.8
2A:3N CPP	12 \pm 0.4	11 \pm 1.1	11 \pm 0.5	11 \pm 0.5	11 \pm 0.5	12 \pm 0.0	8 \pm 0.9
Neut 1% CS	12 \pm 0.7 ^c	7 \pm 0.5	1 \pm 3.1	0	0	0	0
<i>Pseudomonas aeruginosa</i> zone of inhibition diameter (mm, $n = 5$) of amikacin eluates							
3A:2N CPP	10 \pm 0.9	9 \pm 2.3	10 \pm 2.2	8 \pm 1.5	8 \pm 1.8	2 \pm 3.8	0
1A:1N CPP	13 \pm 2.2	10 \pm 2.1	9 \pm 1.1 ^a	5 \pm 3.2 ^a	4 \pm 3.8 ^a	0	0
2A:3N CPP	11 \pm 1.6	9 \pm 1.3	8 \pm 0.7 ^a	9 \pm 1.6	5 \pm 3.2 ^a	0	0
Neut 1% CS	10 \pm 1.9 ^c	5 \pm 3.2	0	0	0	0	0

^a $P < 0.05$ vs hour 1 value; ^c $P < 0.05$ vs all other time points.

from sponges also displayed similar ZOI diameters to the CPP groups at 1 h ($P \geq 0.288$), but the diameters quickly decreased to minimal levels by 6 h. All CPP sample eluates exhibited a significantly lower diameter at 48 and 72 h ($P \leq 0.001$), with only 3A:2N remaining active against *P. aeruginosa* through 48 h.

In vivo functional model

CPP and sponges proved effective in preventing *S. aureus* from contaminating implanted catheters. Vancomycin-loaded CPP resulted in 100% clearance rate of bacterial contamination on the catheters, while vancomycin-loaded sponges cleared bacteria from seven of eight catheters (88%) (Figure 5A). Additionally, PBS-only paste samples were ineffective in preventing bacterial contamination in all catheters; containing CFU levels between 10^3 and 10^4 ($P < 0.001$) (Figure 5B).

Injectability

Average ejection forces for all CPP variations were less than or around 150N, and easily injectable with a handheld repeater pipette (Figure 6). It can be concluded the ratio of acidic to neutral components of the CPP may lead to a significant difference in the ejection force. It can also be concluded that acidity of paste components is inversely related to ejection force.

Adhesion

Adhesion tests illustrated that all variations of CPP and the control chitosan sponges were capable of adhering to both soft and hard tissue long enough to allow proper wound closure and prevent the paste from moving in order to elute antibiotics at the intended location. The completely acidic chitosan paste proved incapable of adhering to either type of tissue for a significant amount

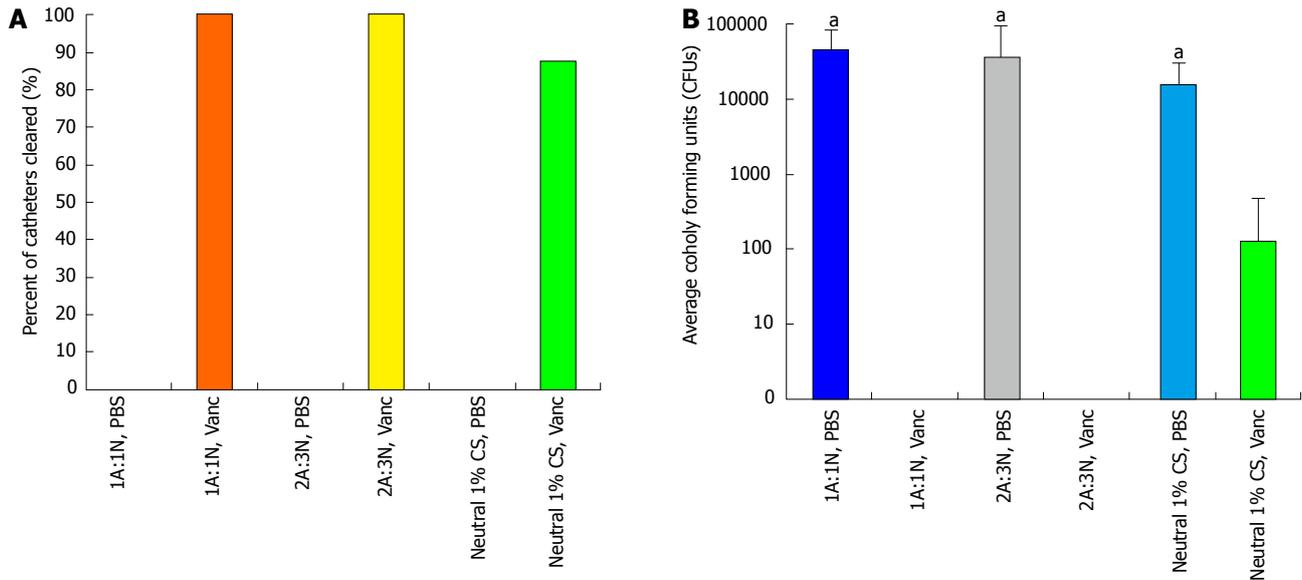


Figure 5 Percentage of catheters cleared (A) and average *Staphylococcus aureus* colony (B) forming units per catheter for those retrieved from mice treated with 1A:1N and 2A:3N chitosan/polyethylene glycol paste variations and neutral 1% chitosan sponges over 48 h ($n = 8$, 2 catheters per mouse). All samples were loaded with either PBS alone or 4 mg/mL of vancomycin. ^a $P < 0.05$ vs all vancomycin samples. PBS: Phosphate buffered saline; CPP: Chitosan/polyethylene glycol paste.

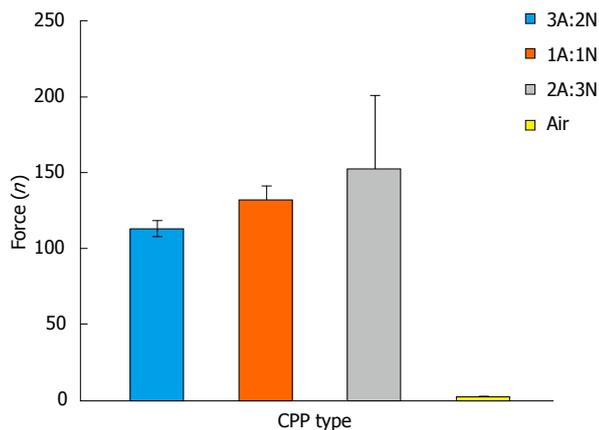


Figure 6 Ejection results represented as the average \pm standard deviation of force required to eject air and 3A:2N, 1A:1N, and 2A:3N chitosan/polyethylene glycol paste variations from a syringe ($n = 3$). CPP: Chitosan/polyethylene glycol paste.

of time.

DISCUSSION

Complex musculoskeletal wound infections, especially those complicated by biofilm-forming bacteria, increase treatment duration, surgeries, total cost, and patient morbidity^[1,6,8,9]. Systemic antibiotic therapy efficacy is substantially reduced at musculoskeletal wound sites with reduced bacteria-clearing ability. Delivery of very high dosages of antibiotics are effective but there is potential of causing adverse effects^[4,5]. The clinical need for local drug delivery devices that effectively eliminate contaminating bacteria while also being biocompatible, biodegradable, and capable of antibiotic application at

the time of surgical intervention resulted in chitosan and chitosan/PEG sponge development^[16-20]. Paste development from these sponges was a modification designed to address device migration and wound coverage while maintaining the beneficial degradability, biocompatibility, and drug elution qualities^[19,26]. The research evaluated whether chitosan/PEG blended sponges fabricated into an injectable form could result in a local antibiotic delivery device that will satisfy clinical needs. The preliminary study evaluates if chitosan/PEG in a paste form can perform as an effective localized delivery device of antibiotics with needed biocompatibility, degradability, antibiotic elution, and the functional *in vivo* antibacterial properties.

There are limitations of this preliminary study that should be noted. Primarily, the *in vivo* animal study of antibiotic activity did not investigate CPP loaded with amikacin against the bacterial contamination prevention of *P. aeruginosa* or polymicrobial infections. Second, the timeline of the *in vitro* drug delivery qualities of the CPP (*i.e.*, degradation, antibiotic elution, biocompatibility) could be lengthened, which would further support the biocompatibility and degradation qualities of CPP. Third, the interaction of CPP with complex musculoskeletal wounds or orthopedic hardware is needed for a more accurate representation of a large, complex, and infected clinical musculoskeletal wound. The results of the *in vitro* and screening model for biofilm formation warrant further investigation into local delivery of antibiotics adjunctive to systemic delivery to prevent infection, especially in at-risk patients. In past studies using the murine catheter model, antibiotics administered systemically were only partially effective in preventing biofilm formation^[35]. Therefore, to avoid confounding effects and also reduce

animal number, systemic delivery of antibiotics was avoided in the present functional model. Since a portion of the CPP variations are acidic, degradation of the acidic components will inevitably lower the pH of the surrounding environment. There is potential for the lowered pH to affect the efficacy of vancomycin and amikacin. However, the *in vitro* antibiotic activity tests revealed there was not a significant effect on the efficacy of the antibiotics in question, suggesting that CPP has the potential to prevent and treat polymicrobial infections in musculoskeletal injuries.

Studies investigating local antibiotic delivery in gels and paste, other than chitosan derivatives, have reported similar results. Overstreet *et al.*^[38] investigated the local delivery of gentamicin from a hydrogel composed of polyN-isopropylacrylamide-co-dimethyl-γ-butyrolactone acrylate-co-Jeffamine® M-1000 acrylamide (PNDJ). It was discovered the gentamicin loaded PNDJ hydrogel was capable of releasing effective levels of gentamicin over 7 d and preventing infection in an *in vivo* model for up to 4 wk. However, there was no significant *in vivo* degradation, meaning the hydrogel may have to be surgically removed after a period of time. Additionally, renal dysfunction was observed at higher doses of applied gentamicin^[38]. Pritchard *et al.*^[39] investigated the efficacy of a silk-fibroin based hydrogel as a local antibiotic delivery device, specifically, for use in avascular wounds. *In vitro* elution profiles of silk hydrogels loaded with ampicillin and penicillin produced eluates active against *S. aureus* for up to 72 h and 48 h, respectively. The *in vivo* efficacy of the ampicillin loaded silk hydrogel was tested on a *S. aureus* infected murine model over 24 h. Results indicated effective infection prevention from the silk hydrogel compared to the control. However, there was no significant difference from local injection of ampicillin alone due to the short test time period. Additionally, the study did not directly test the degradation qualities of the silk hydrogel. It was also noted antibiotics with low water solubility were difficult to conventionally load onto the silk hydrogel^[39].

Studies have been published highlighting the drug delivery qualities of chitosan/PEG blended biomaterial. One study investigated a thermosensitive chitosan/PEG hydrogel drug delivery device administered as a nasal spray^[40]; another developed an injectable chitosan-PEG-tyramine hydrogel to be used as tissue adhesives for wound healing^[41]; while others have explored injectable PEG-grafted-chitosan thermosensitive hydrogels for sustained protein release^[42] and drug delivery^[43]. Many of the researched studies did not explicitly examine injectability. The devices were characterized as *in situ* forming hydrogels injectable from a needle, but the CPP would be injected through a larger cannula device due to higher viscosity. A study found a hydrogel made from tyramine modified polyethylene glycol grafted onto the backbone of a chitosan molecule exhibited similar adhesion to porcine skins as CPP did to porcine vertebral tissue^[41]. Karn *et al.*^[44] determined the cationic nature of chitosan at pH below 6.5-7 is responsible for its mucoadhesion, the strong charge attraction between

chitosan and mucins, negatively charged glycosylated proteins highly concentrated on tissue surfaces such as pulmonary, corneal, intestinal, and gastric mucosal tissues. Sogias *et al.*^[45] reported the mucoadhesive qualities of chitosan can be linked to the electrostatic attraction of the primary amino groups to the negatively charged mucins, as well as the attractive forces caused by hydrogen bonding between the chitosan and the mucosal membranes. Chitosan can adhere to a musculo-skeletal wound *via* negatively charged molecules in the tissue such as the proteoglycans in connective tissue.

There are studies addressing degradation of chitosan/PEG hydrogel. Parker *et al.*^[18] developed neutral chitosan/PEG sponges for drug delivery utilizing 6000 g/mol PEG. *In vitro* degradation studies reported 55%-75% sponge remaining after 10 d of mass-based degradation, significantly higher than CPP with 0%-24% remaining, and 99%-100% of their neutral chitosan sponge remaining after 10 d, comparable to the neutral sponge (100% remaining). Acidic variations of chitosan, compared to neutralized, contain a protonated amine group. In aqueous solution, the proton dissociates from the amine group to join the water molecules; facilitating the solubilization of the chitosan molecules. Therefore, the lower degradation rates of neutral chitosan, compared to acidic, can be attributed to the lack of protonation with the surrounding environment^[46]. Based on previous *in vivo* results^[18,47] and the rapid *in vitro* degradation experienced by CPP, rapid degradation of CPP should be expected *in vivo*. Sample degradation was not measured in the *in vivo* studies due to the short time course of the subcutaneous catheter infection model, but ongoing evaluations will characterize time course of *in vivo* degradation. In previous *in vitro* studies, multiple chitosan/PEG hydrogels were reported to be biocompatible without eliciting significant cytotoxicity^[40,43,48] along with various chitosan hydrogels^[47,49] and chitosan/PEG sponges^[17,18]. Biocompatibility studies involving indirect exposure of CPP to cell culture models demonstrated similar cell viability to control sponges, comparable to results of other *in vitro* studies^[40,43,48]. Based on previously reported *in vivo* biocompatibility for other chitosan/PEG devices, a minimal^[40,41,47] to moderate^[18,43] inflammatory response is expected, which is comparable to other implanted devices^[50].

Other chitosan/PEG hydrogels were successful in releasing bovine serum albumin and cyclosporin A^[42,48]. Although *in vitro* release or activity of antibiotics was not investigated in the studies, the release profiles characterized by PEG content are still relevant. Bhattarai *et al.*^[42] concluded that a hydrogel with a PEG weight percentage of at least 40% demonstrated a burst release of albumin within the first 5 h followed by a steady linear release for approximately 70 h. Tsao *et al.*^[48] reported the grafting of a methoxy-poly(ethylene glycol) onto the hydrophobic chitosan results in a hydrophilic composite material. The hydrophobic-hydrophilic balance among the components instills a multi-stimuli-responsive property into the hydrogel. The degradation of the hydrogel can

be controlled by stimuli involving salt concentration, solute concentration, temperature, and pH. Jiang *et al.*^[43] investigated the release of cyclosporin A from a PEG/chitosan hydrogel; reporting an absence of any significant burst effect and a sustained release at an effective concentration for three weeks *in vitro* and more than five weeks *in vivo*. Parker *et al.*^[17] reported an initial burst release of vancomycin from neutral chitosan/PEG and chitosan sponges after 1 h, with significant decrease in eluted antibiotic thereafter. Noel *et al.*^[16] investigated *in vitro* release of vancomycin from chitosan sponges made with lactic and acetic acid, showing an initial burst release after 1 h with 98% of the loaded vancomycin released after 72 h. The chitosan sponges used as controls in the present study experienced a similar initial burst release of vancomycin after 1 h with a sharp decrease to minimal levels thereafter. The CPP samples displayed a more extended release through 72 h, eluting 35% of the total loaded vancomycin after 72 h. While vancomycin concentrations measured by Parker *et al.*^[17] from chitosan/PEG blend sponges were above the MIC through 24 h, eluates utilized for turbidity testing only remained active against *S. aureus* through 6 h. Noel *et al.*^[16] found levels of vancomycin remained above the MIC and eluates remained active through 72 h, similar to findings with CPP. Noel *et al.*^[16] also reported amikacin eluates from chitosan sponges remaining active through 48 h while amikacin eluates from CPP remained active through 24 h. The PEG/chitosan sponges may not absorb as much solution as the sponges made of chitosan alone. The studies by Parker *et al.*^[17] and Noel *et al.*^[16] did not report the amount of antibiotics absorbed by the sponges while soaking in excess solution; highlighting the limitations of varying elution protocols as well as the need for confirmation of *in vitro* antibiotic elution results in functional animal models. The difference between the elution profiles of vancomycin compared to amikacin within chitosan drug delivery systems may be due to differences in antibiotic structure or charge. It is possible that vancomycin may associate with the chitosan/PEG leading to a more extended release.

Other chitosan/PEG hydrogels were successful in *in vivo* delivery of insulin^[40] and cyclosporin A at effective levels^[43], but none tested the *in vivo* activity of these therapeutic devices. Our control sponge cleared bacteria from 87.5% of catheters, while Parker *et al.*^[17] only reported a 50% clearance rate; however, the number of remaining viable CFUs in both studies was reduced compared to controls. All groups of vancomycin-loaded CPP displayed 100% bacterial clearance of catheter. Longer durations of study are necessary to determine the long-term infection prevention efficacy, as although bacterial counts may be reduced by local delivery of antibiotics, remaining viable bacteria could rebound and lead to infection.

In conclusion, CPP is an injectable, bioadhesive, biodegradable, and biocompatible material with potential to allow variable antibiotic loading at the time of surgical intervention, and active, local antibiotic release to prevent bacterial contamination. *In vitro* studies

confirm CPP is more readily degradable, and displays similar cytocompatibility compared to other chitosan and chitosan/PEG drug delivery devices. CPP also demonstrated a uniform and extended antibiotic release over the course of 72 h. Antibiotic loaded CPP proved to be more effective than chitosan sponges in preventing biofilm formation in a murine catheter model. CPP, unlike other chitosan/PEG hydrogels that form *in situ*^[40,43], must be injected through a larger cannula device, and exhibited adhesion to representative musculoskeletal tissues. The CPP formulations were found to have comparable antimicrobial effects to the control chitosan sponge devices and also infection prevention devices studied in previous studies. Future studies will modify the formulation to improve material properties, such as injectability, and to further evaluate the drug delivery devices in expanded preclinical models of complex extremity trauma, both with and without implanted hardware.

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COMMENTS

Background

Complex musculoskeletal wounds are highly susceptible to polymicrobial infections; severely impairing the healing process and threatening patient health. Systemic delivery of antibiotics can be ineffective in preventing bacterial infection due to the lack of vascularity surrounding a severe complex musculoskeletal wounds. Therefore, a method of locally delivering antibiotics to the wound could prove effective in the prevention of a bacterial infection. Utilizing previously developed chitosan sponges, a polyethylene glycol-chitosan blended paste was investigated as a local delivery device. Chitosan/PEG paste (CPP) was evaluated as an injectable, adhesive device to determine biodegradability, biocompatibility, antibiotic elution and activity, and *in vivo* efficacy.

Research frontiers

Chitosan is being researched as a drug delivery device because it is biocompatible, degradable by enzymes found in the body such as lysozyme, and adhesive to mucins on the surface of visceral tissues. It can be loaded with different types of drugs and applied directly to a wound as a paste, hydrogel, or wound dressing to locally deliver the designated drugs to the surrounding injured tissue. The diversity of drugs chitosan is capable of delivering make it a versatile component to be used in drug delivery devices. The addition of polyethylene glycol to chitosan increases the rate of degradation and also improves the drug releasing ability of the drug delivery device.

Innovations and breakthroughs

The local delivery of antibiotics provides an effective concentration of infection preventing molecules sustained at a more steady concentration over an extended amount of time compared to the peaks and troughs associated systemic delivery. The decrease in bioavailability of antibiotics during breaks

from systemic delivery leaves the wound vulnerable to a bacterial infection. The bacterial population can become resistant to a particular antibiotic if it is being exposed to levels below the minimum inhibitory concentration. Antibiotic loaded CPP has shown to be capable of locally releasing antibiotics while maintaining biocompatibility and being completely biodegradable; qualities that are advantages compared to common methods of local drug delivery such as calcium sulfate and polymethylmethacrylate beads.

Applications

In vitro test results suggest CPP is capable of being loaded with amikacin and successfully inhibiting the growth of *Pseudomonas aeruginosa* (*P. aeruginosa*), a representative Gram negative bacteria. Both *in vitro* studies and *in vivo* functional models proved the bacterial prevention efficacy of vancomycin-loaded CPP against *Staphylococcus aureus* (*S. aureus*), a representative Gram positive bacteria. Therefore, the CPP is being researched as an adjunctive method of bacterial contamination prevention in wounds; particularly in complex musculoskeletal wounds that are inherently at a higher risk of becoming infected.

Terminology

Chitosan is the deacetylated form chitin, the most abundant naturally occurring amino-polysaccharide found in arthropod exoskeletons. Polyethylene glycol is a hydrophilic polyether compound; blended with chitosan to increase the dissociation rate of the paste in an aqueous environment. Biofilm forms when bacteria or other microorganisms attach to a surface, such as a metal implant or damaged tissue, and causes infection that is highly resistant to antibiotics or immune system clearance. *S. aureus* and *P. aeruginosa* are among the common pathogens that cause infections in the musculoskeletal system with the formation of biofilm.

Peer-review

The paper is of interest and well-organized. The aims and objectives are clear, the hypothesis is sound and the data are well presented.

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Basic Study

Neuromuscular trunk activation patterns in back pain patients during one-handed lifting

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Institutional animal care and use committee statement: No animals were analysed during this study.

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Abstract**AIM**

To analyze neuromuscular activity patterns of the trunk in healthy controls (H) and back pain patients (BPP) during one-handed lifting of light to heavy loads.

METHODS

After assessment of back pain (graded chronic pain scale according to von Korff) all subjects ($n = 43$) performed a warm-up (treadmill walking). Next, subjects were instructed to lift $3 \times$ a 20 kg weight placed in front of them (with both hand) onto a table (height: 0.75 m). Subsequently, all subjects lifted with one hand (left-side, 3 repetitions) a weight of 1 kg (light), 10 kg (middle) and 20 kg (heavy) in random order from the ground up onto the table left of them. Trunk muscle activity was assessed with a 12-lead EMG (6 ventral/6 dorsal muscles; 4000 Hz). EMG-RMS (%) was averaged over the 3 repetitions and analyzed for the whole one-handed lifting cycle, then normalized to RMS of the two-handed lifting. Additionally, the mean (normalized) EMG-RMS of four trunk areas [right/left ventral area (VR/VL); right/left dorsal area (DR/DL)] was calculated. Data were analyzed descriptively (mean \pm SD) followed by student's t -test comparing H and BPP ($\alpha = 0.05$). With respect to the unequal distribution of subjects in H and BPP, a matched-group analysis was conducted. Seven healthy controls were gender- and age-

matched (group H_{matched}) to the 7 BPP. In addition, task failure was calculated and compared between H/H_{matched} vs BPP using χ^2 .

RESULTS

Seven subjects (3m/4f; 32 ± 7 years; 171 ± 7 cm; 65 ± 11 kg) were assigned to BPP (pain grade ≥ 2) and 36 (13m/23f; 28 ± 8 years; 174 ± 10 cm; 71 ± 12 kg) to H (pain grade ≤ 1). H and BPP did not differ significantly in anthropometrics ($P > 0.05$). All subjects were able to lift the light and middle loads, but 57% of BPP and 22% of H were not able to lift the heavy load (all women). χ^2 analysis revealed statistically significant differences in task failure between H vs BPP ($P = 0.03$). EMG-RMS ranged from 33% ± 10%/30% ± 9% (DL, 1 kg) to 356% ± 148%/283% ± 80% (VR, 20 kg) in H/BPP with no statistical difference between groups regardless of load ($P > 0.05$). However, the EMG-RMS of the VR was greatest in all lifting tasks for both groups and increased with heavier loads.

CONCLUSION

Heavier loading leads to an increase (2- to 3-fold) in trunk muscle activity with comparable patterns. Heavy loading (20 kg) leads to task failure, especially in women with back pain.

Key words: Lifting; Core; Trunk; EMG; MISPEX

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Core tip: The aim of this study was to analyze neuromuscular activity patterns of the trunk in healthy controls (H) and back pain patients (BPP) during one-handed lifting of light to heavy loads. Neuromuscular trunk compensation strategies for expected loading with different weights did not differ between BPP and H, and showed a similar muscular activation pattern with the highest activity found in the contralateral abdominal muscles (VR). Heavier loading leads to an increase (2- to 3-fold) in trunk muscle activity with comparable patterns between groups. Heavy loading (20 kg) may lead to task failure, especially in women with back pain.

Mueller J, Engel T, Kopinski S, Mayer F, Mueller S. Neuromuscular trunk activation patterns in back pain patients during one-handed lifting. *World J Orthop* 2017; 8(2): 142-148 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/142.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.142>

INTRODUCTION

Back pain places a large burden on the societies and healthcare systems of western industrialized nations with high direct (e.g., therapy measures) and indirect costs (e.g., loss of working hours)^[1-3]. Hence, research to develop approaches for the prevention and/or re-

habilitation of back pain is extremely interesting and could have a very beneficial effect. Consequently, the investigation of differences in trunk function between people with and without back pain is of primary interest in order to define adequate therapy and/or prevention strategies.

In etiology, repetitive micro-trauma, as well as insufficiency of the muscle-tendon complex based on inadequate postural and neuromuscular control, reduced maximum trunk strength capacity and trunk muscle fatigue during dynamic loading, have been supposed^[4,5]. Thus, an altered neuromuscular activity of the trunk muscles is already evident in back pain patients (BPP)^[6-12]. Longer response times^[6,12], altered recruiting or activation patterns^[8,11,12], extended activation times^[7] and increased co-contractions^[10,11] have been described in affected patients^[13]. However, these differences are only valid in situations where the load is applied rapidly or suddenly either directly to the trunk or to the upper/lower limbs. Nevertheless, these situations are often limited in representing daily life activities which is highly comprised of lifting tasks. Since lifting tasks are omnipresent in daily life and correspond with an automated movement pattern, they seem expedient for the comparison of trunk muscle activity pattern between H and BPP.

In terms of lifting tasks, McGill *et al.*^[14] investigated the influence of different loads (5, 10, 15, 20, 30 kg) and carrying conditions (one-handed vs two-handed) on low back load. One-handed carrying led to greater low back loads compared to two-handed carrying of the same weight due to an increased shear stress on the spine. Therefore, one-handed lifting proposes a more challenging situation compared to two-handed lifting. Moreover, different loads might provoke different muscular activation patterns of the trunk and its regions as part of the compensation strategy of the trunk, even in healthy controls.

Nevertheless, it is ultimately unclear whether BPP suffer from altered trunk neuromuscular activity during expected, continuous loading, while lifting different loads. Therefore, the aim of this study is to analyze neuromuscular activity patterns of the trunk in healthy controls (H) and BPP during one-handed lifting with different loads. It is hypothesized that both healthy controls (H) and BPP will show increased trunk muscle activity with heavier loads, especially for muscles opposite the lifting hand. In addition, BPP might show increased activity and an altered activation pattern compared to healthy controls to compensate for pain. Consequently, this trunk muscle activation analysis could help define adequate therapy and/or prevention strategies for back pain.

MATERIALS AND METHODS

Subjects

Forty-eight subjects were initially recruited and explained the procedures by the study coordinator. Forty-three (16m/27f; 29 ± 7 years; 174 ± 10 cm; 70 ± 12 kg)

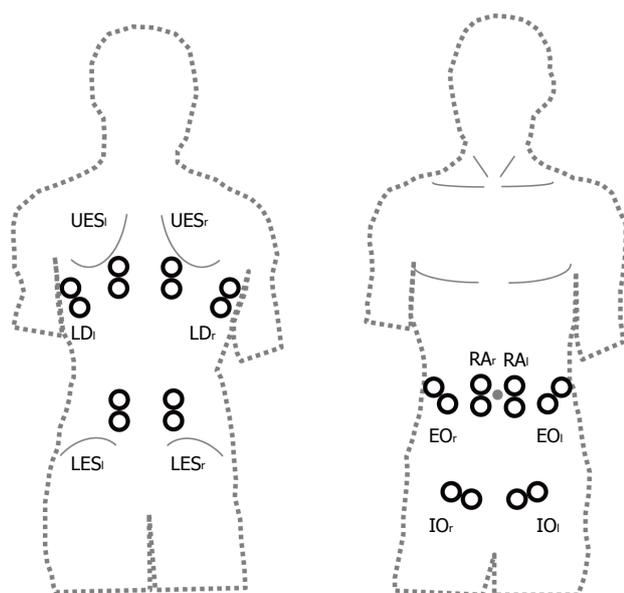


Figure 1 12-lead EMG trunk-setup. Single muscles: RA^{rite}: M. rec. abd. right/left; EO^{rite}: M. obl. ext. abd. right/left; IO^{rite}: M. obl. int. abd. right/left; LD^{rite}: M. latis. dorsi right/left; UES^{rite}: M. erc. spinae thoracic (T9) right/left; LES^{rite}: M. erc. spinae lumbar (L3) right/left.

subjects agreed to participate and formally gave written informed consent before voluntary participation. The University's Ethical Commission approved the study.

With respect to the unequal distribution of subjects included in H and BPP, an additional matched-group analysis was conducted. Therefore, an equal number of healthy controls were gender-, age- and anthropometrically matched (group H_{matched}) to the number of BPP.

Measurement protocol

Initially, all participants answered an online-based (Pro WebDB, Germany) version of a back-pain questionnaire (von Korff) determining the presence of back pain^[15]. Next, subjects were prepared for electromyographic measurements of the trunk. Before the lifting tasks, every subject performed a 5-min warm-up (treadmill walking). Subsequently, the lifting protocol started with a two-handed task, used as reference for EMG-normalization. Therefore, subjects lifted a 20 kg weight from the ground up and onto a table (height: 0.75 m) being positioned in front of them three times. Afterwards, all subject performed exclusively one-sided left-handed liftings. In random order, three times each, subjects lifted a light (1 kg), a middle (10 kg) and a heavy (20 kg) load with the left hand from the ground up and onto a table (height: 0.75 m). The table was positioned on the left side of the subjects. Subjects began all lifting tasks in an identical neutral position (hip-width bipedal upright stance) and were instructed to lift the load with a self-selected moderate speed, starting with slight bending of the knees and the trunk. Each lifting task was first demonstrated by the examiner, then subjects performed one test trial before starting the measurement.

Back pain questionnaire

The back pain questionnaire consisted of 7 items, including pain intensity and disability (acute and last 3 mo)^[15]. Six out of seven items are analyzed by a numeric rating scale ranging from 0 (no pain/disability) to 10 (highest pain/disability). Based on the grading score of the questionnaire, subjects were assigned to the healthy control group (H; Korff grades 0 and 1) or back pain patient group (BPP; Korff grades 2-4). Back pain prevalence was calculated based on this group assignment.

EMG analysis

Trunk muscle activity was assessed by means of a 12-lead surface EMG^[12] including six ventral [Mm rectus abdominis (RA), obliquus externus abdominis (EO), obliquus internus abdominis (IO) of left and right side] and six dorsal [Mm erector spinae thoracic (T9; UES)/lumbar (L3; LES), latissimus dorsi (LD) of left and right side] muscles (Figure 1). Muscular activity was analyzed using bilateral, bipolar surface EMG (bandpass filter: 5-500 Hz; sampling frequency: 4000 Hz, amplification: overall gain: 1000; myon, Switzerland). Before electrodes were applied (AMBU Medicotest, Denmark, Type N-00-S, inter-electrode distance: 2 cm), the skin was shaved, slightly exfoliated to remove surface epithelial layers and finally disinfected. In addition, skin resistance was measured and controlled to be less than 5 kΩ. The longitudinal axes of the electrodes were aligned with the presumed direction of the underlying muscle fibers.

The mean amplitude of the whole lifting cycle (average of 3 repetitions) was calculated for all lifting loads (1, 10, 20 kg). As a main outcome measurement, the one-handed lifting root mean square [EMG-RMS; (%)] normalized to EMG-RMS of the two-handed lifting task (with 20 kg) was calculated. In addition, the mean (normalized) EMG-RMS for muscle groups was calculated and therefore averaged of the EMG-RMS of the three single muscles per group: right ventral area ((VR: RA, EO, IO of right side), left ventral area (VL: RA, EO, IO of left side), right dorsal area (DR: UES, LES, LD of right side) and left dorsal area (DL: UES, LES, LD of left side)^[12].

Statistical analysis

All non-digital data were documented in a paper and pencil-based case report form (CRF) and transferred to a statistical database (JMP Statistical Software Package 9, SAS Institute®). After plausibility checks, data was analyzed descriptively (means, SD) for all given outcome measures followed by student's *t*-tests to investigate for differences between H and BPP. The level of significance was set $\alpha = 0.05$. In addition, task failure was calculated and compared between H (H_{matched}) vs BPP using χ^2 . Multiple testing was controlled *via* Bonferroni adjustment (e.g., 4 muscle groups: $P = 0.01$; 12 single muscles: $P = 0.004$). In addition, the statistical review of the study was performed by a

Table 1 Anthropometrics and back pain status of healthy controls (H; H_{matched}) and back pain group

Group	n	Gender (f/m)	Age (yr)	Body weight (kg)	Body height (cm)	Pain Intensity score ^{b,d}	Disability score ^{b,d}	Korff grade
H	36	23/13	28 ± 8	71 ± 12	174 ± 10	16 ± 11	7 ± 12	0.9 ± 0.3
BPP	7	4/3	32 ± 7	65 ± 11	171 ± 7	50 ± 17	43 ± 10	2.6 ± 0.8
H _{matched}	7	4/3	30 ± 7	64 ± 6	170 ± 9	15 ± 9	6 ± 9	1.0 ± 0.0

^bSignificant differences between H and BPP ($P < 0.001$); ^dSignificant differences between H_{matched} and BPP ($P < 0.001$). BPP: Back pain patients.

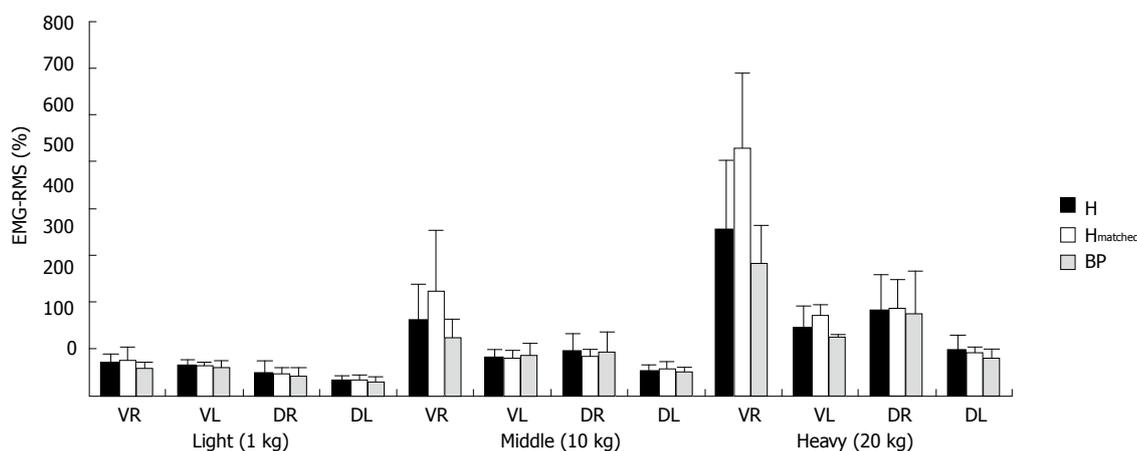


Figure 2 Neuromuscular activity (EMG-RMS; %) of trunk areas for healthy controls (H; H_{matched}) and back pain patients for the lifting tasks with 1, 10 and 20 kg (VR/VL: RA, EO, IO_{right}; DR/DL: LD, UES, LES_{right}). BPP: Back pain patients; VR/VL: Right/left ventral area; DR/DL: Right/left dorsal area.

biomedical statistician.

RESULTS

Back pain prevalence

Thirty-six subjects were allocated as healthy controls (H) and seven as BPP. This represents a back pain prevalence of 16% in the cohort analyzed. Anthropometrics and pain subscores (pain intensity/disability score) of both groups are presented in Table 1. Statistically significant differences between H and BPP were present in the pain subscores ($P < 0.001$), but not in anthropometrics.

Regarding matched-group analysis, seven healthy subjects were age- and gender-matched (group H_{matched}) to the seven BPP. Again, statistically significant differences between H_{matched} and BPP were present in the pain subscores ($P < 0.001$), but not in anthropometrics.

Task failure

All subjects were able to lift the light (1 kg) and middle (10 kg) loads. However, 57% ($n = 4$) of BPP and 22% ($n = 8$) of H/29% of H_{matched} ($n = 2$) were unable to lift the heavy (20 kg) load. All of them were female. χ^2 analysis revealed significant differences here between H and BPP ($P = 0.03$), but not for H_{matched} vs BPP ($P = 0.06$).

Trunk muscle activity during lifting

In EMG-RMS analysis, no statistically significant group differences (BPP vs H; BPP vs H_{matched}) were found ($P > 0.05$) (Figure 2). However, H showed higher mean EMG-RMS compared to BPP in all four trunk areas analyzed (P

> 0.05) (Figure 2).

EMG-RMS during lifting of the light load (1 kg) ranged between 33% ± 10% (DL) to 71% ± 18% (VR) for H, between 33% ± 9% (DL) to 76% ± 27% (VR) in H_{matched} and between 30% ± 9% (DL) to 59% ± 11% (VR) in BPP. During lifting of the middle load (10 kg), EMG-RMS varied between 52% ± 12% (DL) to 161% ± 76% (VR) for H, between 58% ± 15% (DL) to 224% ± 129% (VR) in H_{matched} and between 50% ± 11% (DL) to 124% ± 39% (VR) in BPP. Regarding high loading (20 kg), EMG-RMS ranged between 97% ± 30% (DL) to 356% ± 148% (VR) for H, between 92% ± 10% (DL) to 530% ± 157% (VR) in H_{matched} and between 80% ± 19% (DL) to 283% ± 80% (VR) in BPP. Regardless of load, no significant differences in trunk muscle activity could be found between groups ($P > 0.05$).

Regardless, VR produced the greatest EMG-RMS during all lifting tasks in both groups. In addition, EMG-RMS increased in all four trunk areas with heavier loading, especially VR and DR muscle groups. The polar plot (Figure 3) shows the activation pattern of all 12 muscles comparing H (H_{matched}) and BPP.

In addition, matched group analysis did not show any significant differences between groups with regards to loading tasks ($P > 0.05$; BPP vs H_{matched}) (Figures 2 and 3).

DISCUSSION

The main purpose of this study was to analyze neuromuscular activity patterns of the trunk in healthy con-

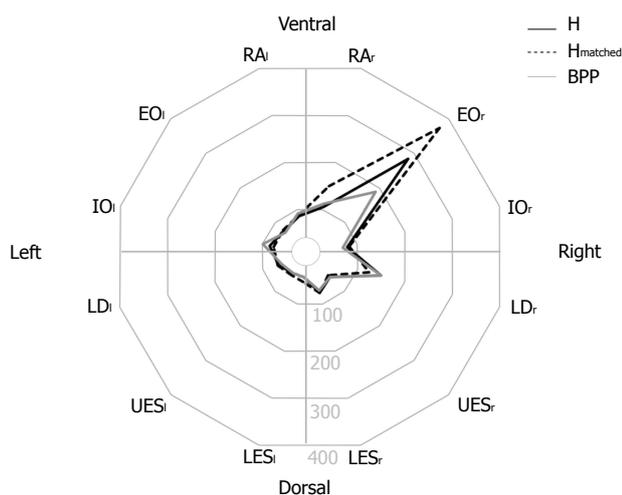


Figure 3 Polarplot of neuromuscular activity (EMG-RMS; %) of the 12 trunk muscles in healthy controls (H/H_{matched}) and back pain patients for lifting of middle load (10 kg).

trols (H) and BPP during one-handed lifting of different loads. This study demonstrates that BPP do not show an altered neuromuscular activity pattern, in terms of EMG amplitude, of the trunk during one-handed lifting of three different loads compared to healthy controls. Nevertheless, a significantly greater rate of task failure, while lifting heavy loads (20 kg), could be shown in BPP.

In contrast to the known alterations of the neuromuscular activation pattern of the trunk during suddenly applied loads^[12,16], no significant differences in trunk muscle amplitudes could be shown between BPP and H (H_{matched}) during one-handed lifting of expected loads. This can be discussed in the context of the experimental task: lifting vs quick-release experiments. The used lifting task correlates to an expected, continuous loading of the trunk. It could be discussed that due to the knowledge of the task, as well as the low (1 kg) and middle (10 kg) lifting weight, BPP are able to use an adequate - comparable to healthy controls - activation strategy to perform the task despite pain. In contrast, frequently used quick-release experiments apply a sudden, unexpected load to either the trunk or the limbs^[12,13,17]. In these studies, patients could not prepare themselves for the high loading and therefore showed altered neuromuscular activity pattern. However, lifting tasks are omnipresent in daily life, thus adequately represent functional movements. It could be speculated that the lifting pattern is an automated movement pattern, comparable to the human gait, and therefore BPP are able to reproduce an adequate neuromuscular activation pattern showing no difference to healthy controls. However, the presented EMG-RMS differences between H (H_{matched}) and BPP showed no statistical significance, but could be interpreted as clinically relevant with differences up to 250% between groups [e.g., 530% ± 157% (H_{matched}) vs 283% ± 80% (BPP)]. Due to a high inter-individual variability and the small sample size, especially the low number of BPP, statistically significant differences

would have been difficult to yield. Additionally, it should be mentioned that the acute pain level of the BPP group was actually quite low. In detail, it ranged between 0 and 8 on the numeric rating scale (0-10) (mean ± SD: 2.9 ± 2.5).

Despite finding no effect of back pain on neuromuscular activity patterns, lifting of a heavy load (20 kg) led to a significant increase in task failure in the BPP group, especially in women. The frequently observed trunk strength deficits in BPP could be a cause for the task failure at high loads (20 kg)^[18]. In addition, task failure in women could correspond to the higher prevalence of back pain and reduced trunk stability in females documented by Schneider *et al.*^[19]. As a consequence, back pain therapy, especially in females, should focus on the preparation of adequate compensation of high loading (expected, continuous). Moreover, the results imply that an overall reduced performance capacity in BPP leads to task failure. Therefore, additional diagnostics are recommended, e.g., strength assessment, to deliver individual therapy regimes.

Although BPP neuromuscular activity levels did not differ, both groups revealed a specific neuromuscular activity pattern of the trunk with muscle activity becoming more pronounced with rising load (20 kg). With increased loading, neuromuscular activity level also increased in all trunk muscles. In addition, the ventral muscle group (VR) ipsilateral to the side of the applied load (left hand) revealed the greatest activity during all loading conditions (1, 10, 20 kg). Therefore, a task-specific compensation strategy could be assumed in healthy controls and in BPP during continuous lifting of (expected) weights.

Certain limitations of the study, however, have to be considered. During the experiment, all participants lifted the same defined weights (1, 10, 20 kg) regardless of their body weight. In addition, a standardized table height (0.75 m) was used regardless of individual body height. These methods were chosen for comparability to certain daily life tasks, e.g., carrying a crate full of bottles. Therefore, no individual adaptations were made. Additionally, giving instructions to the subjects as to how to lift the objects could have influenced results. Therefore, with respect to standardization and demands in daily life, a consistent test situation for all subjects was favored^[20]. Except for sample size, there were no baseline (anthropometric) differences between groups. The added matched group analysis (BPP vs H_{matched}) did not change results of trunk EMG pattern analysis.

Conclusion

Neuromuscular trunk compensation strategies during one-handed lifting of different loads did not differ between H and BPP. Heavier loads led to an increase in trunk muscle activity (2- to 3-fold) with comparable patterns between groups. In both groups, the greatest activity was found in the contralateral abdominal muscles (VR). Heavy loading (20 kg) led to task failure, especially in women with back pain, implying reduced performance

for these subjects. Consequently, the application of additional diagnostics are recommended, *e.g.*, strength assessment. Moreover, rehabilitation and prevention of back pain should focus on the preparation and compensation of high loading.

ACKNOWLEDGMENTS

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COMMENTS

Background

Back pain places a large burden on the healthcare systems of western industrialized nations. Research to develop approaches for the prevention of back pain could have a very beneficial effect. Therefore, the investigation of differences in trunk function between people with and without back pain is of primary interest in order to define adequate therapy and prevention strategies.

Research frontiers

An altered neuromuscular activity of the trunk muscles in back pain patients (BPP) is evident: Longer response times, altered recruiting patterns, extended activation times and increased co-contractions. Besides, these differences are only valid in situations where the load is applied suddenly either directly to the trunk or to the limbs. These situations are often limited in representing daily life activities which is highly comprised of lifting tasks. Since lifting tasks are omnipresent in daily life and correspond with an automated movement pattern, they seem expedient for the comparison of trunk muscle activity pattern between H and BPP. In terms of lifting tasks, one-handed carrying led to greater low back loads compared to two-handed carrying of the same weight due to an increased shear stress on the spine. Therefore, one-handed lifting proposes a more challenging situation compared to two-handed lifting.

Innovation and breakthroughs

This study demonstrates that BPP do not show an altered neuromuscular activity pattern, in terms of EMG amplitude, of the trunk during one-handed lifting of three different loads compared to healthy controls. Nevertheless, a significantly greater rate of task failure, while lifting heavy loads (20 kg), could be shown in BPP.

Applications

Neuromuscular trunk compensation strategies during one-handed lifting of different loads did not differ between healthy controls and BPP. Heavier loads led to an increase in trunk muscle activity (2- to 3-fold) with comparable patterns between groups. In both groups, the greatest activity was found in the contralateral abdominal muscles (VR). Heavy loading (20 kg) led to task failure, especially in women with back pain, implying reduced performance for these subjects. Consequently, the application of additional diagnostics are recommended, *e.g.*, strength assessment. Moreover, rehabilitation and prevention of back pain should focus on the preparation and compensation of high loading.

Peer-review

The authors investigated EMG of back muscles of people with or without back pain when they underwent one handed lift task. The methods were clear, and the results were easy to imagine and understand.

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Case Control Study

**Interleukin-6 and ratio of plasma interleukin-6/
interleukin-10 as risk factors of symptomatic lumbar
osteoarthritis**

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Author contributions: Suyasa IK designed the research and collect material and clinical data from patients; Kawiyaana IKS collect material and clinical data from patients; Bakta IM wrote the paper; Widiana IGR analyzed the data.

Institutional review board statement: The study was approved by the ethics committee of Sanglah General Hospital (Bali, Indonesia).

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Abstract**AIM**

To determine the role of cartilage oligomeric matrix protein (COMP), interleukin (IL)-6, IL-10 and ratio of IL-6/IL-10 as risk factors of symptomatic lumbar osteoarthritis (OA) in postmenopausal women with estrogen deficiency.

METHODS

Case-control study had been conducted in Sanglah General Hospital from October 2015 until March 2016. The blood samples were obtained and analyzed by enzyme-linked immunosorbent assay (ELISA).

RESULTS

From 44 pairs of samples which divided into 44 samples as case group and 44 samples as control group showed that high level of COMP in estrogen deficiency postmenopausal women were not at risk (OR = 0.7; 95%CI: 0.261-1.751; $P = 0.393$) for symptomatic lumbar OA (cut-off point 0.946). Estrogen deficiency in postmenopausal women with the high level of IL-6 had 2.7 times risk (OR = 2.7; 95%CI: 0.991-8.320; $P = 0.033$) for symptomatic lumbar OA from the low level of IL-6 (cut-off point 2.264). At lower level of IL-10, there was no risk for symptomatic lumbar OA (OR = 0.6; 95%CI: 0.209-1.798; $P = 0.345$) than with the higher level of IL-10 (cut-off point 6.049). While the high ratio of IL-6/IL-10 level in estrogen deficiency postmenopausal women gave 3.4 times risk (OR = 3.4; 95%CI: 1.204-11.787; $P = 0.011$)

for symptomatic lumbar OA than the low ratio of IL-6/IL-10 level (cut-off point 0.364).

CONCLUSION

High ratio of IL-6/IL-10 plasma level was the highest risk factor for causing symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Key words: Symptomatic lumbar osteoarthritis; Ratio of interleukin-6/interleukin-10; Interleukin-6; Interleukin-10; Cartilage oligomeric matrix protein

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Core tip: High levels of cartilage oligomeric matrix protein in estrogen deficiency postmenopausal women were not at risk for symptomatic lumbar osteoarthritis (OA). Estrogen-deficient postmenopausal women with the high levels of interleukin (IL)-6 had higher risk for symptomatic lumbar OA from the low level of IL-6. At lower levels of IL-10, there was no risk for symptomatic lumbar OA than with the higher levels of IL-10. High ratio of IL-6/IL-10 levels in estrogen deficiency postmenopausal women produced higher risk for symptomatic lumbar OA.

Suyasa IK, Kawiya IK, Bakta IM, Widiana IGR. Interleukin-6 and ratio of plasma interleukin-6/interleukin-10 as risk factors of symptomatic lumbar osteoarthritis. *World J Orthop* 2017; 8(2): 149-155 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/149.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.149>

INTRODUCTION

Low back pain is a common symptom in elderly due to spine degeneration process which is termed as osteoarthritis (OA) of the lumbar. The prevalence of OA both in men and women at 50 years are alike, while prevalence in over 50 years are increasing in women. However, the etiology remains unknown. Numerous factors are thought to be the cause of low back pain, such as estrogen changes that often occur in older women at postmenopause^[1].

Low back pain in postmenopausal women is a clinical manifestation of degeneration process over the most mobile spine main areas/segments. Lumbar OA is the degeneration of cartilage which involves three joints complex that are characterized by narrowing of the lumbar intervertebral disc, vertebral osteophytes formation and occurrence of OA in the facet joints^[2,3]. These pathological processes can be resulted from mechanical stress loads due to weight gain and aging that will lead to cartilage thinning, as well as inflammatory process.

Inflammatory process that occurs in the lumbar OA is a chronic inflammatory process which involve the role of cytokines, either proinflammatory cytokines such as interleukin (IL)-6, or antiinflammatory cytokines such as

IL-1ra or IL-10. Production of IL-6 by human chondrocytes are also affected by estradiol, suggesting the possibility of a mechanism that affect the metabolism of cartilage^[4]. Increased IL-6 will facilitate degeneration process and stimulates the formation of osteoclast precursors of granulocyte macrophage colony-forming units and increase the number of osteoclasts *in vivo* which leads to increase bone resorption, contributes to the change in spondyloarthritis^[5]. IL-6 are also produced by fat cells. Inhibitors of IL-6 (including estrogen) are used for the treatment of osteoporosis in postmenopausal women^[6].

IL-6 also plays an important role in bone metabolism *via* induction of osteoclastogenesis and stimulates osteoclast activity^[7]. IL-6 increases the formation of osteoclasts, especially when estrogen levels decline^[8]. IL-6 stimulates formation of osteoclast precursors of granulocyte macrophage colony-forming units and increases the number of osteoclasts *in vivo*, leading to increased bone resorption, which contributes to spondyloarthritis and degeneration of intervertebral discs^[5]. Increasing amount of IL-6 in patients with aging and menopause are suspected that IL-6 is one of cytokine which plays an important role in the process of bone resorption, by affecting activity of osteoclasts, including the subcondral bone, followed by destruction of cartilage^[5].

IL-10 is formerly known as cytokine synthesis inhibitory factor, plays an important role as an anti-inflammatory and immunosuppressive cytokines. IL-10 is produced from regulatory of T cells, also produced by a large number of other cells including macrophages^[9]. IL-10 is very effective when suppressing macrophages to release tumor necrosis factor (TNF)- α ^[5].

Degradation of cartilage resulting in increasing level of cartilage oligomeric matrix protein (COMP) in synovial fluid and serum. The products of cartilage degradation will be phagocytosed by the synovium and stimulate the inflammatory process. Synovium cells are activated and produce various catabolic, proinflammatory mediators and proteolytic enzymes which will cause cartilage damage^[10]. Increased of COMP level indicates an increase in cartilage damage, as well as the IL-6 increasing the number of osteoclasts which leads to increased bone resorption including subchondral bone^[11]. Estrogen deficiency will affect the metabolism of the chondrocytes.

In postmenopausal women with estrogen deficiency prone to have cartilage damage. It is supported by the study of the OA prevalence in postmenopausal women with and without hormone replacement therapy (HRT) showed strong evidence of the benefits of estrogen on OA. Identification over two estrogen receptors: ER α and ER β proves that the cartilage chondrocytes sensitive to estrogen^[1]. Several *in vivo* and *in vitro* studies showed that chondrocytes respond to estrogen and its mechanisms that affect the metabolism of the chondrocytes^[3,12].

To date, it is still unclear whether high levels of COMP and IL-6 and low level of IL-10 in postmenopausal women with estrogen deficiency could be determined as risk factors for symptomatic lumbar OA. In this study, the

Table 1 Characteristic of symptomatic and asymptomatic lumbar osteoarthritis

Characteristic	Cases (<i>n</i> = 44) median (interquartile range)	Controls (<i>n</i> = 44) median (interquartile range)
Age (yr)	58 (54-61)	58 (53-60)
Length of menopause (yr)	7 (4-10)	8 (3-10)
Blood estrogen levels (pg/mL)	12.7 (9.00-20.87)	14.16 (9.51-19.23)
Body mass indexes (kg/m ²)	25.92 (23.27-28.06)	25.28 (22.86-27.37)

authors aimed to prove that the COMP, IL-6 and IL-10 are risk factors for symptomatic lumbar OA in postmenopausal women with estrogen deficiency. By determining the role of COMP, IL-6 and IL-10 as risk factors for the occurrence of symptomatic lumbar OA in postmenopausal women with estrogen deficiency, it is expected that early prediction, prevention and management can be recognized in the future.

MATERIALS AND METHODS

The study was conducted from October 2015 until March 2016 at Sanglah General Hospital, Denpasar, Bali. The aim of this study was to determine the role of COMP, IL-6, IL-10 and IL-6 to IL-10 ratio as risk factors of lumbar symptomatic OA in postmenopausal women with estrogen deficiency.

This was a case control study with consecutive sampling method. It started with identification for group of cases which was defined as postmenopausal women with estrogen deficiency and symptomatic lumbar OA. The pair of the cases was taken with control group, which was defined as postmenopausal women with estrogen deficiency and asymptomatic lumbar OA. The independent variables were measured retrospectively. The analysis continued with comparison of exposure probability to risk factors. The case group later compared with the control group to describe baseline characteristics and analyzed using two by two table to obtain odds ratio (OR). Odds ratio described as the risk effects, which result from exposure to the risk factors.

Forty four post-menopausal women from the population were identified and defined for both cases and controls and matched by age and body mass index. The blood sampling was performed to measure serum COMP levels and plasma cytokine levels consisting of IL-6 and IL-10 using ELISA. The obtained data were analyzed for normality and the characteristics of cases and controls equality were analyzed by comparing the mean length of menopause, age, BMI and estrogen levels. Analysis of risk factors for symptomatic lumbar OA performed with bivariate analysis (McNemar's Chi Square). The risk estimation was calculated with OR.

RESULTS

Subjects in this study were aged 57 years old in average,

Table 2 Bivariate analysis of cartilage oligomeric matrix protein, interleukin-6, interleukin-10 and ratio of interleukin-6/interleukin-10 in symptomatic lumbar osteoarthritis

Variables	OR	<i>P</i> ^a	95%CI
All subjects (44 pairs)			
COMP	0.7	0.393	0.261-1.751
IL-6	2.7	0.033	0.991-8.320
IL-10	0.6	0.345	0.209-1.798
Ratio IL-6/IL-10	3.4	0.011	1.204-11.787

^aSignificant at value < 0.05. COMP: Cartilage oligomeric matrix protein; IL: Interleukin.

with BMI of 25.8 kg/m² and length of menopause about 6 years with the levels of estrogen approximately 15 pg/mL (Table 1).

By using the serum COMP levels of 0.946 as the cut-off point, the OR between symptomatic lumbar OA in postmenopausal women with estrogen deficiency and asymptomatic lumbar OA was 0.7 (95%CI: 0.261 to 1.751), and statistically not significant with *P* value of < 0.05 (*P* = 0.393) (Table 2). This suggests that postmenopausal women with estrogen deficiency and high levels of serum COMP is not a risk factor for symptomatic lumbar OA. Whereas, by using the plasma IL-6 levels of 2.264 as the cut-off point, the OR between symptomatic lumbar OA and asymptomatic lumbar OA in postmenopausal women with estrogen deficiency was 2.7 (95%CI: 0.991 to 8.320) with *P* < 0.05 (*P* = 0.033) (Table 2 and Figure 1). This suggest that postmenopausal women with estrogen deficiency who had high levels of plasma IL-6 were associated with increased risk for symptomatic lumbar OA with calculated risk 2.7 times than those having low levels of plasma IL-6.

The risk difference was statistically significant with *P* < 0.05. By using the plasma IL-10 levels of 6.049 as the cut-off point, the OR between symptomatic lumbar OA and asymptomatic lumbar OA in postmenopausal women with estrogen deficiency was 0.6 (95%CI: 0.209 to 1.798) with *P* > 0.05 (*P* = 0.345). This suggests that low levels of plasma IL-10 in postmenopausal women with estrogen deficiency was not a risk factor for symptomatic lumbar OA (Table 2).

Using the ratio levels of plasma IL-6/IL-10 0.364 as the cut-off point, the OR between symptomatic lumbar OA in postmenopausal women with estrogen deficiency and asymptomatic lumbar OA was 3.4 (95%CI: 1.204 to 11.787) with *P* value of < 0.05 (*P* = 0.011) (Table 2 and Figure 2). This suggest that high ratio of plasma IL-6/IL-10 in postmenopausal women with estrogen deficiency had significantly higher risk for symptomatic lumbar OA with calculated risk 23.4 times than those having low ratio of plasma IL-6/IL-10.

DISCUSSION

Postmenopausal women who enrolled in the study were aged 58 years old in average, most of them had BMI

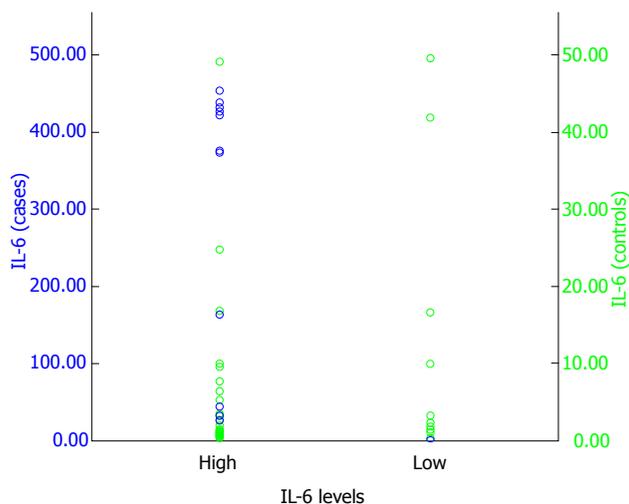


Figure 1 Distribution of interleukin-6 levels in cases and controls. IL: Interleukin.

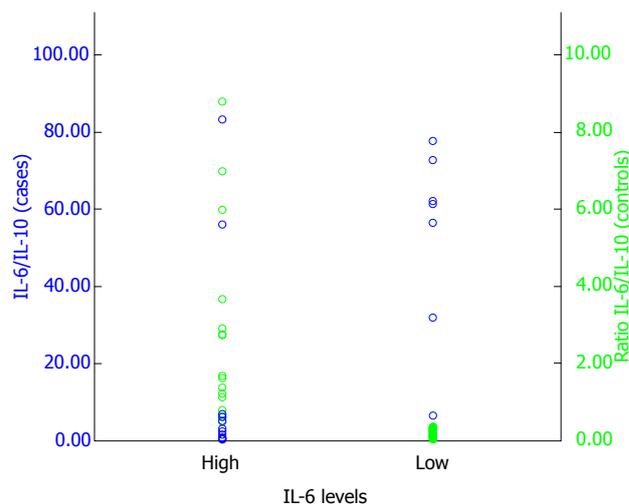


Figure 2 Distribution of ratio interleukin-6/interleukin-10 levels in cases and controls. IL: Interleukin.

category of overweight, length of menopause about 6 years and estrogen deficiency.

According to Richette *et al.*^[11] (2003), there is a relationship between estrogen decline and progression of OA, and it was found that its prevalence increases over age 50 years. Suyasa IK and Setiawan IGNY (2016) also found relationship of aging, BMI and estrogen deficiency with symptomatic lumbar OA^[13]. The lumbar OA defined as a degeneration of cartilage which involves three joint complexes which characterized by narrowing of lumbar intervertebral disc, vertebral osteophytes formation and occurrence of OA in facet joints. These pathological conditions potentially caused by mechanical stress load due to aging, weight gain and hormonal changes that occur in joint cartilage thinning process^[3].

Two estrogen receptors: ER α and ER β , identified in chondrocytes and has proven sensitive to estrogen. *In vivo* animal studies showed that intra-articular injection of estrogen have a dose dependent; supraphysiological dose of 17 β estradiol histologically induces OA histologically, on the other hand, it had no effect when given in low dose. In postmenopausal women, estrogen may decrease the speed of subchondral bone remodelling, which is a key factor in the pathophysiology of OA. Furthermore, estrogen receptor expression was shown in sinoviocytes, which are targets effect of estrogen on the joints^[1,3,5].

Role of serum COMP levels in symptomatic lumbar OA

In this study, the levels of serum COMP was not significantly with different risk for symptomatic lumbar OA with OR of 0.7 (95%CI: 0.261 to 1.751; $P = 0.393$). These results are in contrast to recent research by Goode *et al.*^[11] (2012) regarding the relationship between narrowing of the intervertebral discs, COMP and low back pain. Among patients with low back pain, strong correlations between COMP and narrowing of the intervertebral discs was found with OR of 1.82 (95%CI: 1:02 to 3:27). These finding reflects the degeneration of the intervertebral disc which characterized by narrowing of the intervertebral discs

and any other symptoms associated with degeneration process^[11].

COMP is a non-collagen protein which originated from cartilage extracellular matrix, act as a prognostic marker for OA. The levels of COMP can be used to predict the severity of damage in large joints, in addition, it can also predict the narrowing gap of joints^[14]. As a biomarker, the concentration of COMP in synovial fluid or serum can be used as an indicator of early abnormalities^[15,16], thus, COMP is very sensitive to detect early occurrence of premature OA in patients whom genetically suffering from OA^[17].

OA is characterized by the destruction of cartilage and subchondral bone. Similarly, in lumbar OA which involved three joint complex, those pathological changes will occur in the cartilage of facet joint. Cartilage damage can be induced by mechanical factors, in which antigen release by the joint cartilage occurred. This situation will stimulate immune system, causing immunological reaction such as release of inflammatory mediators and proteases that are destructive and can aggravate the cartilage damage^[11]. Cartilage damage characterized by the increase levels of COMP. As a diagnosis indicator, COMP correlated with disease severity. It is proved by detection of COMP levels 10 times higher in the synovial fluid of patients with OA.

Degradation of cartilage resulted in increased levels of COMP in synovial fluid and serum. These cartilage degradation products will be fagocyted by the synovium and stimulate inflammatory process. Synovium cells are activated and produce various catabolic and pro-inflammatory mediators and proteolytic enzymes which will lead to cartilage damage^[10].

However, serum COMP levels can not be stated as a specific indicator that reflects the facet joint cartilage damage because serum COMP levels generally increased as a result of damage to the cartilage in the various joints of the body. This is in correspond with research of Söderlin *et al.*^[18] (2004), which stated that

increase in serum COMP levels is a common finding in OA that indicate cartilage involvement. These are due to the narrow facet cartilage surface area and the serum COMP does not fully describe the extent of cartilage damage.

According to Neidhart *et al.*^[19] (1997), serum COMP levels constantly lower in the synovial fluid than cartilage matrix, so that taking samples from cartilage matrix might provide more accurate results. In addition, the concept of three joint complex in the lumbar OA involves only a small portion of cartilage in the facet joints, because 2/3 of load movement in one single functional unit is in the anterior unit^[19].

The levels of serum COMP in this study gathered due to differences in OA stages of the subjects as well as differences in affinity or specificity of primary antibody used in the detection of COMP. Western blot analysis with the mAbs 12C4 showed higher affinity towards COMP fragments which had low molecular weight compared to mAbs 14G4^[20]. According to Tseng *et al.*^[21] (2009), specificity of COMP against cartilage and specific reagent for degradation of COMP is still lacking. These conditions would limit its usefulness in determining the presence of OA as well as for the examination of dichotomous outcome in the population (normal vs abnormal)^[21]. Another study by Lohmander *et al.*^[22] (1994) also stated that high concentration of COMP can be found only at the early stages of OA development and not at the advanced stage.

According to Mobasher and Henrotin^[23] (2011), COMP has the ability to mediate interaction between chondrocytes and cartilage extracellular matrix. COMP suppresses apoptosis in primary chondrocytes through activation of caspase-3 and induction of apoptosis inhibitor protein family (IAP) on survival proteins such as Baculoviral IAP Repeat Containing 3 and 5, X-linked IAP (BIRC3, BIRC5, XIAP). This is certainly in accordance with the study where investigated that COMP may be a protective factor against Symptomatic lumbar OA although not proven to be statistically significant.

The role of IL-6 plasma levels in symptomatic lumbar OA

In this study, IL-6 plasma levels were high (above median) in postmenopausal women with estrogen deficiency. This finding suggested that high levels of IL-6 plasma significantly act as a risk factor for symptomatic lumbar OA with OR of 2.7 (95%CI: 0.991 to 8.320; $P = 0.033$). This finding was in line with the study of Weber *et al.*^[24] (2016) and Valdes^[25] (2010), that IL-6 was significantly higher in patients with low back pain (LBP), moreover, IL-6, BMI, duration of symptoms and age were significantly correlated with low back pain. IL-1, IL-6 and IL-10 that involved in the inflammatory process were also correlated with the risk of OA.

IL-6 is a cytokine that acts as an innate and acquired immunity, formed by many cells and affect multiple targets. The main sources of IL-6 are macrophages and lymphocytes in inflammatory area. IL-6 also plays an important role in enhancing the formation of osteodasts,

especially when estrogen levels are declining^[8]. IL-6 stimulates formation of osteoclast precursors of granulocyte macrophage colony-forming units and increase the number of osteodasts *in vivo*, leading to increased bone resorption, which contributed to spondyloarthritis and degeneration of intervertebral discs^[5]. While Ershler, Harman and Keller^[7] (2002) found an increase in IL-6 on aging and menopausal women. The levels of IL-6 increased in older age^[26] and significantly increased at the age of 70^[27].

In OA, the production of IL-6 is mainly stimulated by increased catabolic cytokines that are IL-1 and TNF- α , and then IL-6 will potentiate the effect of IL-1. In the pathogenesis of OA, IL-6 has dual functions that are as a trigger of the inflammatory process and has the ability to down-regulate the factors involved catabolic role in the degeneration of cartilage^[28]. In addition, IL-6 is also plays an important role in bone resorption including subchondral bone through the activity of osteodasts.

The role of IL-6 plasma against symptomatic lumbar OA is through the activation of transducer glycoprotein 130 (gp130) on neurons due to the formation of complex IL-6/soluble IL-6R. Transducer glycoprotein 130 (gp130) is associated with sensitization taste buds of pain through activation of phosphoinositide 3-kinase, protein kinase C-delta and Janus kinase as well as the regulation of ion channel transient receptor potential cation channels vanilloid 1 (TRPV1)^[29].

IL-6 is regarded as a key cytokine, which cause changes in the subchondral bone layer. The effect is largely based on the formation of osteodasts resulting in bone resorption and also showed synergism with IL-1 β and TNF^[30].

Plasma levels of IL-10 in symptomatic lumbar OA

In this study, the plasma levels of IL-10 were not proven to be significant as a risk factor for symptomatic lumbar OA with OR of 0.6 (95%CI: 0.209 to 1.798; $P = 0.345$). This is in contrast with the study by John *et al.*^[31] (2007) and Wang *et al.*^[32] (2001) which found that IL-10 not only inhibits the synthesis of inflammatory cytokines, but also protect the chondrocytes directly to antagonize the role of IL-1. Immunoregulatory cytokine IL-10 modulates a series of apoptosis in TNF- α such as caspase activity in human articular chondrocytes.

IL-10, known as cytokine synthesis inhibitory factor, is an anti-inflammatory and immunosuppressive cytokine, produced by T-regulatory cells and macrophages. IL-10 is a cytokine that is highly effective on suppressing the release of TNF- α by macrophages. There are two main functions of IL-10 such as inhibit the production of several cytokines (TNF, IL-1, and the chemokine IL-12) and inhibit the function of macrophages and dendritic cells in the activation of T-cell, generally it has an immunosuppressive effect. Suppression on macrophage function occurs because IL-10 suppressing the expression of MHC class II molecules on macrophages, and reduce the expression of co-stimulatory (a.l. B7-1 and B7-2). The final impact of IL-10 activities is specific and non-specific suppression

of inflammatory reactions which mediated by T-cells. According to those, IL-10 known as cytokine synthesis inhibitory factor and anti-inflammatory cytokines^[9].

IL-10 also able to show chondroprotective effect in the course of OA. Chondrocytes express the cytokines IL-10 and IL-10R receptor. It has been proven that IL-10 is involved in stimulating the synthesis of collagen type II and aggrecan. After administration of IL-10 *in vitro*, the healthy articular cartilage over the course of OA showed increased in proteoglycan synthesis and its percentage in the extracellular matrix. IL-10 inhibits apoptosis of chondrocytes, which might be a result of stimulation on IL-1 β antagonist synthesis, IL-1Ra, tissue inhibitor of metalloproteinase-1 (TIMP-1) and growth factors. IL-10 reduces the effect of TNF- α in synovial fibroblasts in patients with OA^[16].

In lumbar OA, IL-10 alone can not be used as a risk factor, because the inflammatory process is chronic involving *via* complex interaction by various cytokines, both pro-inflammatory cytokines such as TNF- α and IL-6, as well as cytokines anti-inflammatory such as IL-1ra or IL-10. Increased levels of TNF- α and IL-6 will be responded by anti-inflammatory cytokines. IL-10 is very powerful suppressor for TNF- α released by macrophages. The low levels of IL-10 can be used as an indicator of failure in the process of TNF- α and IL-6 suppression.

The role of IL-10 plasma in symptomatic lumbar OA is a protective factor although not clearly proved. To determine the role of IL-10 levels as a risk factor, it can be evaluated on the expression of IL-10 ratio against other potential cytokines such as ratio of IL-6/IL-10^[33].

The ratio of plasma levels IL-6 / IL-10 in symptomatic lumbar OA

In this study, the ratio levels of plasma IL-6/IL-10 were high (above median) in postmenopausal women estrogen deficiency. This finding showed that high ratio levels of plasma IL-6/IL-10 significantly acts as a risk factor for symptomatic lumbar OA with OR of 3.4 (95%CI: 1.204 to 11.787; $P = 0.011$). The results of this study showed the concept of balance between proinflammatory cytokines and anti-inflammatory cytokines. Until now, data and research on the ratio of IL-6/IL-10 in symptomatic lumbar OA in postmenopausal women with estrogen deficiency does not exist. And the role of inflammatory and anti-inflammatory cytokines in the pathogenesis of OA on inter and intracellular signaling pathways are still under study^[30].

Based on the explanation, the levels of IL-6 or IL-10 alone did not reflect the existence of symptomatic lumbar OA in postmenopausal women with estrogen deficiency. The ratio of both IL-6 and IL-10 is required to obtain more accurate result and reflect incidence of symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

The role of the IL-6 to IL-10 ratio levels against symptomatic lumbar OA is through the interaction of pro-inflammatory cytokines with anti-inflammatory cytokines.

Both of these cytokines potentially provide accurate information on the risk of symptomatic lumbar OA. IL-6 plasma has a function as a trigger of the inflammatory process and has the ability to down-regulation the catabolic factors that involved in cartilage degeneration, while IL-10 inhibits specific and non-specific inflammatory reactions as a response to the increase of cytokines TNF- α and IL-6.

From the data analysis that had been done in this study, it is concluded that the high ratio of IL-6/IL-10 plasma levels is the strongest risk factor of symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Plasma COMP can not be considered as a biomarker of symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

COMMENTS

Background

Lumbar osteoarthritis (OA) is the degeneration of cartilage which involves three joint complex. Indeed, the inflammatory process, which is a chronic inflammatory process, influence this pathological process especially if alteration of estrogen levels occurs. Furthermore, degradation of cartilage lead to increased cartilage oligomeric matrix protein (COMP) levels. Either proinflammatory cytokines [interleukin (IL-6) or anti-inflammatory cytokines (IL-1ra or IL-10) and COMP are thought to be relevant as risk factor for symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Research frontiers

IL-6, IL-10, and COMP had been extensively studied in relation to inflammatory process and cartilage damage. Chronic inflammatory process occurs in individuals with lumbar OA and this inflammatory process related to estrogen levels. Thus, it is of interest whether IL-6, IL-10, and COMP are risk factors for symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Innovations and breakthroughs

The authors confirm that high ratio of IL-6/IL-10 plasma level was the highest risk factor for causing symptomatic lumbar OA in postmenopausal women with estrogen deficiency.

Applications

Determining ratio of IL-6/IL-10 could be used as risk factors for causing symptomatic lumbar OA in postmenopausal women with estrogen deficiency. It is expected that early prediction, prevention and management can be recognized.

Terminology

COMP: Cartilage oligomeric matrix protein; IL-6: Interleukin-6; IL-10: Interleukin-10; OA: Osteoarthritis.

Peer-review

This is an interesting paper.

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Retrospective Study

Titanium elastic nailing in diaphyseal femoral fractures of children below six years of age

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Institutional review board statement: The study was reviewed and approved by the Internal ethics committee of orthopedics and traumatology department of Policlinico Gemelli Hospital.

Informed consent statement: All involved persons (subjects or legally authorized representative) gave their informed consent (written or verbal) prior to study inclusion.

Conflict-of-interest statement: No conflict of interest to be declared.

Data sharing statement: Technical appendix, statistical code, and dataset available the first author at fabriziodonati2@hotmail.it.

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Abstract**AIM**

To report the clinical and radiographic results of titanium elastic nail (TEN) in diaphyseal femoral fractures of children below age of six years.

METHODS

A retrospective analysis of 27 diaphyseal femoral fractures in children younger than six years treated with TEN between 2005 and 2015 was conducted. Patients were immobilized in a cast for 5 wk and the nails were removed from 6 to 12 wk after surgery. Twenty-four cases were clinically and radiographically re-evaluated using the Flynn's scoring criteria, focusing on: Limb length discrepancy, rotational deformity, angulation, hip and knee range of motion (ROM), functional status, complications, and parent's satisfaction.

RESULTS

Sixteen males and eight females with a mean age of 3.2 years at the time of treatment were re-evaluated at an average follow-up of 58.9 mo. No cases of delayed union were observed. The mean limb lengthening was 0.3 cm. Four cases experienced limb lengthening greater than 1 cm and always minor than 2 cm. Twelve point five percent of the cases showed an angulation < 10°. Complete functional recovery (hip and knee ROM, ability to run and

jump on the operated limb) occurred in 95.7% of cases. Complications included two cases of superficial infection of the TEN entry point, one case of refracture following a new trauma, and one TEN mobilization. According to the Flynn's scoring criteria, excellent results were obtained in 79.2% of patients and satisfactory results in the remaining 20.8%, with an average parent's satisfaction level of 9.1/10.

CONCLUSION

TEN is as a safe, mini-invasive and surgeon-friendly technique and, considering specific inclusion criteria, it represents a useful and efficacy option for the treatment of diaphyseal femoral fractures even in patients younger than six years of age.

Key words: Titanium elastic nailing; Pediatric femoral fractures; Elastic stable intramedullary nailing; Surgical treatment; Femoral shaft

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Core tip: A retrospective analysis of 27 diaphyseal femoral fractures in children younger than six years treated with titanium elastic nailing (TEN) was conducted. Clinical and radiographic evaluations performed using Flynn's scoring criteria at an average follow-up of 58.9 mo showed 79.2% of excellent results and 20.8% satisfactory results, without delayed union or major complications. Considering the good clinical and radiographic results at mid-term follow-up, TEN showed to be a safe, mini-invasive and surgeon-friendly technique even in patients younger than six years of age.

Donati F, Mazzitelli G, Lillo M, Menghi A, Conti C, Valassina A, Marzetti E, Maccauro G. Titanium elastic nailing in diaphyseal femoral fractures of children below six years of age. *World J Orthop* 2017; 8(2): 156-162 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/156.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.156>

INTRODUCTION

The treatment of diaphyseal femoral fractures in pediatric age has traditionally been a matter of debate. Several conservative and surgical treatments have been proposed^[1]. The treatment choice is typically based on patient's age, fracture type^[2], associated injuries, and the physical characteristics of the child. Diaphyseal femoral fractures in children less than six years of age are usually treated with nonsurgical methods, such as casting, tractions or Pavlik harness^[3]. These methods show good clinical and radiological results at mid- and long-term follow-up and represent the gold standard treatment^[4]. However conservative treatments are not suitable in specific cases such as polytraumatized patients, unstable fracture with risk of redisplacement and difficulty to

obtain an acceptable reduction.

Other concerns have been moved to conservative treatments like the long hospitalization, the necessity of general anesthesia and treatment in the operating theatre, prolonged weight-bearing restrictions and the high cost associated, sparking a renewed interest in surgical approaches^[5].

Intramedullary nailing with titanium elastic nails (TENs) offers several advantages, including early union, lower rate of malunion, spare of the physis, early mobilization and weight-bearing, mini-invasive approach with easy implant removal, and high patients' and parents' satisfaction rates. Good results at mid-term follow-up have been reported in children older than six years of age^[6]. Little is known on the effectiveness of TEN for the treatment of diaphyseal femoral fractures in pre-school children. The present study was therefore undertaken to verify the clinical and surgical outcomes of intramedullary nailing with TEN in a sample of children younger than six years presenting with diaphyseal femoral fractures.

MATERIALS AND METHODS

Study design and participants

The study was reviewed and approved by the Internal ethics committee of Orthopedics and Traumatology Department of Teaching Hospital "Agostino Gemelli" (Rome, Italy). We conducted a retrospective analysis in 27 patients younger than six years of age, surgically treated for diaphyseal femoral fractures in our center between 2005 and 2015. The sample comprised eighteen males and eight females with a mean age of 3.2 years (range: 1-6 years). The right femur was involved in 15 cases. One patient presented with bilateral femoral fracture, and one with an open fracture. The inclusion criteria for operative treatment should be reserved for certain cases such as polytraumatized patients, unstable fracture with risk of redisplacement and difficulty to obtain an acceptable reduction.

Twenty-four patients were treated for undisplaced fracture classified as 32-D/4.1 or 32-D/5.1 according to the AO pediatrics classification, while 3 cases showed slightly comminuted fractures classified as 32-D/4.2 or 32-D/5.2 (Figure 1).

Eight cases presented with associated lesions, involving the head, the abdom, or the thorax, or other fractures (one patellar fracture, three humeral fractures). Patients with associated neurological damage or pathological fracture were excluded. The more frequent cause of trauma was car accident (14 cases). The patients did not receive any other surgical treatment before orthopedic surgery. They were immobilized in a cast or with a skin traction and they were surgically treated as soon as their general conditions allowed surgery to be performed (on average, 36 h from their admission to the Emergency Department). The criteria of treatment were determined by a single operator and surgery performed by four different surgeons.



Figure 1 Undisplaced diaphyseal femoral fracture classified as 32-D/5.1 according to AO pediatrics classification. Associated injuries, such as thoracic or abdominal traumata, often require surgical management of this kind of fracture.



Figure 3 X-ray control at 5 wk of follow-up: Weight-bearing was allowed when advanced consolidation of the fracture with an evident bone callus formation was evident. Titanium elastic nail was then planned to be removed.



Figure 2 Intraoperative X-rays showing the correct positioning of titanium elastic nail. Entry points were performed, almost 2.5 cm proximal to the distal physis, one medial and one lateral. To facilitate the removal of the titanium elastic nail, its tail could be left over the skin surface as evident from the clinical intraoperative picture.

Surgical procedure and postoperative management

Surgery was performed under general anesthesia, and reduction under fluoroscopic guide with the patient in supine position without the necessity of traction operating table. Only in 1 case was necessary to perform open reduction for soft tissue interposition. Two TENs of identical diameter (Synthes Italy, Milan®) were used calculating

the diameter as the 40% of the medullary canal^[7]. In two cases it was not possible to drive the second nail in the proximal fragment, and a nail with smaller diameter was used. The entry points in the bone were performed using a drill bit with a diameter of 3.5 mm, almost 2.5 cm proximal to the distal physis, one medial and one lateral. The nail was inserted retrogradely after adequate pre-bending to improve stability^[8]. Long-knee brace was used in the postoperative period for an average of five weeks. Patients were discharged from hospital after an average of 5.7 d, and were followed up in our outpatients clinic after one week, at the fifth postoperative week, and at the end of treatment (8-14 wk from surgery). Patients were mobilized without weight-bearing during the fifth to seventh postoperative week, while full weight-bearing was allowed from six to eight weeks after surgery, depending on the fracture type, radiographic results and associated injuries. TENs were removed under general anesthesia when the fracture was considered healed, at an average of 7.8 wk (range: 6-12 wk) postoperatively, without encountering any intraoperative problems (Figures 2 and 3).

Patient follow-up

The clinical evaluation was always performed in the presence of at least one of the patient’s parents and after signing a detailed consensus about the study. The patients were evaluated in supine and standing positions focusing on limb length discrepancy, pelvic asymmetries, rotational deformity, axial angulation, and hip and knee range of motion (ROM). The occurrence of complications was explored by reviewing medical records whenever available or through the use of an ad hoc questionnaire.

A self-evaluation test was administered to the patient’s parents to explore the functional level obtained by the patients about running, jumping on the injured limb, and participating in common sports or physical activity at the same level of other children. The parent’s satisfaction about the treatment management was expressed on a scale ranging from 0 to 10.

The results were classified as excellent, satisfactory

Table 1 Flynn scoring criteria for titanium elastic nail

	Excellent result	Satisfactory result	Poor result
Leg length discrepancy	< 1 cm	< 2 cm	> 2 cm
Malalignment	< 5 degrees	< 10 degrees	> 10 degrees
Pain	None	None	Present
Complication	None	Minor and resolved complication	Major complication or lasting morbidity

According to Flynn scoring criteria for titanium elastic nail, a malalignment over 5°, internal or external rotation over 5° and shortening over 1 cm were considered pathological, in addition to the presence of pain or complications.



Figure 4 Clinical and radiographic examination 12 mo after fracture with residual varus deformity (< 10°) of the fractured femur. At longer follow-up, no axial deformities were observed in any patient, while the lengthening of the fractured femur was a common finding, but always < 2 cm.

or poor according to the Flynn scoring criteria for TEN^[9] (Table 1).

Radiographic evaluations were performed on the last full weight-bearing limb radiographs, in available antero-posterior and lateral views. Only in case of clinically evident limb length differences or malalignment, new X-rays were obtained. Limb lengthening and axial and rotational deformity were always considered in comparison to the contralateral limb.

RESULTS

The average clinical follow-up was 58.9 mo (12-113 mo). Of the 27 cases, 24 were available for a new clinical and radiographic evaluation. Three cases were lost at follow-up because they lived in a different region. No functional limitations or complications were reported by those three cases according to phone interview and to available information.

No cases of delayed union were recorded. The mean limb lengthening was 0.3 cm (-0.5 cm/+1.6 cm), with three cases of shortening and seven of lengthening. In four cases, the limb length discrepancy was > 1 cm, but never > 2 cm.

Twelve point five percent of the cases showed a femoral angulation > 5°, but always < 10° (two varus and one valgus). No cases of significant rotational deformity were observed (Figure 4).

Complete hip ROM was recovered by 100% of patients. One patient showed a knee flexion < 120°

after an associated patellar fracture treated for hardware removal three weeks before our evaluation (Figure 5).

Complete functional recovery was reported by 95.7% of cases. All patients were able to run and to jump on the fractured femur. The most practiced sports were swimming and soccer. The average parent's satisfaction rate was 9.1/10. Lower results were observed in the cases who needed longer hospitalization or cast immobilization. No significant aesthetic concern was reported by any of the patients.

The reported complications included two cases of superficial infection/cutaneous irritation of the TEN entry point resolved after TEN removal or with short-term oral antibiotic treatment, one refracture of the same femur occurred three months after TEN removal following a new trauma, one TEN mobilization managed with prolonged casting and healed 10 wk from the trauma without surgery.

According to the Flynn's scoring criteria, excellent results were registered in 79.2% of the cases, and satisfactory results in the remaining 20.8%.

DISCUSSION

The treatment of diaphyseal femoral fractures in preschool age is still debated. Conservative treatments remain the primary approach in most children of six years of age and younger considering the high healing power, the high remodeling power and the wide range of acceptance in this group of patients^[1,10]. All conservative treatments have shown to be safe and to offer good clinical results. However, none of them has shown a clear superiority over the other methods^[5,11]. Pavlik harness application vs spica casting were compared without showing any differences in clinical or radiographic outcomes^[3]. Conservative treatments have many advantages being less invasive and practically without risk of soft tissues or growth plate injuries that are described in surgical procedures. On the other hand, conservative treatments present some important limitations: Prolonged skin traction with long hospitalization, significant patient discomfort, difficulties with hygienic care, and long weight-bearing restrictions^[12]. Moreover, casting needs to be done in the operation theatre under general anaesthesia with similar time of surgical procedures, and similar radiation exposure for closed reductions in which sometimes it is necessary to use a specific invasive device^[4].

Considering such limitations, surgical treatments have



Figure 5 One patient had a limitation in knee flexion due to associated patellar fracture that was treated for hardware removal three weeks before our evaluation.

been increasingly used, particularly in patients with multiple traumata. Associated injuries involving the abdomen, the thorax, the spine or the head could represent a contraindication to conservative treatment^[13,14].

Different studies compared clinical and radiographic results obtained with conservative and surgical treatment after femoral fracture in adolescence. A recent systematic literature review of 531 femoral fractures confirmed comparable clinical results, with a slightly higher risk of malunion between conservative and surgical treatment (11.5% vs 8.1%), but a lower risk of complications (1% vs 4%)^[5]. The authors concluded that there was insufficient evidence to determine if long-term function differed between surgical and conservative treatment.

Some authors recommend considering the characteristics of the fracture (*e.g.*, degree of displacement and possible comminution) and the child's weight (higher or lower than 80 pounds/35 kg) when deciding on the type of fracture treatment^[1,3,7].

TEN showed to be a safe and useful treatment in the management of such condition allowing for easier nursing and avoiding pressure ulcer^[11]. Analyzing the good results obtained, TEN has become the first choice treatment even in isolated femoral fractures in children older than six years of age and under 45 kg of weight^[6]. Most children and adolescents with femoral fractures can be treated successfully with a brief hospital course without compromising care or outcomes^[15].

Surgical management is being increasingly used to assure optimal alignment, allow early motion, or facilitate early weight bearing^[16]. Intramedullary nailing with TEN offers a stable fixation controlling also the rotational deformity if applied according to the known basic surgical rule^[17]. Moreover, TEN is minimally invasive, surgeon-friendly with a mean surgical time (after an appropriate learning curve) comparable with conservative treatment, and with

a low complication rate^[13,18].

Nevertheless, it is still unclear what the first-option treatment should be in pre-school children with diaphyseal femoral fracture. Indeed, these patients have a great potential of growth and bone remodeling after fracture. For many types of fractures, both nonsurgical and surgical methods have yielded good results, but conservative treatment has traditionally been the first choice^[1,4].

Considering the experience reported in older children undergone intramedullary nailing with TEN, it is evident that, besides clinical and radiographic outcomes, other parameters need to be taken into account for treatment choice^[18].

Long hospitalization with long time in traction or uncomfortable immobilization is no longer acceptable in many situations. A faster recovery with early motion and weight-bearing should therefore be prioritized also in very young patients. In addition, surgical treatment allows for reducing the care costs relative to conservative options^[15].

In our experience, treatment with TEN showed good mid-term clinical and radiographic results in patients younger than six years, in the absence of severe complications and with a high level of parents satisfaction rate even though a second operation to remove the pins was performed in each case treated.

Our results support the analysis of Rapp *et al.*^[19] who extended the indication to TEN as the standard treatment to patients at least 3-year-old. External fixation is another option that could be considered in patients younger than six years, but it is less comfortable for the patients and less accepted by their parents, besides requiring longer time of treatment to achieve optimal healing^[20,21].

It should be considered that good results with TEN are only obtained when surgeons have a good

knowledge of the technique^[22,23]. Complications are indeed mainly caused by technical errors including insertion of too thin nails, frame asymmetry, and implant malorientation^[24]. This implies that the surgeon's experience remains one of the most important factors in the choice of treatment^[25].

Finally, radiation exposure could be a critical point of TEN treatment. However, even if intraoperative fluoroscopic exposure is higher than with conservative treatment, the higher stability obtained and the lower rate of malunion, allow reducing the number of postoperative X-ray control radiographs^[5].

Considering the good clinical and radiographic results at mid-term follow-up, TEN showed to be a safe, mini-invasive and surgeon-friendly technique even in patients younger than six years of age. Titanium elastic nailing, with specific indications, represents a useful and efficacy option for the treatment of diaphyseal femoral fractures even in patients younger than six years of age especially when the surgeon possesses good experience with this surgical technique. Further studies are necessary to evaluate if this method has any significant advantages in comparison to conservative treatments.

COMMENTS

Background

The treatment of diaphyseal femoral fractures in pediatric age is typically selected on the base of patient's age, fracture type, associated injuries, and the physical characteristics of the child. Diaphyseal femoral fracture in children less than six years of age is usually treated conservatively with several limitations. Intramedullary nailing with titanium elastic nails (TENs) shows good results at mid-term follow-up in children older than six years of age. The present study was therefore undertaken to verify the clinical and surgical outcomes of intramedullary nailing with TEN in a sample of children younger than six years presenting with diaphyseal femoral fractures.

Research frontiers

Different studies compared clinical and radiographic results obtained with conservative and surgical treatment after femoral fracture in adolescence: both nonsurgical and surgical methods have yielded good results. A recent systematic review confirmed comparable clinical results, but conservative treatment was demonstrated more expensive, and was associated with longer hospitalization and longer weight bearing restriction. External fixation is another option that could be considered in patients younger than six years, but it is less comfortable for the patients and less accepted by their parents, besides requiring longer time of treatment to achieve optimal healing. On this basis, Rapp *et al* proposed to extended the indication to TEN as the standard treatment to patients at least 3-year-old.

Innovations and breakthroughs

This retrospective study confirmed that TEN leads to good clinical and radiological results allowing optimal alignment, early motion and early weight bearing. TEN demonstrated to be effective for the treatment of diaphyseal femoral fractures even in patients younger than six years of age: It is a safe and surgeon-friendly technique and it is indicated particularly in patients with multiple traumata, and it guarantees a low rate of complications.

Applications

TEN represents a useful and efficacy option for the treatment of diaphyseal femoral fractures even in patients younger than six years of age especially when the surgeon possesses a good experience with this surgical technique.

Terminology

TEN: Titanium elastic nail.

Peer-review

The authors demonstrated an excellent result for treatment of diaphyseal femoral fractures in children with TEN. The paper is well written.

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Clinical Trials Study

Comparative clinical study of ultrasound-guided A1 pulley release vs open surgical intervention in the treatment of trigger finger

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Author contributions: Nikolaou VS analyzed data and edited the manuscript; Malahias MA conducted ultrasound exams and wrote the manuscript; Nikolaou VS and Malahias MA have contributed equally to this work; Kaseta MK and Sourlas I assisted during the operations; Babis GC had the final checking and proof editing of the manuscript.

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Abstract**AIM**

To investigate the effectiveness of ultrasound-guided release of the first annular pulley and compare results with the conventional open operative technique.

METHODS

In this prospective randomized, single-center, clinical study, 32 patients with trigger finger or trigger thumb, grade II-IV according to Green classification system, were recruited. Two groups were formed; Group A (16 patients) was treated with an ultrasound-guided percutaneous release of the affected A1 pulley under local anesthesia. Group B (16 patients) underwent an open surgical release of the A1 pulley, through a 10-15 mm incision. Patients were assessed pre- and postoperatively (follow-up: 2, 4 and 12 wk) by physicians blinded to the procedures. Treatment of triggering (primary variable of interest) was expressed as the "success rate" per digit. The time for taking postoperative pain killers, range of motion recovery, QuickDASH test scores (Greek version), return to normal activities (including work), complications and cosmetic results were assessed.

RESULTS

The success rate in group A was 93.75% (15/16) and in group B 100% (16/16). Mean times in group A patients were 3.5 d for taking pain killers, 4.1 d for returning to normal activities, and 7.2 and 3.9 d for complete extension and flexion recovery, respectively. Mean QuickDASH scores in group A were 45.5 preoperatively and, 7.5, 0.5 and 0 after 2, 4, and 12 wk postoperatively. Mean times in group B patients were 2.9 d for taking pain killers, 17.8 d for returning to normal activities, and 5.6 and 3 d for complete extension and flexion recovery. Mean QuickDASH scores in group B were 43.2 preoperatively and, 8.2, 1.3 and 0 after 2, 4, and 12 wk postoperatively. The cosmetic results found excellent or good in 87.5% (14/16) of group A patients, while in 56.25% (9/16) of group B patients were evaluated as fair or poor.

CONCLUSION

Treatment of the trigger finger using ultrasonography resulted in fewer absence of work days, and better cosmetic results, in comparison with the open surgery technique. It is a promising method that represents excellent results without major complications, so that it could be possibly be established as a first-line treatment in the trigger finger's disease.

Key words: Ultrasound-guided; Trigger finger; A1 release; Comparative; V-lance knife; Percutaneous; Minimally-invasive

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Core tip: In this randomized, prospective clinical trial, of 32 patients with trigger finger or trigger thumb, ultrasound assisted treatment of the A1 pulley, revealed better outcome in comparison with the open technique. Patients had fewer work absence days and improved surgical scar. To the best of our knowledge this is the first randomized trial in this field. These promising results have to be further confirmed with larger trials in the future.

Nikolaou VS, Malahias MA, Kaseta MK, Sourlas I, Babis GC. Comparative clinical study of ultrasound-guided A1 pulley release vs open surgical intervention in the treatment of trigger finger. *World J Orthop* 2017; 8(2): 163-169 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/163.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.163>

INTRODUCTION

Stenosing tenosynovitis with mechanical impingement of the flexor tendons at the A1 pulley is a common condition affecting the digits in the following order of decreasing prevalence: Thumb, ring, middle, small and index. A nodule or thickening in the flexor tendon becomes trapped

proximal to the pulley, making finger extension difficult.

There have been described several management approaches in the treatment of trigger finger disease. Nonsurgical management includes corticosteroid injection and splinting. However, according to a level I systematic review^[1] corticosteroid injections are effective in just 57% of patients. Additionally, that technique can result in up to 29% recurrence^[2]. Furthermore, many patients treated by conservative means, like immobilization or injections, may additionally require surgery^[3]. In a recent clinical trial, designed to compare the effectiveness of 2 splint designs in treating trigger finger^[4], the results showed positive outcomes in 50%-77% of the patients, depending on the type of splinting.

On the other hand, many authors support the superiority of surgical procedures for the definite treatment of the disease^[5]. Indeed, the percutaneous and open surgery methods have been proved more efficient than simple corticosteroid injection, regarding the cure and relapse of the disease^[5,6]. Conventional open surgical technique remains the gold standard of treatment options^[7]. However, surgical treatment also has complications, including scarring, surgical site infections and nerve injuries, in addition to possible disease relapse^[8].

Percutaneous surgical release of trigger finger is a preferable alternative to open surgery^[9], although a potential disadvantage can be the injury to either nerve or tendon due to the limited visibility^[7]. Many hand surgeons avoid this treatment option due to the close proximity to the digital nerve^[10]. According to a meta-analysis of current literature^[11], blind percutaneous release has become more and more popular lately, with overall increased success rates.

Ultrasound can be a helpful tool for better success by means of assisting the placement of the the needle during percutaneous procedure^[12]. There is a controversy regarding the safety and usefulness of this technique. Paulius *et al*^[13] showed that ultrasound-guided treatment has disadvantages like tendon injuries, neural or vascular lacerations and no complete release of the first annular pulleys. As an answer to them, Wu *et al*^[14] support the usage of ultrasound assistance to avoid iatrogenic damage.

In a recent systematic review of current evidence, it is revealed that percutaneous release with ultrasonography, resulted in higher success rate than non-sonography release^[11]. Despite that, till now, no randomized controlled trials could be found at the Medline and Cochrane Database, comparing open surgery to ultrasound-guided percutaneous release.

This lack of reliable trials comparing open surgery to ultrasound-guided A1 pulley release is pronounced. In the present randomized controlled trial, we tried to compare the efficacy of a single ultrasound-guided percutaneous A1 pulley release with conventional open surgery in terms of ability to correct the trigger finger.

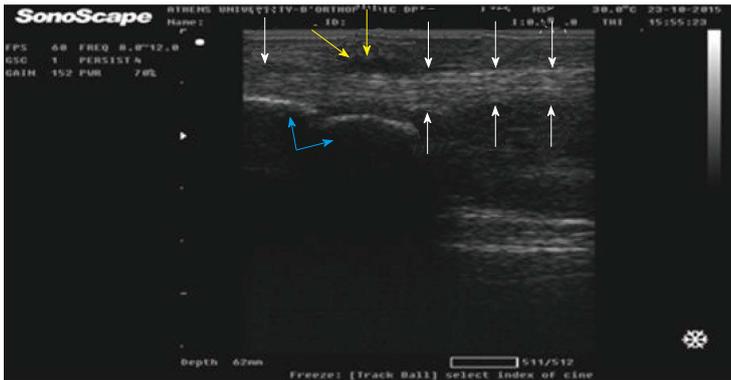


Figure 1 Longitudinal view of the middle finger's flexor tendons (white arrows) volarly to the metacarpal-phalangeal joint (blue double arrow). The A1 pulley appears swollen and anechoic (yellow arrows), establishing the trigger finger disease.



Figure 2 Positioning of the V-Lance Knife almost parallel to the probe.

MATERIALS AND METHODS

We conducted a randomized, prospective, controlled, single-center, clinical trial of 32 patients with resistant - after conservative treatment - trigger finger or trigger thumb, suffering at least for 3 mo. The majority of the patients were middle-aged women (62.5% females, mean age: 45.5 years old), evaluated as grade II to IV according to Green classification system of the trigger finger disease.

We excluded patients under 18 years old, those who were treated with a previous operation or a corticosteroid injection for their disease and those who were suffering by inflammatory arthritis, tumor or autoimmune disease. Moreover, we did not include patients with multiple trigger fingers trying to evaluate our study groups strictly using the model one patient-one trigger finger. We did not exclude patients with insulin-dependent diabetes mellitus and a history of other tendon related pathology of the upper extremity, although it is known that they might be linked with a higher rate of treatment failure^[15].

The patients were clinically and ultrasonographically examined and then they were randomly divided into two groups using a closed envelope. The ultrasonography was performed with a portable grey scale ultrasound (frequency of 10-12 MHz, 5-12 MHz, Linear Array, A6 Portable Ultrasonic Diagnostic System, SonoScape Company Limited, Shenzhen, China) by a doctor of our department. The patients were informed with an oral and written manner for their options of treatment and

they received clear explanations about their suggested treatment. For confirmation, they signed full written consent.

Group A (16 patients) was treated with an ultrasound-guided percutaneous release of the affected first annular pulley under local anesthesia and without any corticosteroid injection.

In addition, group B (16 patients) underwent a conventional open surgical release of the A1 pulley, through a 10-15 mm incision. The technique in group A included initially a sonographically guided local anesthetic injection, proximally to the metacarpal-phalangeal joint (Figure 1). The infiltration was done under sterile conditions (sterilization of the skin, coverage of the ultrasound probe with sterile pad, use of appropriate gel) by a physician that simultaneously managed the ultrasound device (one man's technique). Under continuous sonographic imaging of the digital neurovascular structures, the physician inserted percutaneously - through a negligible section < 1 mm - an ophthalmic corneal/scleral V-Lance knife (Alcon, Novartis company), over flexor tendons (Verdan's zone 3, proximally to the A1 pulley) and towards their longitudinal axis (Figure 2). Then, the knife was advanced distally, just below A1 pulley (Figure 3) and pressed palmar so as to loosen the thickened pulley (the intersecting part).

Thus, after having withdrawn the V-Lance knife (which had created the necessary space intrasheath), a thin hook with a long neck was introduced under the - now extended - A1 pulley (Figure 4). The hook penetrated the annular ligamentous structure facing palmar in order to protect the flexor tendons and subsequently removed proximally (in a steady quick move) carrying along and dissecting the A1 pulley. Intraoperatively and right after the performed dissection, each patient was clinically and sonographically evaluated for the achieved resolution of the triggering.

All patients were estimated with the completion of Q-DASH score before and after the operation (1, 4, 12 wk). Resolution of triggering (primary variable of interest) was expressed as the "success rate" per digit. The time for taking postoperative pain killers, range of motion recovery, return to normal activities (including work), complications and cosmetic results were assessed. Differences among groups were analysed using Student's *t* test. Statistical significant difference was considered if *P*

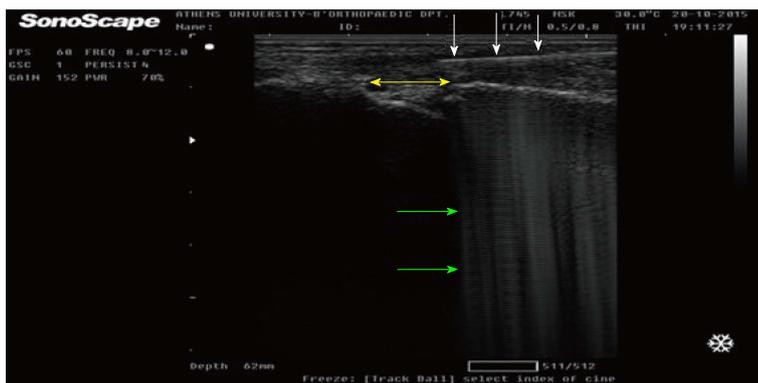


Figure 3 Longitudinal ultrasound-guided release of the A1 pulley. The knife -with its acoustic shadowing (green arrows) - is clearly visible (white arrows). Its tip is advanced over the metacarpal-phalangeal joint (yellow arrow), parallel to the superficial flexor tendon.

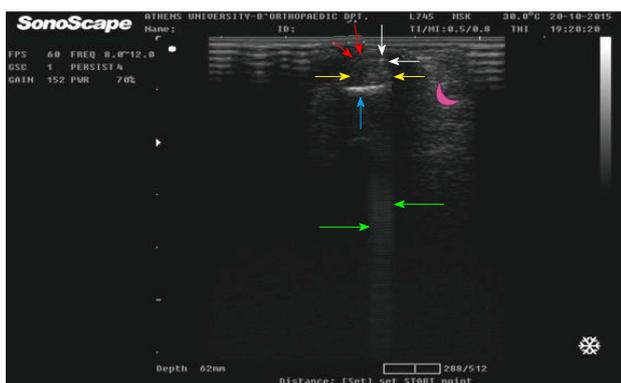


Figure 4 In order to be assured for the right position of the knife, we are transferred in transverse view of the tendons (flexor's transverse cut: Yellow arrows, lying on the bone: Light blue arrow). Here, we certify that the tip of the knife (tip as a white dot: white arrows, sending its characteristic acoustic shadow: Green arrows) is attaching the volar end of the tendons (without penetrating them), under the A1 pulley (the sheath is appeared as a thin line under the red arrows). Moreover, it is vital to avoid the neurovascular digital structures (digital artery in the curved side of the purple moon).

< 0.05.

The same doctor did the procedure in all patients (Group A and Group B) and evaluated them prior to the injection through Q-DASH questionnaire, clinical and ultrasound examination. Another doctor evaluated the patients in the follow-up period. This physician was blinded to the procedure (ultrasound-guided or open) and to the pre-injection scores of these patients as far as Q-DASH, resolution of triggering, painkillers and return to normal activities, but he was non blinded as far as cosmetic results, range of motion and complications. Instructions for return to work (or usual activities in elderly people) were different in group A patients than in group B. We were able to be more aggressive with group A patients which we advised to start their work from the first postoperative day. On the contrary, group B patients could not be managed to start working before removing their sutures (12-14 d).

Our study protocol (plus our written consent form) was approved by our Health's Institution Scientific Committee and the Athens University, School of Medicine.

RESULTS

We were able to visualize the flexor tendons under

the A1 pulley and recognise the digital neurovascular bundles in all group A patients. The whole percutaneous procedure was real-time documented and there was no mentioned intraoperative complication in anyone of our patients.

We managed to obtain follow-up in 100% (32 out of 32) of our patients. The success rate in group A was 93.75% (15/16) and in group B 100% (16/16) ($P > 0.05$). There was just one patient (female, 53 years old, white collar worker, with uncontrolled hypothyroidism, index finger) who appeared to have no improvement in her triggering after the percutaneous ultrasound-guided procedure. Apart from this exception, both techniques proved to be well tolerated, with no side effects, infections or complaints for persistent pain.

Mean times in group A patients were 3.5 d for taking pain killers, and 7.2 and 3.9 d for complete extension and flexion recovery, respectively (Table 1). Mean Quick DASH scores in group A were 45.5 preoperatively and, 7.5, 0.5 and 0 after 2, 4, and 12 wk postoperatively (Figure 5A).

Mean times in group B patients were 2.9 d for taking pain killers, and 5.6 and 3 d for complete extension and flexion recovery (Table 2). Mean QuickDASH scores in group B were 43.2 preoperatively and, 8.2, 1.3 and 0 after 2, 4, and 12 wk postoperatively (Figure 5B). These differences were not statistically significant ($P > 0.05$) among the two groups.

However, mean time for returning to normal activities in group A patients was 4.1 d as opposite to 17.8 d for Group B patients ($P < 0.05$).

Additionally, the cosmetic results found excellent or good in 87.5% (14/16) of group A patients, while in 56.25% (9/16) of group B patients were evaluated as fair or poor ($P < 0.05$) (Figure 6).

DISCUSSION

According to the literature, there is an emerging number of cadaveric and clinical studies investigating the use of ultrasound in hand and wrist tendinopathies^[15-17]. Especially in the trigger finger disease we were able to find a wide variety of anatomic or therapeutic trials^[18-20].

Ultrasound examination can diagnose secondary causes of trigger finger^[21], while it could be a valuable

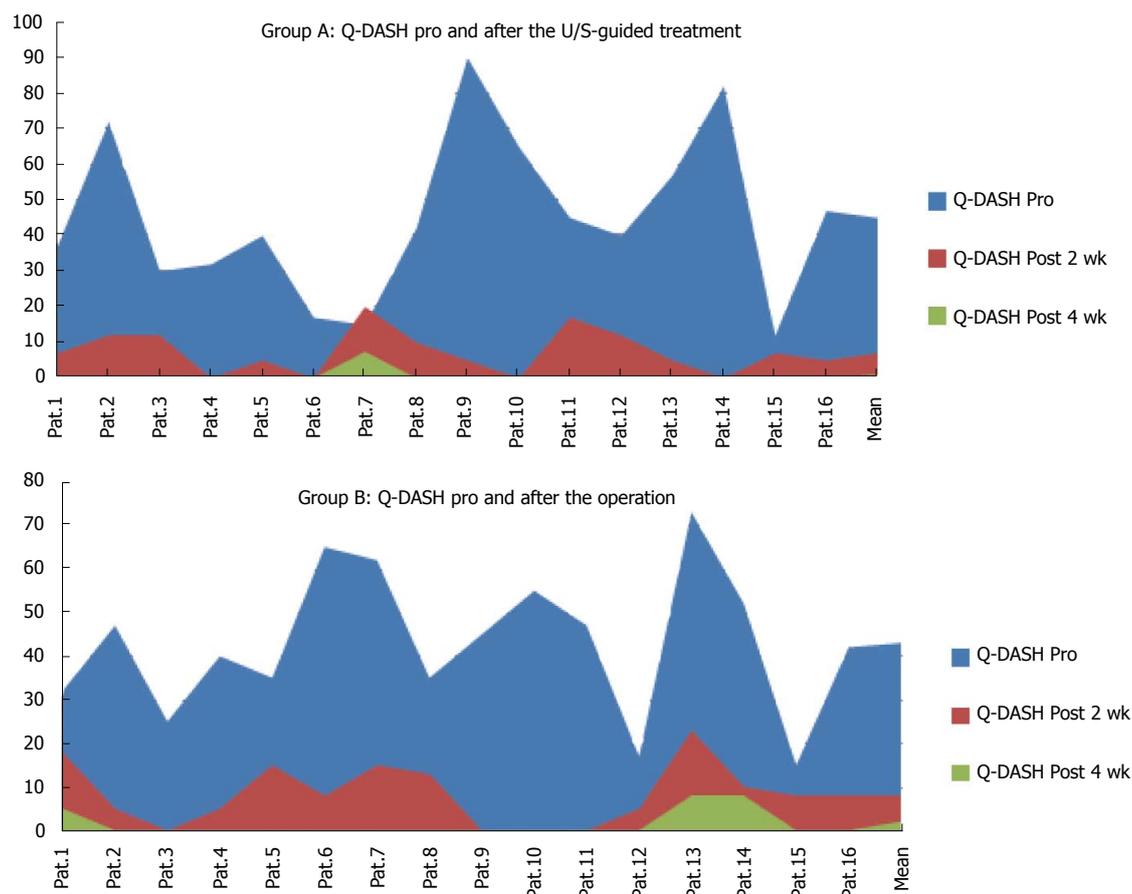


Figure 5 The Q-DASH fluctuation per patient in (A) and (B) respectively.

Table 1 Group A, data per patient: Days for: (1) taking pain killers; (2) returning to normal activities; (3) complete extension; and (4) flexion recovery

Group A	Post painkillers (d)	Return to normal (d)	Full extension (d)	Full flexion (d)
Patient 1	4	3	8	4
Patient 2	7	8	9	5
Patient 3	1	2	3	1
Patient 4	5	6	5	3
Patient 5	1	3	6	2
Patient 6	2	2	5	0
Patient 7	3	2	7	6
Patient 8	5	4	10	7
Patient 9	0	2	4	1
Patient 10	1	2	8	4
Patient 11	6	10	12	7
Patient 12	1	0	5	2
Patient 13	3	3	6	5
Patient 14	4	4	11	5
Patient 15	10	8	7	5
Patient 16	3	6	9	6
Total	56	65	115	63
Mean	3.5	4.1	7.2	3.9

Table 2 Group B, data per patient: days for: (1) taking pain killers; (2) returning to normal activities; (3) complete extension; and (4) flexion recovery

Group B	Post painkillers (d)	Return to normal (d)	Full extension (d)	Full flexion (d)
Patients 1	5	23	7	3
Patients 2	0	15	5	4
Patients 3	2	14	1	1
Patients 4	1	15	3	1
Patients 5	3	17	11	4
Patients 6	3	15	4	3
Patients 7	4	21	8	4
Patients 8	6	22	9	5
Patients 9	0	14	1	1
Patients 10	2	18	6	3
Patients 11	5	18	6	5
Patients 12	1	16	2	2
Patients 13	6	23	16	3
Patients 14	4	22	4	3
Patients 15	3	17	2	4
Patients 16	1	15	5	2
Total	46	285	90	48
Mean	2.9	17.8	5.6	3

tool in guiding therapeutic procedures. However, it can demand extra time and effort and the potential clinical benefits compared to the blind technique can be questionable^[22].

According to Rojo-Manaute *et al.*^[23], good knowledge of the anatomy, and excellent handling of the ultrasound machine, can result to safe and successful treatment of the trigger finger. Thus, offering an alternative to

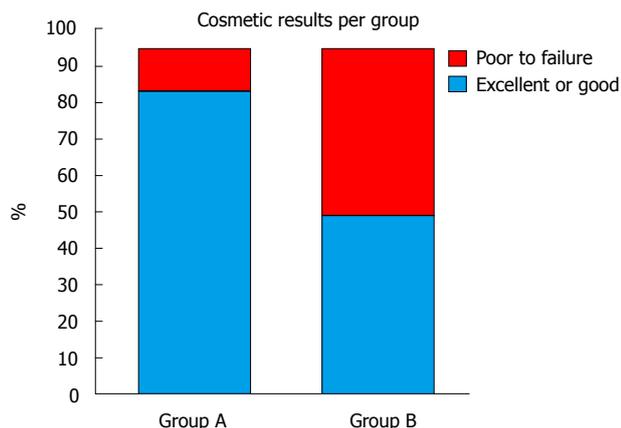


Figure 6 Regarding the cosmetic results, there is a clear difference between the two groups, in favor of the ultrasound-treated patients.

traditional open surgery. This specific procedure can be performed in the medical office with the use of a portable ultrasound device for the purpose of improving the cost-effectiveness of the treatment and reducing the surgery-related anxiety of patients. Furthermore, this technique promises to minimize postoperative short-term morbidity^[24].

Rajeswaran *et al.*^[25] described an ultrasound-guided procedure using a modified hypodermic needle to resolve trigger finger. He documented no complications and a complete resolution of triggering in 91% of his patients^[25]. Besides, using a knife result in a complete pulley release significantly better compared to the needle technique^[26]. On the other hand, in an experimental cadaveric study, ultrasound-guided percutaneous A1 pulley release resulted in repeated injuries of the tendon sheath and of the proximal neural or vascular structures^[13].

Finally, in the most recent study, Lapègue *et al.*^[27] conclude that US-guided treatment of the trigger finger is feasible in current practice, with minimal complications, even if their trial showed a 17% postoperative persistence of triggering.

In our study we aimed to prove that an ultrasound assisted release of the A1 pulley is - at least - not inferior than the open technique in a matched controlled population, regarding the clinical outcome scores. Strong points of our trial are that as far as we know, this is the first prospective randomized trial published in the English speaking literature. We have used different qualitative and quantitative scales to document our results. Apropos of indexes like Q-DASH, resolution of triggering, painkillers and return to normal activities, the follow-up of our patients was blinded.

Limitations of this study also merit to be mentioned. Statistical power is reduced due to the small sample size in the present study ($n = 32$). This could have played a role in reducing the significance of some of the statistical tests. A post hoc power analysis, using the GPower software (Faul and Erdfelder, 1992) showed that on the basis of the means, among groups, an n of

approximately 60 (30 in each group) would be needed to give better statistical power at the recommended 0.80 level. Additionally, We had only short- to mid-term results in the follow-up of our patients but at the other end of the spectrum this seems to be the usual postoperative protocol according to the literature^[28]. Another weakness of our study is that it was not as cost-effective as it could be. That was because we avoided treating our ultrasound-guided patients at the medical office but exclusively in the operative theater in order to eradicate extrinsic factors between the two groups.

Our study revealed that ultrasound assisted release of the A1 pulley resulted in less days of work absence and better cosmetic results, in comparison with the traditional open technique. Notwithstanding, it is necessary more clinical trials to be followed through on this area of interest in order to obtain more secure conclusions.

ACKNOWLEDGMENTS

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COMMENTS

Background

Stenosing tenosynovitis with mechanical impingement of the flexor tendons at the A1 pulley is a common condition affecting the digits in the following order of decreasing prevalence: Thumb, ring, middle, small and index. A nodule or thickening in the flexor tendon becomes trapped proximal to the pulley, making finger extension difficult. There have been described several management approaches in the treatment of trigger finger disease. Surgery is recommended in those cases that conservative treatment has failed. Conventional open surgical technique remains the gold standard of treatment. However, complications do exist, such as painful scarring, infections and nerve damage, in addition to recurrence of the disease.

Research frontiers

In a recent systematic review of current evidence, it is revealed that percutaneous release with sonography guidance had a significantly higher success rate than non-sonography guidance. Despite that, no randomized controlled trials exist comparing open surgery to ultrasound-guided percutaneous release. In the present randomized controlled trial, they compared the efficacy of a single ultrasound-guided percutaneous A1 pulley release with conventional open surgery in terms of ability to correct the trigger finger. To the best of our knowledge this is the first randomized trial in this field.

Applications

Ultrasound-guided release of the A1 pulley yielded better results compared to the traditional open technique, in respect to fewer working days lost and improved cosmetic results. It is a promising method that produces excellent results without major complications, so that it could be possibly be established as a first-line treatment in the trigger finger's disease. However, in order to be established as a first-line treatment in the trigger finger's disease, it is necessary more clinical trials to be followed through on this area of interest.

Terminology

Trigger finger: Stenosing tenosynovitis with mechanical impingement of the flexor tendons at the A1 pulley. Condition affects the digits in the following order

of decreasing prevalence: Thumb, ring, middle, small and index. A nodule or thickening in the flexor tendon becomes trapped proximal to the pulley, making finger extension difficult.

Peer-review

This manuscript investigated the usefulness of ultrasonography for the surgical treatment of finger.

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Observational Study

Lower limb intracast pressures generated by different types of immobilisation casts

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Abstract**AIM**

To determine if complete, split casts and backslabs [plaster of Paris (POP) and fiberglass] generate different intracast pressures and pain.

METHODS

Increased swelling within casts was modeled by a closed water system attached to an expandable bag placed directly under different types of casts applied to a healthy lower limb. Complete fiberglass and POP casts, split casts and backslabs were applied. Twenty-five milliliter aliquots of saline were injected into the system and the generated intracast pressures were measured using a sphygmomanometer. The subject was blinded to the pressure scores to avoid bias. All casts were applied to the same right limb on the same subject to avoid the effects of variations in anatomy or physiology on intracast pressures. Pain levels were evaluated using the Visual Analogue Score after each sequential saline injection. Each type of cast was reapplied four times and the measurements were repeated on four separate occasions. Sample sizes were determined by a pre-study 90% power calculation to detect a 20% difference in intracast pressures between cast groups.

RESULTS

A significant difference between the various types of

casts was noted when the saline volume was greater than 100 mL ($P = 0.009$). The greatest intracast pressure was generated by complete fiberglass casts, which were significantly higher than complete POP casts or backslabs ($P = 0.018$ and $P = 0.008$ respectively) at intracast saline volumes of 100 mL and higher. Backslabs produced a significantly lower intracast pressure compared to complete POP only once the saline volume within casts exceeded 225 mL ($P = 0.009$). Intracast pressures were significantly lower in split casts ($P = 0.003$). Split POP and fiberglass casts produced the lowest intracast pressures, even compared to backslabs ($P = 0.009$). Complete fiberglass casts generated the highest pain levels at manometer pressures of 75 mmHg and greater ($P = 0.001$). Split fiberglass casts had significantly reduced pain levels ($P = 0.001$). In contrast, a split complete POP cast did not produce significantly reduced pain levels at pressures between 25-150 mmHg. There was no difference in pain generated by complete POP and backslabs at manometer pressures of 200 mmHg and lower.

CONCLUSION

Fiberglass casts generate significantly higher intracast pressures and pain than POP casts. Split casts cause lower intracast pressures regardless of material, than complete casts and backslabs.

Key words: Fracture; Pressure; Lower limb; Plaster of Paris; Cast; Fiberglass; Backslab; Compartment syndrome

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Core tip: Little information is available regarding whether different lower limb casts generate different intracast pressures and pain during swelling, increasing the risk of compartment syndrome. Increased swelling within casts was modeled by a closed water system attached to an expandable bag placed directly under different types of casts. Our study suggests that split casts generate lower intracast pressures than backslabs, which are traditionally thought to accommodate swelling better. Fiberglass casts generate significantly higher intracast pressures and pain levels than plaster of Paris casts. Judicious use of complete casts, particularly fiberglass, and backslabs may be advisable for lower limb immobilisation.

Chaudhury S, Hazlerigg A, Vusirikala A, Nguyen J, Matthews S. Lower limb intracast pressures generated by different types of immobilisation casts. *World J Orthop* 2017; 8(2): 170-177 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/170.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.170>

INTRODUCTION

It is common practice to apply lower limb casts to manage non-displaced fractures, following lower limb surgery or

the temporary stabilisation of ankle fractures awaiting surgery so as to maintain a plantar grade position and to prevent contracture. Charnley originally described the principle of three-point loading of casts in the management of fractures^[1]. Fractures and subsequent immobilization with a constraining cast are associated with a potentially devastating risk of compartment syndrome, which results from elevated pressures within a confined space that results in occlusion of the arterial blood supply to muscles. Consequently it has become usual practice to apply backslabs instead of complete casts to obviate this risk. Casts can be applied either as backslabs, or as complete casts that may or may not be split. Splitting of casts is thought to allow for swelling, although they are no longer able to provide three point fixation. Clinical experience from the senior author has suggested that backslabs can also be associated with pain and compartment syndrome.

Previous studies have demonstrated that skin surface pressure under a cast correlates to intracompartmental pressure^[2]. There has been no detailed analysis to date of the effect of swelling on intracast pressures generated by backslabs or different commonly utilized casts materials applied as complete casts, and whether splitting the cast alleviates these pressures. In view of the increased risk of pain and compartment syndrome following fractures and subsequent immobilization with a cast, it is important to address whether different casting materials and types vary in their ability to accommodate swelling.

Backslabs are commonly applied to the acutely fractured limb as a temporizing measure to provide splintage and prevent displacement. This modality is employed on the assumption that the backslab will accommodate swelling, whereas application of a complete cast is thought to constrain any ensuing swelling. The effects of complete casts on generating intracast pressures within the upper limb have been investigated in a small number of studies, but have not been investigated in such detail in the lower limb. Younger *et al*^[3] compared the cast pressures associated with forearm plaster of Paris (POP) backslabs and complete POP casts that were split with different methods. The authors concluded that a split and spread cast was better able to accommodate intracompartmental swelling compared to backslabs. A study by Moir *et al*^[4] investigating intracast pressures in distal radius fractures showed that intracast pressures fall over the first week as swelling subsides. Interestingly, they demonstrated that a small immediate pressure rise is recorded as soon as the backslab is completed, even if completion occurs as late as 14 d. Another study using encircling distal radius plasters that were applied post manipulation of Colles fractures, failed to show any sustained increase in pressure. Despite this, the authors advocate that this technique is to be avoided and proposed a U-slab as a more favourable option in order to avoid the risk of Volkmann's ischaemic contracture^[5].

Split casts have been advocated by many as an alternative to backslabs, allowing sufficient compliance for swelling whilst retaining enough rigidity to support



Figure 1 Photo demonstrating the application of a 1-L emptied expandable bag onto a healthy right lower leg.



Figure 2 Photo demonstrating the placement of a closed water system circuit attached to a 1-L expandable bag under different types of casts, which had been applied to a healthy right lower limb. An intravenous giving set was connected the emptied bag with a three-way tap.

the fracture. A single split in cast in animal study was shown to reduce cast pressure by 65%^[6]. Weiner *et al*^[7] investigated the effect of bivalving casts and spreading each side by approximately half a centimeter, and subsequently measured the effects on intramuscular pressures in lower leg anterior and posterior compartments in healthy volunteers. It was reported that bivalving casts significantly reduced the pressures by 47% and 33% in the anterior and posterior compartment respectively ($P < 0.05$).

Two of the most commonly used materials for casts are POP and fiberglass; differences in their mechanical properties are well documented. Fiberglass is more expensive and less easy to mould, however it is lighter and less permeable to water than POP. This study addressed whether different types of commonly utilized plaster materials for forming lower limb casts generate different surface pressures. As backslabs concentrate any pressures over a smaller surface area, we hypothesized that backslabs may generate higher intracast pressures than complete casts.

The primary aim of this study was to evaluate the intracast pressures generated by different types of commonly used casts used to immobilize lower limb fractures, such as a complete POP or fiberglass casts,

and how they compared to POP backslabs. This study also assessed whether splitting the casts significantly reduced the intracast pressures. A secondary aim was to ascertain whether there were differences in subjective pain levels associated with intracast pressure changes generated by different cast materials based on the senior author's experience of compressive pain in postoperative patients being immediately relieved by removal of the back slab. Our working null hypothesis was that there is no difference in the intracast pressures or pain generated by different complete casts or backslabs. Our second null hypothesis was that split complete casts would not have reduced intracast pressures or associated pain levels compared to complete casts.

MATERIALS AND METHODS

Measurements of intracast pressures

This study modeled increased swelling within casts that may occur after lower limb injuries or surgery. A closed water system circuit attached to a 1-L expandable bag (Figure 1) was placed directly under different types of casts that had been applied to a healthy right lower limb (Figure 2). Intracast pressures were measured from the right leg for all of the readings, with the ankle in a neutral position with the knee extended while the subject rested on an examination bed. An intravenous giving set was connected to the emptied bag with a three-way tap. The three-way tap was connected to a sphygmomanometer through one portal and a 50 mL syringe through another portal, with a Luer lock used to secure all lines. Twenty-five milliliter aliquots of saline were injected into the system and the intracast pressures were directly measured using a sphygmomanometer (Figure 3). Measurements were started after an initial injection of 25 mL of saline, which were increased in increments of 25 mL until a total of 300 mL of saline had been injected. Two commonly utilized cast materials, fiberglass and POP were applied to the healthy lower limb before measurements were taken in a random order. The subject was blinded to the pressure scores in order to avoid bias.



Figure 3 Photo demonstrating how 25 mL aliquots of saline were injected into the system and the surface cast pressures were directly measured using a sphygmomanometer.

During each pressure reading, a subjective assessment of any pain was also made using the Visual Analogue Score (VAS). The VAS score ranges from 1 to 10, with 10 indicating the most severe pain. Between each recording, the system was fully drained of all liquid before recommencing the next casting. The sphygmomanometer was returned to zero in between castings. The measurements were terminated early before 300 mL had been injected if the subject reported a VAS score of 10 or when three identical consecutive pressure readings were measured after injection of sequential 25 mL aliquots. Each type of cast was reapplied four times and the entire measurement process was repeated on four separate occasions. A pre-study power calculation based upon pilot data determined that $n = 4$ was sufficient to achieve 90% power to detect a 20% difference in intracast pressures between different cast groups, with $\alpha = 0.05$. In order to reduce the effects of bias or multiple castings on VAS pain scores, a random order was selected for application of the different cast materials to try to reduce variability.

Plastering technique

A single healthy subject with no history of lower limb trauma was fitted with sequential casts. All casts were applied to the same right limb on the same subject to avoid the effects of any variations in anatomy or physiology on intracast pressures that may arise from using different subjects. The subject had no previous experience of any casts.

In order to reduce variability in application techniques, the plastering for the different cast groups was carried out in exactly the same manner by a single orthopaedic plaster technician with over 15 years of experience. The expandable bag was placed on the anterolateral aspect of the right calf. Marks on the calf delineated exactly where the bag should be placed for all castings and the saline bag was taped in place to assist reproducible placement. A 4-inch stockinette was used, followed by 2 layers of Velband® (Velband®, Smith and Nephew, Hull, United Kingdom) before the top layers of the casts were applied using a standard technique. For the POP casts, 3 rolls (Gypsona®, BSN Medical, France) were used per cast

and for the fibreglass casts (BSN Medical) 4 rolls were utilized. When splitting of the cast was required, a single medial split was made along the medial edge of the tibia and the cast was cut to skin. Backslabs were applied with a single slab of POP posteriorly, consisting of 4 layers of POP. The backslabs were further reinforced on the medial and lateral sides, as per standard local protocol. The casts were allowed to harden fully before the data was collected from the lower leg.

Statistical analysis

Any differences between the 5 cast groups were assessed using a repeated measures ANOVA with a Bonferroni multiple comparison test to compare individual cast types and account for potential type-I errors associated with multiple statistical tests. All tests were two tailed and a significance level of $P < 0.05$ was set. GraphPad Prism 5 (Graph Pad Software, LaJolla, California) software was used for statistical analysis.

RESULTS

The results indicated that the introduction of fluid into the different casts generated different intracast pressures (Table 1). A significant difference between the various types of casts was noted when the saline volume was greater than 100 mL ($P = 0.009$, Figure 4). The greatest intracast pressure was measured from complete fibreglass casts and this was significantly greater than complete POP casts ($P = 0.018$) and backslabs ($P = 0.008$) at intracast saline volumes of 100 mL and higher. Backslabs produced a significantly lower intracast pressure compared to complete POP only once the saline volume within casts exceeded 225 mL ($P = 0.009$).

Split POP casts generated the lowest intracast pressure of all the different casts. Split POP casts produced significantly less intracast pressure compared to backslabs when saline volumes were greater than 100 mL. At this volume of 100 mL, a significant reduction in intracast pressures were noted after splitting of both the complete POP and complete fibreglass casts ($P = 0.003$). Once both types of complete casts had been split, there was no significant difference between the two different groups of split casts.

The effects of different types of casts on pain levels were also investigated. Fibreglass casts generated significantly greater pain levels when saline volumes were as low as 75 mL ($P = 0.001$) and continued to produce the highest pain levels at all measured volumes between 75-200 mL ($P < 0.05$, Figure 5). Splitting the complete fibreglass cast at 75 mL of saline significantly reduced pain levels ($P = 0.001$) and this trend was also seen between 100-200 mL of saline ($P < 0.001$). In contrast, splitting a complete POP cast did not significantly reduce the pain levels at saline volumes between 25-150 mL. When the intracast volumes were set at 175 mL, splitting the complete POP cast does result in a significant reduction in pain ($P = 0.013$). This trend towards no reduction in pain is also seen at saline volumes between 200-250 mL ($P <$

Table 1 Summary of intracast pressures and pain scores recorded after application of the different cast types

		Mean	Std. deviation	Std. error	95%CI for mean		Minimum	Maximum	P-value
					Lower bound	Upper bound			
Intracast pressure (mmHg)	Backslab	47.05	31.8	4.79	37.38	56.71	2	120	< 0.001
	Full POP	72.28	60.3	9.66	52.73	91.83	2	230	
	Split POP	17.15	7.53	1.29	14.52	19.77	1	28	
	Fibreglass	82.73	67.01	12.23	57.71	107.76	2	240	
	Split Fibreglass	26.58	21.33	3.25	20.02	33.15	0	70	
	Total	47.88	48.48	3.52	40.94	54.82	0	240	
Pain (VAS score)	Backslab	3.99	2.9	0.44	3.11	4.87	0	10	< 0.001
	Full POP	4.77	3.73	0.6	3.56	5.98	0	10	
	Split POP	1.04	1.06	0.18	0.67	1.41	0	3	
	Fibreglass	5.8	3.37	0.62	4.54	7.06	0	10	
	Split Fibreglass	1.9	2.09	0.32	1.25	2.54	0	7	
	Total	3.43	3.24	0.24	2.97	3.9	0	10	

POP: Plaster of Paris; VAS: Visual Analog Scores.

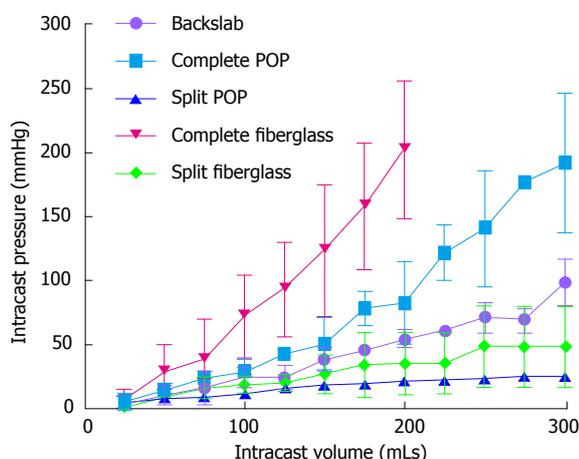


Figure 4 Graph indicating intracast pressures (mmHg) generated by different types of lower limb casts (mean + standard error bars). Both complete fiberglass and complete plaster of Paris casts (POP) generated the greatest casts pressures. The surface pressures were significantly reduced when these casts were split. Split POP and fiberglass casts generated significantly less pressure than backslabs.

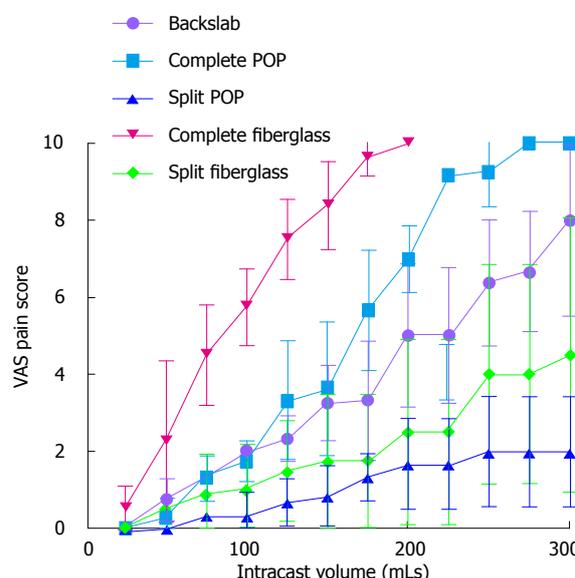


Figure 5 Graph indicating pain levels generated by different types of lower limb casts, as measured by Visual Analog Scores (mean + standard error bars). Complete fiberglass casts generated the highest pain levels. Split fiberglass casts produced significantly less pain at intracast volumes of 75 mL and greater. There was no significant difference in pain generated by complete plaster of Paris casts (POP) and backslabs when the intracast volume was 200 mL or lower. VAS: Visual Analog Scores.

0.003).

DISCUSSION

Closed splinting techniques with casts are commonly used in orthopaedics as a temporizing management technique for both conservatively and operatively treated lower limb injuries to prevent secondary equinus deformities. POP casts are frequently applied in the immediate acute setting, and these are often later changed to synthetic casts. Controversies exist between the ideal cast material and application mode. Important material properties that need to be considered for orthopaedic splints include strength, stiffness, compliance and weight. If constrictive casts increase the extra or intracast pressure in swollen lower limbs carries, they can potentially contribute to compartment syndrome, as well as other complications such as increasing pain, skin necrosis, circulatory compromise and fracture displacement. Thus, minimizing

pressures associated with casts is imperative.

This study found that different casts produce different intracast pressures and fiberglass casts generate significantly higher intracast pressures than POP casts, rejecting our null hypothesis. These findings are consistent with results from published studies^[8]. Fiberglass casts are frequently utilized to form casts due to a number of advantageous material properties, including its lighter weight compared to POP. The time taken to reach maximum strength is much shorter in fiberglass compared to POP^[9] and the strength and stiffness achieved with fiberglass has been shown to be greater than POP^[10,11]. The polyurethane in standard fiberglass undergoes a chemical change during hardening^[12]. We hypothesize that fiberglass casts generated higher intracast pressures

due to their higher recoil element, which is not applicable to POP, and their lower compliance^[8]. Compliance between fiberglass and POP has been compared in previous studies. Fiberglass was shown to require a greater volume change to generate the same pressure rise during the initial stages of swelling^[13]. However, once a certain pressure threshold had been exceeded, fiberglass pressures were found to rise steeply with less volume change. Our study found that once the intracast volume of saline exceeded 75 mL, fiberglass casts produced a rapid rise in intracast pressures. Stress relaxation has been demonstrated in both POP and fiberglass and attributed to the composite nature of fiberglass and POP, as well as the mesh design. These properties are presumed to allow relaxation within the materials over a constant volume distention, ultimately allowing pressures to reduce. Clinically this is advantageous as otherwise peak pressures generated by both materials would be much higher and sustained for longer periods^[13]. In view of the persistently higher pressures demonstrated by fiberglass casts in this study, the authors advocate POP casts over fiberglass for injured lower limbs in the acute phase, particularly for the first 24 h.

Backslabs were associated with significantly higher intracast pressures than split POP casts at saline volumes of greater than 125 mL, suggesting that split POP generate less intracast pressure when the swelling and volume rises within a cast. Interestingly, these results suggest that split POP are more effective than backslabs at avoiding the generation of high intracast pressures when the swelling and volume of saline within the cast increases. Ultimately, split POP casts may be a safer choice for casting technique in situations when swelling is expected, such as immediately following fractures or post-operatively. According to our results, backslabs were associated with lower intracast pressures in comparison to complete fiberglass or POP casts. Despite the fact that backslabs only cover a smaller surface area compared to complete casts, backslabs do not concentrate the intracast pressures and thus our null hypothesis was rejected. This study supports the widely assumed theory that backslabs are better able to facilitate acute swelling and supports the use of backslabs immediately after injury or after surgery when further swelling is anticipated. While backslabs may accommodate further swelling, this must be balanced against the risk that once the swelling reduces, backslab provide less resistance to deforming forces compared to complete casts which ultimately increases the potential for fracture displacement. While Charnley's three-point loading of casts for the management of fractures is a commonly accepted and applied principle^[1], this appears to be more difficult to achieve with backslabs. Wytch *et al.*^[14] used intracast pressure measuring techniques to demonstrate that loading in backslabs is low and although this is improved with moulding, they did not find evidence of Charnley's three-point loading principle.

Issues of generating high intracast pressures are applicable to both upper and lower limb fractures, as the former are also often managed with an initial backslab

that may later be converted into a complete cast. As an example, a common preliminary method of managing Colles fracture includes application of an initial dorsoradial plaster that is later completed to a complete below elbow cast once a sufficient time period has elapsed and the risk of significant swelling is assumed to have diminished.

Splitting the casts resulted in a universal decrease in intracast pressures, regardless of cast material. However the reduction in cast pressures following splitting was more marked in fiberglass than in POP casts. This study suggests that splitting complete casts, particularly fiberglass casts, may be advisable in clinical scenarios associated with acute limb swelling. This difference may be attributable to the greater ability of fiberglass to recoil at the site of splitting the cast.

Measuring compliance of material and pressures generated from encasement with a cast has been investigated with a variety of different methodologies. This study utilized a saline bladder system rather than an air-filled system as it is easier to detect any leaks. Sensors can directly be applied to the skin to measure surface cast pressures, however they do not allow a spectrum of recordings to be carried out in a dynamic volumetric distension system, as was permitted by our study design. A study used a modified Sengstaken tube to investigate intracast pressures generated within backslabs that had been applied following surgical fixation of ankle fractures in 15 patients^[15]. The mean pressure rise reported was 3.4 mmHg and the maximum measured pressure was 20.2 mmHg. The study also showed that maximum pressure peaked within 2 h of surgical fixation. This study measured a much wider range of manometer and surface pressures.

A number of limitations are associated with this study. A healthy subject was used and a saline system was used to emulate soft tissue swelling that may occur in an acutely fractured lower limb and the authors appreciate that this is not a direct measurement of compartment pressure. Previous studies investigating intracast pressures have found lower readings in healthy subjects compared to injured patients^[5]. However, the aim of this study was to investigate the effects of soft tissue swelling on intracast pressures and this could be achieved using a healthy subject. This study cannot extrapolate how intracast pressures are related to intracompartmental pressures or compartment syndrome, even though a strong correlation between extra and intracompartmental pressures has been previously demonstrated^[16]. The direct effect of different casts on intracompartmental pressures was beyond the scope of this study and ideally should be addressed by future studies. All measurements in this study were performed on a single subject to avoid inter-subject variations in pain threshold, thus avoiding potential bias. However, there was potential for the subject to become sensitized to pain, following repeated measurements after multiple cast applications. To avoid this, different casts were applied in a random order. Although the subject was blinded to pressure readings, the subject would have been aware of the increase in pressure as the study progressed with each individual

cast and may have anticipated increasing pain.

This study only investigated the pressures generated immediately after cast application and did not model any delayed increases that may occur following swelling of fractured limbs as a healthy limb was utilized. Patrick *et al.*^[5] measured intracast pressures in healthy subjects and patients with Colles fractures. In the Colles fracture group they observed a first and second peak phenomenon, whereby pressures rose immediately after application of the plaster and then rose again after an average of 13 h before gradually declining to reach a resting value after 72 h. The first peak was observed in healthy subjects however the second peak was not and the authors concluded that the second peak was due to delayed swelling associated with the fracture. Attempts were made to keep the infusion rate constant, but this was not verified by any measurements. A previous study showed using pressure volume dynamics that fluid infused at a faster rate led to a quicker pressure rise and decreased accommodation in POP and fibreglass. Interestingly, the decreased stiffness observed in the two materials at slower infusion rates was more apparent at lower pressures in the POP group than the fibreglass^[13].

External splinting is widely utilized in orthopaedics and trauma to stabilize fractures or support surgical constructs. Casts are associated with rare but potentially devastating complications of compartment syndrome and skin necrosis. This study demonstrated that as the volume within a cast rose, complete fibreglass casts generated significantly higher intracast pressures than complete POP casts. Complete fibreglass and POP casts were associated with significantly greater pressures than backslabs. Splitting casts confirmed a universal decrease in intracast pressures regardless of the material utilized. Backslabs are traditionally thought to allow greater swelling and produce lower pressures within the cast, yet our findings suggest that split POP produces the lowest intracast pressures and may be the most appropriate casting technique in situations where swelling is anticipated. Thus judicious use of complete casts, particularly fibreglass casts may be advisable in cases where significant swelling is anticipated in fractured limbs. The application of split POP casts in the immediate acute setting may be more beneficial in high-risk patients such as neuropathic, diabetic and unconscious patients. Further research is required to determine the pressure rises associated with a broader range of casts such as soft casts and hybrid fibreglass reinforced POPs as well as whether the stockinette or Velband® generate higher constraint and pressures than other materials.

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COMMENTS

Background

Lower limb fractures with subsequent immobilisation with a cast are associated with a potential risk of developing compartment syndrome.

Research frontiers

Different types of casts could potentially produce different intracast pressures which could ultimately increase intracompartmental pressures. There has been no detailed analysis to date of the effect of swelling on intracast pressures generated by backslabs or different commonly utilized cast materials applied as complete casts, and whether splitting the cast alleviates the pressures.

Innovations and breakthroughs

Introduction of fluid into different casts was used as a surrogate for volume expansion. This generated different intracast pressures. When increase in saline volume was greater than 100 mL, a significant difference in intracast pressures was observed between various types of casts. Intracast pressures were significantly greater in complete fibreglass casts in comparison to complete plaster of Paris (POP) casts and backslabs. Backslabs produced a significantly lower intracast pressure compared to complete POP casts only once the saline volume within casts exceeded 225 mL. Split POP casts generated the lowest intracast pressures of all casts and less than backslabs when saline volume exceeded 100 mL. Splitting casts reduced intracast pressures of both POP casts and fibreglass casts. When split, no significant difference was observed in intracast pressures between the two types of split casts. Fibreglass casts produced greater pain levels when saline volume was as low as 75 mL and it continued to produce the highest pain levels. The data indicates that split fibreglass casts were associated with significantly less pain than complete fibreglass casts. Splitting the complete POP cast did not significantly reduce the pain levels until saline volume was 175 mL.

Applications

Judicious use of complete casts, particularly fibreglass casts and backslabs may be advisable for lower limb immobilisation. The use of a split cast for lower limb immobilisation in the immediate acute setting may be more beneficial for high risk patients such as neuropathic, diabetic and unconscious patients.

Terminology

POP cast: Plaster of Paris is a hemihydrated calcium sulfate material which solidifies when mixed with water. It is used as a cast for immobilisation of a fractured limb. Fibreglass is a synthetic alternative to the traditional POP. The fibreglass bandages are impregnated with a quick setting water-soluble resin. It is a lighter, water proof cast used for immobilisation of fractured limbs. Backslabs are partial casts applied to the posterior aspect of the limb. They are held onto the limb with a bandage.

Peer-review

This is a good manuscript on a clinical relevant issue. Style and study design are fine.

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Internet and social media usage of orthopaedic patients: A questionnaire-based survey

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Abstract

AIM

To evaluate social media usage of orthopaedic patients to search for solutions to their health problems.

METHODS

The study data were collected using face-to-face questionnaire with randomly selected 1890 patients aged over 18 years who had been admitted to the orthopaedic clinics in different cities and provinces across Turkey. The questionnaire consists of a total of 16 questions pertaining to internet and social media usage and demographics of patients, patients' choice of institution for treatment, patient complaints on admission, online hospital and physician ratings, communication between the patient and the physician and its effects.

RESULTS

It was found that 34.2% ($n = 647$) of the participants consulted with an orthopaedist using the internet and 48.7% ($n = 315$) of them preferred websites that allow users to ask questions to a physician. Of all question-askers, 48.5% ($n = 314$) reported having found the answers helpful. Based on the educational level of the participants, there was a highly significant difference between the rates of asking questions to an orthopaedist

using the internet ($P = 0.001$). The rate of question-asking was significantly lower in patients with an elementary education than that in those with secondary, high school and undergraduate education ($P = 0.001$). The rate of reporting that the answers given was helpful was significantly higher in participants with an undergraduate degree compared to those who were illiterate, those with primary, elementary or high school education ($P = 0.001$). It was also found that the usage of the internet for health problems was higher among managers-qualified participants than unemployed-housewives, officers, workers-intermediate staff ($P < 0.05$).

CONCLUSION

We concluded that patients have been increasingly using the internet and social media to select a specific physician or to seek solution to their health problems in an effective way. Even though the internet and social media offer beneficial effects for physicians or patients, there is still much obscurity regarding their harms and further studies are warranted for necessary arrangements to be made.

Key words: Patient; Internet; Orthopedist; Social media; Communication

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Core tip: There is an ongoing increase in the use of social media and internet for health information. Patients can share their health-related experiences or issues online *via* social media and discussion forums or can consult with experienced physicians. Despite benefits and advantages of social media for patient-physician relationship, legal liability and possible harms and risks of the shared information and communication should be born in mind.

Duymus TM, Karadeniz H, Çaçan MA, Kömür B, Demirtaş A, Zehir S, Azboy İ. Internet and social media usage of orthopaedic patients: A questionnaire-based survey. *World J Orthop* 2017; 8(2): 178-186 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/178.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.178>

INTRODUCTION

The effects of patient-physician communication through social media or internet have long been of interest^[1,2]. Facebook, Twitter, My Space and Linked In have been reported to be the most commonly used social networking sites around the world, being Facebook the most popular, whose use has increased rapidly in recent years^[3]. Social media tools enable patients to communicate with their physicians faster online and help them clarify their understanding of their illness, express themselves better and share their problems visually or in writing^[4,5]. Social media tools have been increasingly used as a means to share their health issues and seek solutions and have changed the nature

of traditional patient-physician relationship^[6-8]. On the other hand, problems arising from the interpretation and implementation of the information shared online have recently gained attention. In addition, there are possible risks associated with the spread of unnecessary and inaccurate information easily and the legal gaps in this area^[9,10]. Therefore, further research and specific arrangements should be made on how, to what extent and when social media and internet to be used. As far as we are aware, there are few studies dedicated to address how orthopaedic patients use social media for their health issues, choice of hospital and physician and patient-physician relationships. The identification of how orthopaedic patients view and use social media can shed light on studies and arrangements of physicians, health bureaucracy and health legislation committees in our country.

The objective of this study was to identify the prevalence of orthopaedic patients' usage of internet and social media and the effects of internet and social media on hospital and physician selection, patient-physician communication and choice of treatment.

MATERIALS AND METHODS

A face-to-face questionnaire with a total of randomly selected 1890 patients aged over 18 years who were admitted to the orthopaedic clinics of private and public hospitals in different regions of Turkey between January 2016 and March 2016 was conducted. The participants were informed about the content and purpose of the questionnaire and were asked to fill in the questionnaire. Patients' identity information was not included in the questionnaire and each questionnaire was numbered. All data were collected and analyzed. Participants received no financial or educational incentive. The questionnaire consisted of a total of 16 questions pertaining to patients' personal information (age, sex, educational level, occupation), the healthcare institution the questionnaire was conducted, patients' complaints on admission, duration of complaints, the effects of social media and internet on patients' choice of hospital and physician and patient-physician communication and patients' usage of internet and social media (Table 1).

Statistical analysis

Statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, United States). Data were analyzed using descriptive statistics (mean, standard deviation, median, frequency, rate, minimum, maximum) whereas qualitative data were compared using the Pearson χ^2 test, Fisher Freeman Halton test and Yates' continuity correction test (Yates corrected χ^2). P values of < 0.01 and 0.05 were considered statistically significant.

RESULTS

Of all participants, 52% ($n = 982$) were females and 48% ($n = 908$) were males. The mean age of the

Table 1 Questions designed to identify patients' usage of internet and social media

Age
Sex
Occupation
Educational level
Place of residence
Hospital where the questionnaire was administered
Question 1: What's your complaint?
Question 2: How long have you had this complaint?
Question 3: Have you ever been examined in an orthopaedic clinic?
Question 4: Have you ever had an orthopaedic surgery?
Question 5: Did the internet have an impact on your choice of this hospital?
Question 6: Which one(s) of the following had an impact on your choice of hospital? (you can select more than one option)
Question 7: Which one(s) of the following had an impact on your choice of physician? (you can select more than one option)
Question 8: Have you ever asked an orthopaedist his/her opinion about your disease using the internet?
Question 9: Which options do you prefer to ask an orthopaedist his/her opinion? (you can select more than one option)
Question 10: With which of the following you can describe the answers you were given? (you can select more than one option)
Question 11: Have you ever sent a friend request to an orthopaedist on Facebook?
Question 12: Do you have orthopaedist friends on Facebook?
Question 13: Do you think that orthopaedists should keep in contact with you through the internet?
Question 14: Which one(s) of the following do you use to ask your physician a question? (you can select more than one option)
Question 15: Have you ever attempted to treat your disease/orthopaedic problem based on the information you obtained from the internet?
Question 16: What do you think about having X-rays performed in the nearest hospital and sending them to your physician over the internet for your post-operative follow ups?

Table 2 Participants' demographics

		<i>n</i>	%
Educational level	Illiterate	119	6.6
	Primary school	598	33.2
	Secondary school	214	11.9
	High school	500	27.7
	Undergraduate	330	18.3
	Master's degree	42	2.3
Occupation	layperson (unemployed or retired)	546	28.9
	Officer	80	4.2
	Housewife	587	31.1
	Worker - Intermediate staff	342	18.1
	High-status position in the public sector	139	7.4
	Manager in the private sector - Qualified	116	6.1
	Other	80	4.2
Hospital where the study was conducted	Training and Research Hospital Public	400	21.2
	University Hospital	694	36.7
	City Public Hospital	546	28.9
	Province Public Hospital	135	7.1
	Private Hospital	115	6.1
Complaint(s)	Knee pain	469	24.8
	Low-back pain	329	17.4
	Shoulder pain	217	11.5
	Foot pain	346	18.3
	Fracture treatment	217	11.5
	Hip pain	147	7.8
	Prosthesis surgery	38	2.0
	Arthroscopy	32	1.7
	Fracture surgery	98	5.2

participants was 40.64 ± 15.35 years (18-88 years) (Table 2).

The rate of the effect of internet on participants' choice of hospital was 50.9% (*n* = 962) and on participants' choice of physician was 39.4%. It was found that 14.4% (*n* = 273) of the participants preferred the Ministry of Health's (MH) Centralized Hospital Appointment System whereas 2.9% (*n* = 54) used Facebook to select a physician online. Of all

participants, 34.2% (*n* = 647) reported having asked an orthopaedist his/her opinion about their diseases using the internet and the question-askers most often preferred the web-sites allowing question-asking. In addition, 48.5% (*n* = 314) of the question-askers reported that the answers given were helpful (Table 3).

Of the participants, 46.7% (*n* = 883) thought that orthopaedists should keep in contact with patients over

Table 3 The distribution of participants' choice of hospital or physician and the distribution of data about asking an orthopaedist his/her opinion about a disease (*n* = 1890)

	<i>n</i>	%
The effect of the internet on hospital choice	962	50.9
¹ Which one(s) of the following had an impact on your hospital choice		
Centralized Hospital Appointment system	212	22.0
Website of the hospital	100	10.4
Hospital rating websites	100	10.4
Peer advice on the internet	66	6.9
Facebook	57	5.9
Other (182MHRS call center)	487	50.6
¹ Which one(s) of the following had an impact on your physician choice		
Random choice from the MHRS system	723	14.4
Other patients' advices on the internet	169	8.9
Physician rating websites	101	5.3
Website of the hospital	123	6.5
Physician personal website	110	5.8
Facebook	54	2.9
Other(MHRS 182 call center)	1146	60.6
Asking an orthopaedist his/her opinion about a disease using the internet	647 (n)	34.2 (%)
¹ Which option(s) do you prefer to ask an orthopaedist his/her opinion?		
Websites allowing asking physicians questions	315	48.7
Physician's personal website	149	23.0
Facebook	103	15.9
E-mail	72	11.1
With which of the following can you describe the answers you were given?		
Helpful	314	48.5
Effective in my choice of hospital/physician	137	21.2
I became more confused	102	15.8

¹More than one option was selected.

the internet. The rate of asking an orthopaedist his/her opinion about their diseases in participants aged between 18-30 years was statistically significantly higher than that in patients aged between 31-45 years, 46-60 years, 61-75 years and older than 75 years ($P = 0.001$; $P = 0.001$; $P = 0.001$; $P < 0.01$, respectively). It was noted that males used internet more often for asking questions compared to females ($P < 0.01$). Of all participants, 19.5% (*n*: 368) attempted to treat their orthopaedic problems/diseases using the information they obtained online. There was a strong statistically significant relationship in the rate of participants' using online information to treat their orthopedic problems/diseases according to the age groups ($P = 0.001$; $P < 0.01$). The rate of attempting to treat their orthopedic diseases/problems using online information was statistically significantly higher in the participants aged between 18-30 years than that in those aged between 61-75 years and older than 75 years ($P = 0.030$; $P = 0.003$; $P = 0.049$; $P < 0.05$) (Table 4). Thirty-four percent of the patients wanted to get postoperative X-ray controls performed using the internet whereas 66% of the participants stated that postoperative follow-ups should be face-to-face.

There was a strong statistically significant difference in the rates of answering "yes" to the question of "Have you ever asked an orthopaedist his/her opinion about your disease" according to the educational level of the participants ($P = 0.001$; $P < 0.01$). The rate of answering "yes" to the question of "Have you ever asked an ortho-

pedist his/her opinion about your disease using the internet" was statistically significantly lower in participants who were illiterate compared to that in those with secondary, high school and undergraduate education ($P = 0.004$; $P = 0.003$; $P = 0.001$; $P < 0.01$). Similarly, the rate answering "yes" to the question of "Have you ever asked an orthopaedist his/her opinion about your disease using the internet" was statistically significantly lower among participants with elementary level of education compared to that in those with secondary, high school and undergraduate education" ($P = 0.022$; $P = 0.010$; $P = 0.001$; $P < 0.05$) (Table 5). The rate of reporting that the answers given was helpful was significantly higher in participants with an undergraduate degree compared to those who were illiterate, those with primary, elementary or high school education ($P = 0.014$; $P = 0.001$; $P = 0.004$; $P = 0.001$, respectively). The rate of stating "I became more confused" was significantly lower in patients with an undergraduate degree compared to those with elementary and secondary education ($P = 0.006$; $P = 0.001$) (Table 5).

According to the occupational status, the rate of internet use for asking an orthopaedist a question was higher in managers-qualified employees compared to unemployed-housewives, officers, workers-intermediate staff ($P = 0.001$; $P = 0.013$; $P = 0.001$). The rate of reporting that the answers given by the orthopaedist were useful was significantly higher in managers-qualified employees compared to unemployed participants-

Table 4 The distribution of data about befriending with an orthopaedist, utilizing the information obtained and postoperative follow-ups (*n* = 1890)

	<i>n</i>	(%)
Sending friend request to an orthopaedist on Facebook	162	(8.6)
Befriending with an orthopaedist on Facebook	142	(7.5)
Do you think that orthopaedists should keep in contact with you over the internet?		
Not necessary	1007	(53.3)
Necessary	883	(46.7)
¹ Which one(s) of the following do you prefer to ask your physician a question?		
LinkedIn	17	(0.9)
Twitter	54	(2.9)
Facebook	144	(7.6)
Text-message to cell-phone	150	(7.9)
E-Mail	176	(9.3)
What's App	204	(10.8)
Call his/her cell-phone	814	(43.1)
Other	301	(15.9)

¹More than one option was selected.

Table 5 Asking an orthopaedist his/her opinion over the internet and interpreting the information obtained according to educational level *n* (%)

	Educational Level						<i>P</i>
	Illiterate	Primary	Secondary	High-school	Under graduate	Post graduate	
Participants who asked an orthopaedist his/her opinion about a disease?							
Yes	26 (21.8)	173 (28.9)	80 (37.4)	181 (36.2)	147 (44.5)	14 (33.3)	¹ 0.001 ^b
No	93 (78.2)	425 (71.1)	134 (62.6)	319 (63.8)	183 (55.5)	28 (66.7)	
With which one(s) of the following can you describe the answers you were given?							
Helpfull							
Yes	5 (19.2)	34 (19.7)	12 (15)	29 (16)	10 (6.8)	1 (7.1)	² 0.021 ^a
No	21 (80.8)	139 (80.3)	68 (85)	152 (84)	137 (93.2)	13 (92.9)	
I became more confused							
Yes	11 (42.3)	71 (41)	24 (30)	89 (49.2)	102 (69.4)	7 (50)	¹ 0.001 ^b
No	15 (57.7)	102 (59)	56 (70)	92 (50.8)	45 (30.6)	7 (50)	
Participants who attempted to treat their orthopaedic diseases based on the information they obtained from the internet							
Yes	17 (14.3)	92 (15.4)	32 (15)	112 (22.4)	78 (23.6)	8 (19)	¹ 0.004 ^b
No	102 (85.7)	506 (84.6)	182 (85)	388 (77.6)	252 (76.4)	34 (81)	

^a*P* < 0.05, ^b*P* < 0.01. ¹Pearson χ^2 test; ²Fisher Freeman Halton test.

housewives and workers-intermediate staff (*P* = 0.001, *P* = 0.002). The rate of stating "I became more confused" about the answers they were given was significantly lower in unemployed participants-housewives than managers-qualified employees (*P* = 0.003) (Table 6).

DISCUSSION

In recent years, social media or internet have evolved as a new communication tool between patients and physicians that is becoming increasingly popular and developed^[11]. About 4% of daily searches on the internet daily are health-related globally^[12]. The prevalence of the social media usage in patient-physician communication and the effects of the social media and internet on patients' choice of physician and hospital and their search for treatment options have been increasingly addressed in recent studies^[11,13].

In the United States, 41% of the adults use forums,

blogs and websites allowing patients to ask physicians questions whereas 35% make online research for the physician who will treat them, and 28% for the hospital they will be treated at^[14]. The internet or social media and Facebook were reported to be the most commonly used social media tools in England^[10]. A similar study of orthopedic patients by Curry *et al*^[15] reported that over 50% of patients had used social media for their orthopedic issues and 26% had seen a physician review site before their initial visit. Similar to these findings, 34.2% of all orthopaedic patients used internet to ask a physician questions about their diseases and 46.7% reported that orthopaedists should keep in contact with their patients over the internet. It was found that patients prefer websites allowing asking questions to orthopaedists (48.7%). On the other hand, social networking sites of a private type such as Facebook was less commonly used in patient-physician communication and only 7.5% of the patients friended

Table 6 The comparison of the participants' asking an orthopaedist his/her opinion and applying the information they obtained according to their occupations

	Occupations										P
	Unemployed - Housewife		Officer		Worker		Manager-Qualified		Other		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Participants who asked an orthopaedist his/her opinion about a disease											
Yes	349	30.8	26	32.5	97	28.4	123	48.2	52	65	¹ 0.001 ^b
No	784	69.2	54	67.5	245	71.6	132	51.8	28	35	
Which one(s) of the following do you prefer to ask an orthopaedist his/her opinion?											
Facebook											
Yes	59	16.9	3	11.5	24	24.7	14	11.4	3	5.8	² 0.018 ^a
No	290	83.1	23	88.5	73	75.3	109	88.6	49	94.2	
Twitter											
Yes	12	3.4	1	3.8	4	4.1	8	6.5	2	3.8	³ 0.645
No	337	96.6	25	96.2	93	95.9	115	93.5	50	96.2	
Physician's personal website											
Yes	76	21.8	9	34.6	17	17.5	32	26	15	28.8	¹ 0.236
No	273	78.2	17	65.4	80	82.5	91	74	37	71.2	
Websites allowing asking physicians questions											
Yes	177	50.7	13	50	35	36.1	62	50.4	28	53.8	¹ 0.113
No	172	49.3	13	50	62	63.9	61	49.6	24	46.2	
With which one(s) of the following can you describe the answers you were given?											
I became more confused											
Yes	67	19.2	5	19.2	11	11.3	9	7.3	10	19.2	² 0.012 ^a
No	282	80.8	21	80.8	86	88.7	114	92.7	42	80.8	
Helpful											
Yes	150	43	12	46.2	42	43.3	79	64.2	31	59.6	¹ 0.001 ^b
No	199	57	14	53.8	55	56.7	44	35.8	21	40.4	
Participants who attempted to treat their orthopaedic diseases based on the information they obtained from the internet											
Yes	193	17	19	23.8	86	25.1	58	22.7	12	15	¹ 0.005 ^b
No	940	83	61	76.3	256	74.9	197	77.3	68	85	

^aP < 0.05, ^bP < 0.01. ¹Pearson χ^2 test; ²Fisher Freeman Halton test.

an orthopaedist on Facebook. Since websites such as Facebook are social networking tools based on close-friendship, a friend request from a patient is accepted only by few physicians^[16], the reason of which may be physicians' concerns about patient privacy and ethical considerations. A review by Moorhead *et al.*^[1] reported that effective mechanisms should be developed for the maintenance of privacy and confidentiality of the information exchanged online between patients and physicians and there are several gaps in the use of social media for health communication. Bacigalupe suggested that physicians should limit social media contact with their patients *via* social networking tools such as Facebook^[17]. It should be born in mind that smartphones, particularly, enable rapid access to social networking sites, thus creating legal risks resulting from rapid spread of an inaccurate content online without verifying it before. Accordingly, Terry reported that a content shared online could be found and exploited, no matter what your privacy setting was, and be used against you in a suit filed in a possible violation of privacy^[18]. We believe that physicians should be careful about the accuracy and transparency of the content shared online and respect for patients with regard to personal liability and the protection of patient privacy, should avoid appearing to provide medical advice and

should routinely monitor their social media accounts backward.

The WhatsApp messenger available for smartphones enables an effective and rapid communication between patients and physicians. Jagannathan *et al.*^[19] reported that the WhatsApp application of smartphones enables sending patient X-rays and clinical photographs or sharing problems effectively and emphasized patient privacy as a disadvantage of the application. A study on how doctors view and use social media in Australia showed that 67% of physicians preferred e-mail to communicate with their patients^[20]. In our study, a majority of the patients preferred to communicate with their physicians using mobile phones (43.1%), which were followed by the WhatsApp (10.9%). Contact *via* e-mail was less common (9.3%), the reason why can be the common use of mobile phones for communication in our country, physician's or patients' finding it more difficult to communicate *via* e-mail or patients' desire to reach their physicians easily and rapidly. Similarly, physicians have to give out their personal cell-phone numbers to patients to communicate *via* WhatsApp, which can bring patient-physician relationship to an informal level. Therefore, we believe that communication *via* e-mail is more formal.

With the advancements of the internet and the creation of various social networks, patients today

have the opportunity to do their routine follow ups online with the physician. Curry *et al*^[15] concluded that orthopaedic patients who travelled between 120-180 miles from the hospital were more likely to use social media for health communication. In this study, 34% of the patients reported that it would be better to send X-rays performed in a hospital to the physician *via* social media tools, which can be attributed to transportation difficulties or easy communication through social media. On the other hand, a majority of patients in our country reported (66%) that follow-ups should be face-to-face with the physician. In light of these data, even though the internet and social media are predicted to be increasingly used in patient follow-ups in our country, in consistent with advances around the world, we believe that the traditional physician-patient relationship is still important for patients.

In this study, the use of the internet and social media was highest in patients aged between 18-30 years and those with an undergraduate level of education. Consistent with our findings, the literature documents that the prevalence of internet and social media usage was higher among young adults and those with high educational level^[15,21,22]. Of the participants who asked physicians questions using social media tools, 45.5% stated that the answers given were helpful. In addition, patients with an undergraduate degree were less confused with the answers they were given whereas illiterate participants or those with primary or secondary education became more confused with the answers they received. We believe that as the educational level increases, so does the capacity to understand and interpret the information in communication between individuals. Younger patients with high educational level particularly showed higher tendency to treat themselves based on the responses they were given by physicians. Accordingly, we believe that physicians should be aware of the patient's age, educational level and expectations before giving patients treatment-related information using social media tools in order to avoid being placed in legal or ethical jeopardy.

There is an ongoing increase in the use of social media and internet for health information. About 61% of United States adults looked online for health information in 2008, which reached 72% in 2013^[23]. Patients can share their health-related experiences or issues online *via* social media and discussion forums or can consult with experienced physicians. In addition, physicians have the opportunity to have more information about their patients^[24-26]. Motivation, encouragement and shared experiences are important features of social network services, particularly for patients^[27]. It has been reported that patients who had access to accurate information about their diseases over the internet displayed higher motivation and treatment compliance^[28]. On the other hand, it appears to be difficult to reach high-quality and reliable information due to the probability of the collection or spread of unnecessary and inaccurate information

through social media, resulting in confusion in patient-physician relationship^[24,29]. Therefore, even though automated scanner tools and alerting systems have been developed by social network servers to prevent harms of the internet and social media, users should compare and verify the accuracy of the information shared^[30]. Moen *et al*^[31] reported that communication over the internet may cause asymmetric results in the patient-physician relationship. Kietzmann *et al*^[32] suggested that long-term results of social media are yet to be fully explored, therefore, how social media activities vary in terms of function and impact should be monitored and understood and a congruent social media strategy should be developed and the social media setting and the frequency of conversations as well as being aware of what other users do in that platform and acting accordingly are of importance for a reliable health communication^[32].

There is a distinct difference between the culture of traditional medicine (which values privacy, confidentiality, one-on-one interactions and professional conduct) and that of social media (which values openness, informality and transparency, connection)^[33]. Accordingly, several professional associations published guidelines to discourage physicians from interacting with their patients on social networking sites, such as Facebook^[34,35]. It is beyond doubt that patients' desire to contact with their physicians about their diseases and maintain the communication over the internet and social media will continue increasing. Therefore, possible advantages and disadvantages should be highlighted to enable physicians to use social media effectively and safely. Further comprehensive studies are warranted to fully elucidate physicians' usage of the internet and social media and to identify current problems and to propose options and solutions. In addition, we believe that professional associations should play an active role regarding studies and necessary arrangements for identifying how patient-physician communication should be on the internet and social media.

In conclusion, even though internet and social media usage among orthopaedic patients for health communication or seeking solutions to health issues varied according to age, educational level and occupational status, its prevalence was found to be high in this study. Despite benefits and advantages of social media for patient-physician relationship, legal liability and possible harms and risks of the shared information and communication should be born in mind. Therefore, future comprehensive studies are warranted for establishing a healthy and effective communication between patient and health-care provider over the internet and social media and for the execution of necessary arrangements.

COMMENTS

Background

Social media tools enable patients to communicate with their physicians faster online and help them clarify their understanding of their illness, express

themselves better and share their problems visually.

Research frontiers

Of all participants, 34.2% ($n = 647$) reported having asked an orthopedist his/her opinion about their diseases using the internet and the question-askers most often preferred the web-sites allowing question-asking. The rate of asking an orthopedist his/her opinion about their diseases in participants aged between 18-30 years was statistically significantly higher than that in patients aged between 31-45 years, 46-60 years, 61-75 years and older than 75 years. According to the occupational status, the rate of internet use for asking an orthopedist a question was higher in managers-qualified employees compared to unemployed-housewives, officers, workers-intermediate staff.

Innovations and breakthroughs

The use of the internet and social media was highest in patients aged between 18-30 years and those with an undergraduate level of education. Younger patients with high educational level particularly showed higher tendency to treat themselves based on the responses they were given by physicians.

Applications

There is an ongoing increase in the use of social media and internet for health information. Physicians should be careful about the accuracy and transparency of the content shared online and respect for patients with regard to personal liability and the protection of patient privacy, should avoid appearing to provide medical advice and should routinely monitor their social media accounts backward.

Terminology

Facebook, Twitter, My Space and LinkedIn have been reported to be the most commonly used social networking sites around the world, being Facebook the most popular. Social media tools are commonly used by orthopedists to communicate with their patients.

Peer-review

This is a very interesting manuscript.

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Knee osteoarthritis: Therapeutic alternatives in primary care

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Abstract

AIM

To discuss pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners.

METHODS

A case example is presented, the evidence-based guideline recommendations of the Osteoarthritis Research Society International and the American Academy of Orthopaedic Surgeons are reviewed, and a plan of care is developed.

RESULTS

Osteoarthritis is the most common form of arthritis seen in primary care, and it is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life. Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for primary health care providers to manage pain, increase quality of life, and decrease risk of disability.

CONCLUSION

Primary health care providers can implement these recommendations in their own practices to provide care to patients with knee osteoarthritis based on current best evidence.

Key words: Osteoarthritis; Knee; Primary care; Nurse practitioner; Guidelines

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Core tip: Osteoarthritis is the most common form of arthritis seen in primary care, and it is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life. Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for primary health care providers to manage pain, increase quality of life, and decrease risk of disability. This manuscript presents and discusses pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners. A case

example is presented, the evidence-based guideline recommendations of the Osteoarthritis Research Society International and the American Academy of Orthopaedic Surgeons are reviewed, and a plan of care is developed. Primary health care providers can implement these recommendations in their own practices to provide care to patients with knee osteoarthritis based on current best evidence.

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INTRODUCTION

An active 56-year-old man presented to his primary health care nurse practitioners (PHCNP) and reported increasing left knee pain. He described the pain as a constant ache that increased with prolonged periods of sitting and after playing sports, and noted that it seemed to have started gradually over the preceding six months. On physical exam, he was noted to be 5'10" and weigh 190 lbs, with a body mass index (BMI) of 27. His vital signs were within normal range. He had a mild amount of swelling to the anterior medial aspect of his left knee; no redness, heat or gross deformities; full extension but limited flexion to 95 degrees; no instability; and a negative McMurray's circumduction test. His strength was grossly normal and equal in both legs and his gait was unremarkable.

This patient's past medical history included gastroesophageal reflux (GERD), irritable bowel syndrome, and previous right hamstring strain. He is an avid recreational athlete player, non-smoker, social drinker, and he denies any drug use. Current medication includes, pantoprazole 40 mg by mouth once daily for GERD, and over the counter ibuprofen and acetaminophen for intermittent knee pain. He has an anaphylactic medication allergy to penicillin, and is also allergic cats and dogs. He attends his family physician's office for an annual physical once per year, and his prostate, colon cancer screening, and immunizations are up to date.

This patient's PHCNP ordered a left knee ultrasound and left knee X-ray, and instructed him to try over the counter acetaminophen and/or ibuprofen for pain relief. This patient returned to clinic two weeks later to review the results. His X-rays revealed early osteoarthritic changes in his medial compartment and his ultrasound showed a small joint effusion with no abnormalities in the surrounding structures. The patient described that he experienced only limited pain relief with ibuprofen and acetaminophen, and his physical examination was unchanged.

MATERIALS AND METHODS

Osteoarthritis is the most common form of arthritis seen

in primary care^[1]. Risk factors for osteoarthritis include obesity, family history, female sex, trauma, and older age^[2], and approximately 25% of patients over 40 years of age and 85% of patients over 65 have radiographic evidence of osteoarthritis^[3]. According to Uphold and Graham, osteoarthritis is the "progressive structural breakdown of articular cartilage that lines the joint surfaces"^[3]. Osteoarthritis is a major public health issue because the aging population and widespread obesity have drastically increased incidence^[4]. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life.

Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for PHCNPs to manage pain, increase quality of life, and decrease risk of disability^[5]. Some patients and health care providers may accept chronic pain as a symptom of osteoarthritis without extensive trialing of non-pharmacological or pharmacological treatments, but inadequate pain management may lead to disability and sedentary activity, subsequently increasing risks for obesity, hypertension, dyslipidemia, coronary artery disease, and diabetes^[5].

Therapeutic goals

The therapeutic goals for patients such as the one in this case example are to alleviate or eliminate knee pain, restore joint mobility, decrease inflammation, improve surrounding muscle strength to protect structures of the knee, minimize complications, and maintain independence and quality of life. This patient expressed the importance of playing sports, as it is his primary form of exercise and an important social activity. He also expressed apprehension about taking oral medications long-term and a preference for non-pharmacological treatment.

Therapeutic alternatives: Pharmacological

According to several clinical practice guidelines, the use of pharmacological therapy to treat pain associated with osteoarthritis should be initiated in a step-wise approach in combination with non-pharmacological therapy^[2,3,6-8]. The Osteoarthritis Research Society International (OARSI) recommends beginning with acetaminophen in patients who report mild to moderate pain from osteoarthritis, but health care providers may consider alternative therapy in the presence of severe pain or inflammation^[8]. The American Academy of Orthopaedic Surgeons (AAOS) reported inconclusive evidence to support the use of acetaminophen, with one cited study concluding no clinical or significant difference in comparison to a placebo^[7]. Others recommend beginning with acetaminophen because it has a relatively low risk profile, in comparison to other analgesic medications^[2].

Nutritional supplements such as glucosamine and chondroitin are available over the counter and are proposed to maintain joint cartilage^[6]. According to the AAOS "at this time, both glucosamine and chondroitin sulphate have been extensively studied. Despite the availability of the literature, there is essentially no evidence

that minimum clinically important outcomes have been achieved compared to placebo, whether evaluated alone or in combination^[7]. The OARSI stated that glucosamine and/or chondroitin may provide symptomatic relief in patients with osteoarthritis, but should be discontinued if no apparent benefit within 6 mo of treatment, although continuation is not likely harmful^[8].

Topical analgesics and capsaicin have also been used in the initial treatment of mild osteoarthritis^[6]. Topical analgesics, such as topical diclofenac, are recommended by the AAOS and OARSI as a potential treatment for patients who have contraindications to oral analgesics^[8,9]. According to the OARSI, efficient pain relief from topical analgesics can take up to two weeks and the patient may experience local irritation. There is no high quality to support routine treatment of osteoarthritis with topical capsaicin, and the burning sensation of the cream is often tolerated poorly by patients^[6].

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective in the treatment of osteoarthritis pain and inflammation^[6,8,9], but their use in many patients with osteoarthritis requires caution due to increased risk of gastrointestinal bleeding, renal dysfunction, blood pressure elevation, and adverse cardiac events^[2,3]. The OARSI recommends starting NSAIDs at the lowest dose possible and avoiding long-term use. Patients at risk of gastrointestinal bleeding may be prescribed a proton pump inhibitor for gastroprotection. Cyclooxygenase-2 inhibitors are a form of NSAIDs that have decreased gastrointestinal complications, but are more expensive and carry a higher risk of cardiovascular events^[2,6].

Opioids have the potential to manage pain in advanced osteoarthritis that has not responded to other pharmacological therapies^[2], but their use requires close monitoring for signs of abuse or adverse effects such as drowsiness, constipation, and dizziness^[6,8]. Stronger opioids should only be prescribed in exceptional circumstances or in patients for whom surgical intervention is planned. According to the College of Nurses of Ontario^[10-15], nurse practitioners are not authorized to prescribe opioids; therefore, patients requiring opioids for osteoarthritis pain management should be referred to a physician.

Intra-articular injections with either corticosteroids or hyaluronic acid may be considered in patients who fail to experience pain relief with pharmacological and non-pharmacological therapies^[6]. Intra-articular corticosteroid injections may provide the patient short-term relief for 4-8 wk and one joint should only be injected 3-5 times per year^[3]. The AAOS reported inconclusive evidence supporting intra-articular corticosteroid injections.

Intra-articular hyaluronic acid is controversial in the literature, with significant variation in recommendations. The AAOS does not recommend the use of hyaluronic acid for patients with osteoarthritis due to conflicting evidence and high variability^[7]. A recent systematic review and network meta-analysis suggested that intra-articular treatments were superior to NSAIDs in the treatment of osteoarthritis, but these effects may

be primarily as a result of large intra-articular placebo effects^[16].

Therapeutic alternatives: Non-pharmacological

PHCNPs should begin the treatment of osteoarthritis with a patient education session about the condition and expand on plans of care incorporating best available evidence^[6]. Non-pharmacological treatment frequently involves life-style modification and should be tailored to fit with patient preferences. For example, strong guideline recommendations highlight the importance of weight-loss in patients with BMIs greater than 25^[3,6,8,9]. Murphy and Helmick described that "strong epidemiological evidence links obesity to an increased risk of symptomatic knee osteoarthritis and knee replacement"^[10]. Sinusas^[2] reported that a 5%-10% weight loss from baseline was sufficient for reducing disability in patients with osteoarthritis, and pain significantly decreased if patients lost more than 6 kg. For optimal care, weight management may involve encouraging patients to participate in exercise programs and referring patients to dieticians for counselling.

The AAOS strongly recommends that patients participate in exercise programs that encourage physical activity according to national guidelines and involve components of strengthening and low-impact aerobic exercise^[7]. Strengthening exercises should be individualized to improve muscular support of the affected joint and aerobic exercises should be encouraged for long-term functional outcomes^[11]. It is important for patients to minimize movements that aggravate their osteoarthritis and balance physical activity with periods of rest to minimize pain^[3]. A recently published Cochrane review reported high-quality evidence demonstrating that individuals with osteoarthritis who engaged in exercise experienced reduced pain and improved quality of life^[4]. The OARSI recommends aquatic exercise for patients with symptomatic osteoarthritis, but another Cochrane review reported further research is required on the long-term benefit of aquatic exercise in patients with osteoarthritis^[12].

Acupuncture and physiotherapy modalities are also cited as possible non-pharmacological interventions for patients with symptomatic osteoarthritis^[6,8,9]. The AAOS does not support the use of acupuncture for the relief of pain secondary to osteoarthritis due to inconclusive evidence^[7], but the OARSI reported that acupuncture might provide some symptomatic relief according to a single randomized control trial^[8,13]. The AAOS cited inconclusive evidence to support the use of physiotherapy modalities such as transcutaneous electrical nerve conduction for pain relief^[7], but the OARSI indicated that heat or cryotherapy might be effective for relieving symptoms in hip or knee osteoarthritis^[8].

External supports such as knee braces and footwear insoles are also discussed in the literature as possible non-pharmacological therapy for patients with knee osteoarthritis. Knee braces are recommended for patients who have associated mild to moderate valgus or varus instability and want to maintain active lifestyles,

but they are often costly and cumbersome for patients to wear^[6,8,11]. Lateral wedged insoles for patients with medial tibio-femoral compartment osteoarthritis may mildly decrease pain and improve instability^[3,8]. The AAOS does not support the use of lateral wedge insoles based on four studies that found no significant benefit for pain and physical function^[7].

RESULTS

In this case example, the PHCNP should arrange another clinic appointment with this patient to discuss his treatment options regarding pharmacological and non-pharmacological care. Reaching therapeutic goals through a plan of care should involve equal input from both the PHCNP and the patient, also known as shared decision-making^[14]. Although PHCNPs provide medical evidence and clinical experience, patients provide important information about their values, beliefs, and lifestyle. When developing plans of care with patients, it is important for PHCNPs to recognize when clinical presentations or treatments are outside their scope of practice or beyond their expertise, in order to provide appropriate referrals according to nurse practitioner practice guidelines^[15]. For example, patients with severe osteoarthritis should be referred if they require opioid prescriptions, intra-articular injections outside of the training or scope of the nurse practitioner, or surgical intervention.

Treatment for this patient's left knee osteoarthritis will focus on managing his pain and inflammation, improving mobility and function, and maintaining his independence. This patient has expressed the importance of continuing to play sports and personal preference for minimal duration of oral medications. Over the counter acetaminophen and/or ibuprofen for approximately three weeks has provided minimal pain relief. According to the step-wise approach outlined in the evidence, the next step is to prescribe an oral NSAID in combination with non-pharmacological therapy^[3,6]. Due to his preference to not take oral medications, the PHCNP should first recommend a topical analgesic prior to moving up to oral NSAIDs as indicated by the treatment guidelines^[6].

Therefore, the first step in this patient's pharmacological plan of care is to try topical analgesics as directed for one week to the left knee. A topical analgesic was selected based on his personal preferences, risk of adverse gastrointestinal effects from oral NSAIDs, high safety rating, low cost, and simplicity of use. The PHCNP should discuss the potential of low adherence due to ongoing application, possibility of adverse topical irritation, and the duration of treatment required.

The second step in this patient's pharmacological plan of care would be to start a low dose of oral NSAIDs, if topical analgesics did not meet therapeutic goals or patient preferences. The PHCNP should ensure that he continues pantoprazole while taking oral NSAIDs and is aware of the risk of gastrointestinal bleeding^[6]. Combination pills that consist of NSAIDs and proton

pump inhibitors are available for patients at increased risk of adverse gastrointestinal effects, but are much more costly than taking the medications separately and no more effective^[6]. The PHCNP should present the options of paying more or taking an extra medication.

Non-pharmacological treatment of this patient's left knee osteoarthritis will focus on improving surrounding muscle strength to protect structures of the knee, reducing complications, and restoring mobility and function. The PHCNP may begin by suggesting six to eight weeks off from sports. Health education should include explaining the importance of maintaining a healthy body weight and recommending at least thirty minutes of moderate low-impact physical activity on most days of the week^[3]. If significant dietary changes are required to achieve weight loss, the PHCNP may refer this patient to a dietician for guidance.

Referral to a physiotherapist could assist this patient in developing a structured low-impact aerobic exercise routine and strengthening program. If this patient does not have coverage or cannot afford physiotherapy, the PHCNP may want to recommend local community programs and resources through the arthritis society^[17]. This patient may also want to try treating his knee with ice for fifteen to twenty minutes three times per day for treatment of acute inflammation^[8,17].

DISCUSSION

The PHCNP should follow up with this patient in one week to assess the effectiveness of the topical analgesic and non-pharmacological treatment. At this time, his pain, mobility, independence, level of activity, and adherence to therapy will be assessed. The PHCNP should also continue to provide health education as required to address health care needs and therapeutic goals. If therapeutic goals were not met by the topical analgesic, the PHCNP and this patient could consider the second step of the pharmacological care plan; which is to discuss trialing a low dose oral NSAID for a short period of time. The PHCNP and this patient should continue regular follow up appointments until therapeutic goals are reached, at which point this patient could consider slowly returning to athletic and recreational activities.

COMMENTS

Background

Osteoarthritis is the most common form of arthritis seen in primary care, and it is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life. Early diagnosis of mild osteoarthritis in relatively young patients presents an opportunity for primary health care providers to manage pain, increase quality of life, and decrease risk of disability.

Research frontiers

This manuscript presents and discusses pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners. A case example is presented, the evidence-based guideline recommendations of the Osteoarthritis Research

Society International and the American Academy of Orthopaedic Surgeons are reviewed, and a plan of care is developed.

Innovations and breakthroughs

According to several clinical practice guidelines, the use of pharmacological therapy to treat pain associated with osteoarthritis should be initiated in a step-wise approach in combination with non-pharmacological therapy. Nutritional supplements such as glucosamine and chondroitin are available over the counter and are proposed to maintain joint cartilage. Topical analgesics and capsaicin have also been used in the initial treatment of mild osteoarthritis. Non-steroidal anti-inflammatory drugs are highly effective, but their use in many patients requires caution due to increased risk of gastrointestinal bleeding, renal dysfunction, blood pressure elevation, and adverse cardiac events. Intra-articular hyaluronic acid is controversial in the literature, with significant variation in recommendations. Non-pharmacological treatment frequently involves lifestyle modification and should be tailored to fit with patient preferences.

Applications

The therapeutic goals for patients with osteoarthritis are to alleviate or eliminate knee pain, restore joint mobility, decrease inflammation, improve surrounding muscle strength to protect structures of the knee, minimize complications, and maintain independence and quality of life. Reaching therapeutic goals through a plan of care should involve equal input from both the primary health care providers and the patient, also known as shared decision-making.

Terminology

According to Uphold and Graham, osteoarthritis is the "progressive structural breakdown of articular cartilage that lines the joint surfaces". Osteoarthritis is a major public health issue because the aging population and widespread obesity have drastically increased incidence. Osteoarthritis is clinically associated with escalating chronic pain, physical disability, and decreased quality of life.

Peer-review

In this Evidence-Based Medicine article, the authors present and discuss pharmacological and non-pharmacological therapeutic alternatives for managing knee osteoarthritis in primary care by primary health care nurse practitioners. Primary health care providers can implement these recommendations in their own practices to provide care to patients with knee osteoarthritis based on current best evidence.

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Total hip replacement: A meta-analysis to evaluate survival of cemented, cementless and hybrid implants

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Abstract

AIM

To determine whether cemented, cementless, or hybrid implant was superior to the other in terms of survival rate.

METHODS

Systematic searches across MEDLINE, CINAHL, and Cochrane that compared cemented, cementless and hybrid total hip replacement (THR) were performed. Two independent reviewers evaluated the risk ratios of revision due to any cause, aseptic loosening, infection, and dislocation rate of each implants with a pre-determined form. The risk ratios were pooled separately for clinical trials, cohorts and registers before pooled altogether using fixed-effect model. Meta-regressions were performed to identify the source of heterogeneity. Funnel plots were analyzed.

RESULTS

Twenty-seven studies comprising 5 clinical trials, 9 cohorts, and 13 registers fulfilled the research criteria and analyzed. Compared to cementless THR, cemented THR have pooled RR of 0.47 (95%CI: 0.45-0.48), 0.9 (0.84-0.95), 1.29 (1.06-1.57) and 0.69 (0.6-0.79) for revision due to any reason, revision due to aseptic loosening, revision due to infection, and dislocation respectively. Compared to hybrid THR, the pooled RRs of cemented THR were 0.82 (0.76-0.89), 2.65 (1.14-6.17), 0.98 (0.7-1.38), and 0.67 (0.57-0.79) respectively. Compared to hybrid THR, cementless THR had RRs of 0.7 (0.65-0.75), 0.85 (0.49-1.5), 1.47 (0.93-2.34) and 1.13 (0.98-1.3).

CONCLUSION

Despite the limitations in this study, there was some tendency that cemented fixation was still superior than other types of fixation in terms of implant survival.

Key words: Total hip replacement; Implant survival;

Cemented; Cementless; Hybrid; Meta-analysis

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Core tip: To determine whether cemented, cementless, or hybrid implant was superior to the other in terms of survival rate, a meta-analysis of 27 studies, comprising 5 clinical trials, 9 cohorts, and 13 registers, were performed to evaluate the risk ratios of revision due to any cause, aseptic loosening, infection, and dislocation rate. The risk ratios were pooled separately for clinical trials, cohorts and registers before pooled altogether using fixed-effect model. Meta-regressions were performed to identify the source of heterogeneity. Despite the limitations in this study, there was some tendency that cemented fixation was still superior than other types of fixation in terms of implant survival.

Phedy P, Ismail HD, Hoo C, Djaja YP. Total hip replacement: A meta-analysis to evaluate survival of cemented, cementless and hybrid implants. *World J Orthop* 2017; 8(2): 192-207 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/192.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.192>

INTRODUCTION

Rationale

Currently, total hip replacement is one of the most performed orthopaedic surgeries. In Sweden, the number of THR performed increased by 20% from 1986-1997 and up to 68% in Netherland during the same period of observation^[1]. In Organisation for Economic Cooperation and Development countries, the rate of THR increase from 50-130/100000 inhabitants to 60-200/100000 inhabitants in the late 1990s^[2]. In United States, more than 200000 THR are conducted annually^[3].

Superiority of either cemented or cementless implants has been a longstanding debate. Wroblewski *et al*^[4] in 1993 reported the superiority of either implants could not be determined on a scientific basis. Rorabeck *et al*^[5,6] reported similar clinical outcome by any of those implants. Zimmerman *et al*^[7] agreed that no significant differences in clinical and functional outcome between the implants and reported non-cemented prosthesis to be more costly. Emerson *et al*^[8] found cementless titanium stems offered better resistance to osteolysis and mechanical failure.

Morshed *et al*^[9] conducted a meta-analysis in 2007 and found no difference in survival between those two groups. Since then, many larger studies with longer duration of follow-up had been conducted and resulted in different results thus resuming the controversy.

Objective

We conducted a meta-analysis of articles published after January 2000 comparing the cemented, cementless and

hybrid THR implants to evaluate the superiority of each in terms of risk of revision due to any reason, revision due to infection, revision due to aseptic loosening, and dislocation.

MATERIALS AND METHODS

The structure of this study was written in accordance with the PRISMA checklist for systematic review and meta-analysis^[10].

Selection criteria

All studies including randomized clinical trials and cohorts reporting direct comparison between cementless, hybrid and cemented implant in primary THR were included. Recent reports from national registry were also included in this study. The inclusion criteria was pre-determined: (1) all patients over 18 years of age; (2) primary total hip replacement; and (3) revision due to any reason as the primary endpoint. Studies about inverse hybrid arthroplasty were excluded from the analysis. These studies were restricted according to these characteristics: (1) published after January 2000; (2) English language; (3) available abstract; and (4) original research.

Information source and search strategy

In June 2012, literature search was conducted across MEDLINE, CINAHL, and The Cochrane Library using strategies listed in appendices 1. Manual search was also conducted to identify studies that were not included by the initial MeSH keyword search. All identified articles were retrieved from previously mentioned databases.

Study selection

Two reviewers independently performed the study selection in accordance with the aforementioned selection criteria by screening the titles and abstracts. Studies were excluded if they don't meet the selection criteria. If the information required determining eligibility was not found in the abstract, a full-text search was run after data extraction. The studies included were determined from the discussion of two reviewers in accordance with the selection criteria. Reviewers were not blinded to any study characteristic such as journal, author or institution. Algorithm in selecting studies included in this meta-analysis is shown in Figure 1.

Data collection process and data items

All results were checked for consistency between the two reviewers independently. Any discrepancies were be judged by a third independent reviewer. Data extraction was performed using a predetermined standardized form as shown in Tables 1 and 2. Study quality was first assessed using sample size, study design, duration of follow up and variability of result. Overall level of evidence was also assessed.

Synthesis of results

Risk ratios were calculated to determine risk of revision due to any cause, revision due to aseptic loosening,

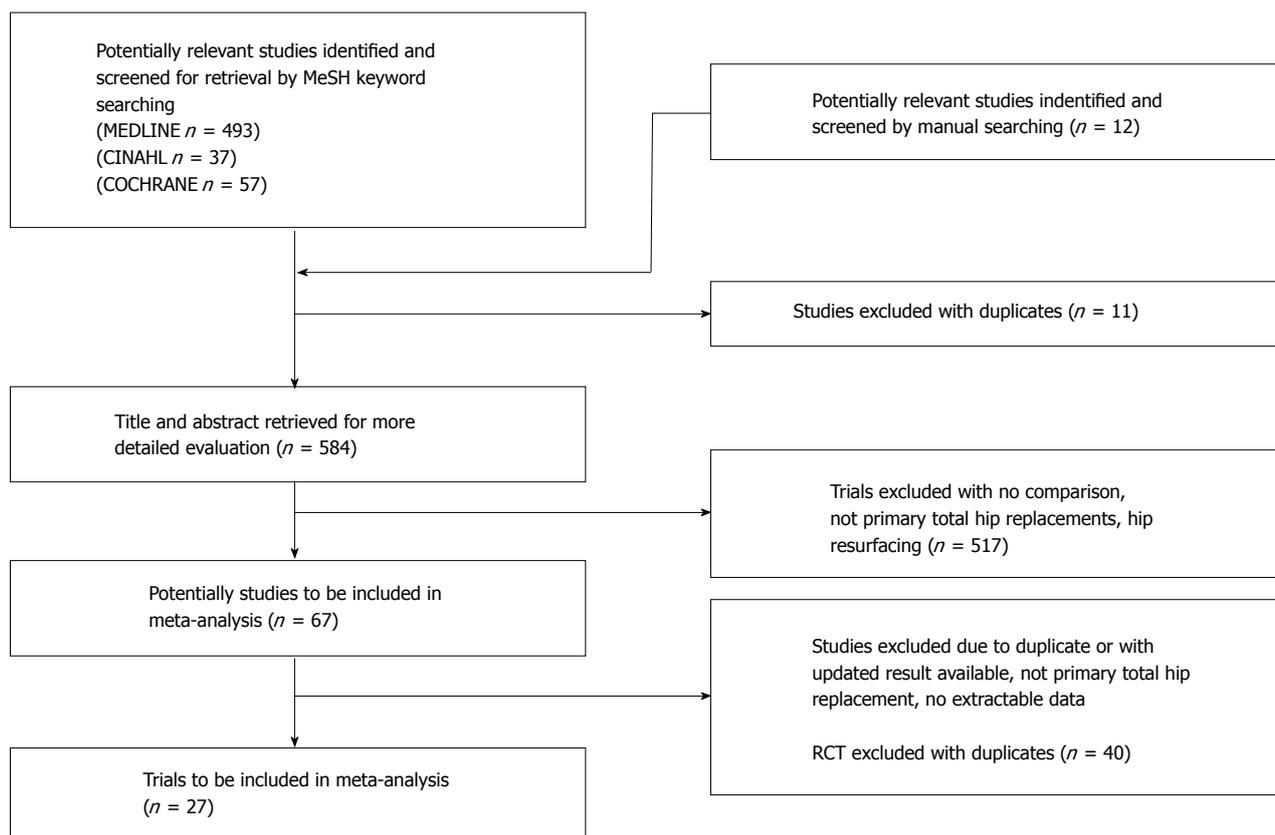


Figure 1 Study selection algorithm.

revision due to infection, and dislocation between each implants. Data were analysed separately for clinical trials, cohorts and registers before pooled altogether. Fixed-effect model was used in the determination of the risk ratio. In comparison with high heterogeneity, we preformed meta-regression to evaluate to identify the source of heterogeneity. Funnel plots for all included trials was constructed to assess the degree of publication bias. The results of the study were graded according to grading system advocated by Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Statistical test was performed using the meta-analysis software of Review Manager 5, Meta-regression was conducted using STATA 10, and grading of the results was performed using GRADEprofiler 3.6.

RESULTS

Following algorithm for study selection, 27 studies were left for final analysis^[8,11-36]. Characteristics of the included studies were outlined in Table 1.

Cemented vs cementless THR

Revision of any component due to any reason:

Two RCTs, one cohort, and ten registers addressed revision of any component due to any reason. The RCTs found no differences between cemented and cementless THR. Analysis of registers supported cemented to be

superior to cementless THR (Figure 2) Pooled all studies together, the RR was 0.47 (95%CI: 0.45-0.48) with a heterogeneity of 98%. Meta-regression using age group, diagnosis, length of follow-up, starting year, publication type, and type of funding failed to correct the heterogeneity.

Revision of any component due to aseptic loosening:

Data regarding revision of any component due to aseptic loosening were available in two RCTs and six registers (Figure 3). Controversy existed between result of analysis of RCTs and registers (RR = 2; 95%CI: 1.2-3.1 and RR = 0.88; 95%CI: 0.83-0.94 respectively). Pooled together, the RR was 0.90 (95%CI: 0.84-0.95) with a heterogeneity of 98%. Meta-regression by age group, diagnosis, length of follow-up, starting year, publication type and funding corrected the heterogeneity into 0%, although none of the factors showed significant influence.

Revision of any component due to infection:

One RCT and six registers provided sufficient data for determination of revision of any component due to infection (Figure 4). Analysis of registers favored cementless implant in term of revision of any component due to infection (RR = 1.25; 95%CI: 1.10-1.42). Pooled together, the RR was 1.26 (95%CI: 1.11-1.42) with heterogeneity of 57%.

Table 1 Characteristics of the included studies

Ref.	Age (years old)	Length of follow-up (years)	Diagnosis	Cementing technique (generation)	Comparison	Approach	Comments	
Bjørgul <i>et al</i> ^[111]	65 to 66	14	Osteoarthritis (most)	3 rd	Cemented (<i>n</i> = 120)	Hybrid (<i>n</i> = 120)	direct lateral	
Chandran <i>et al</i> ^[12]	64.5 to 65.5	14	primary Osteoarthritis	2 nd	Cemented (<i>n</i> = 97)	Cementless (<i>n</i> = 105)	anterolateral	
Corten <i>et al</i> ^[13]	64 (mean)	19.5	primary Osteoarthritis	2 nd	Cemented (<i>n</i> = 124)	Cementless (<i>n</i> = 126)	direct lateral	
Kim <i>et al</i> ^[14]	43.4 to 46.8	18.4	Avascular necrosis (most)	3 rd	Hybrid (<i>n</i> = 109)	Cementless (<i>n</i> = 110)	ND	May overlap with Kim <i>et al</i> ^[15]
McCombe <i>et al</i> ^[16]	67.3	6.5 to 8	Primary OA (most)	2 nd	Cemented (<i>n</i> = 84)	Hybrid (<i>n</i> = 78)	posterolateral	
Berend <i>et al</i> ^[17]	67.1	6.8	Osteoarthritis (most)	ND	Cemented (<i>n</i> = 1908)	Cementless (<i>n</i> = 623)	anterolateral and posterior	
Clohisy <i>et al</i> ^[18]	61 to 62	10 to 11	Osteoarthritis	2 nd	Cemented (<i>n</i> = 45)	Hybrid (<i>n</i> = 45)	posterolateral	
Emerson <i>et al</i> ^[8]	55 to 70	6.7 to 7.2	Osteoarthritis (most)	3 rd	Hybrid (<i>n</i> = 113)	Cementless (<i>n</i> = 88)	anterolateral	
Hartofilakidis <i>et al</i> ^[19]	39.6 to 45.4	12.4 to 15.4	Osteoarthrosis secondary to congenital hip disease (most)	2 nd	Cemented (<i>n</i> = 59)	Hybrid (<i>n</i> = 58)	lateral transtrochanteric	
Kim <i>et al</i> ^[15]	64.6	17.3	Avascular necrosis	3 rd	Hybrid (<i>n</i> = 50)	Cementless (<i>n</i> = 98)	ND	May overlap with <i>et al</i> ^[14]
Pospula <i>et al</i> ^[20]	46.7 to 53.7	3 to 5	Avascular necrosis (most)	ND	Cemented (<i>n</i> = 87)	Cementless (<i>n</i> = 95)	cemented posterolateral cementless transgluteal	
Van Stralen <i>et al</i> ^[21]	69.5	2.5	Primary OA (most)	ND	Cemented (<i>n</i> = 746)	Cementless (<i>n</i> = 138)	posterior	
Thomason <i>et al</i> ^[22]	54	7.4	Rheumatoid arthritis	ND	Hybrid (<i>n</i> = 47)	Cementless (<i>n</i> = 51)	posterior	
Zimmerman <i>et al</i> ^[7]	74.9	1	Osteoarthritis	ND	Hybrid (<i>n</i> = 85)	Cementless (<i>n</i> = 174)	anterolateral, posterior	
Conroy <i>et al</i> ^[23]	Any	5	Osteoarthritis	ND	Cemented (<i>n</i> = 8945); hybrid (<i>n</i> = 20445); Cementless (<i>n</i> = 28582)		ND	
Dale <i>et al</i> ^[24]	Any	0 to 20	Osteoarthritis (most)	ND	Cemented (<i>n</i> = 82996)	Cementless (<i>n</i> = 14348)	ND	May overlap with study of <i>et al</i> ^[16]
Engesaeter <i>et al</i> ^[25]	Any	0 to 16	Primary Osteoarthritis	ND	Cemented (<i>n</i> = 51016)	Cementless (<i>n</i> = 5259)	ND	May overlap with <i>et al</i> ^[15]
Eskelinen <i>et al</i> ^[26]	< 55	0 to 24	Rheumatoid arthritis	ND	Cemented (<i>n</i> = 821)	Cementless (<i>n</i> = 724)	ND	
Hailer <i>et al</i> ^[27]	Any	15	Osteoarthritis (most)	ND	Cemented (<i>n</i> = 161460)	Cementless (<i>n</i> = 8593)	ND	
Hooper <i>et al</i> ^[28]	Any	7	ND	ND	Cemented (<i>n</i> = 16005); hybrid (<i>n</i> = 15189)		ND	
Lucht <i>et al</i> ^[29]	Any	4	ND	ND	Cemented (<i>n</i> = 11671); hybrid (<i>n</i> = 4491)		ND	
Mäkelä <i>et al</i> ^[30]	> 55	15	Osteoarthritis	ND	Cemented (<i>n</i> = 9549)	Cementless (<i>n</i> = 10310)	ND	
Mäkelä <i>et al</i> ^[31]	63 to 69 (> 55)	15	Rheumatoid arthritis	ND	Cemented (<i>n</i> = 3440)	Cementless (<i>n</i> = 579)	ND	
Mäkelä <i>et al</i> ^[32]	< 55	15	Osteoarthritis	ND	Cemented (<i>n</i> = 2342)	Cementless (<i>n</i> = 1326)	ND	
Malchau <i>et al</i> ^[33]	All	8	Osteoarthritis (most)	ND	Cemented (<i>n</i> = 178762)	Cementless (<i>n</i> = 6102)	ND	
Pedersen <i>et al</i> ^[34]	Any	0 to 14	Osteoarthritis (most)	ND	Cemented (<i>n</i> = 34656); cementless (<i>n</i> = 25571)		ND	
Roberts <i>et al</i> ^[35]	All	ND	ND	ND	Hybrid (<i>n</i> = 20539)		ND	
					Cemented (<i>n</i> = 92928)	Cementless (<i>n</i> = 69882)	ND	

Dislocation of any component: Data from two cohorts and five registers were available to determine dislocation of any component (Figure 5). Analysis of cohorts found

no difference in dislocation of any component between any types of THR while analysis of registers favors cemented THR (RR = 0.69; 95%CI: 0.29-1.67 and RR

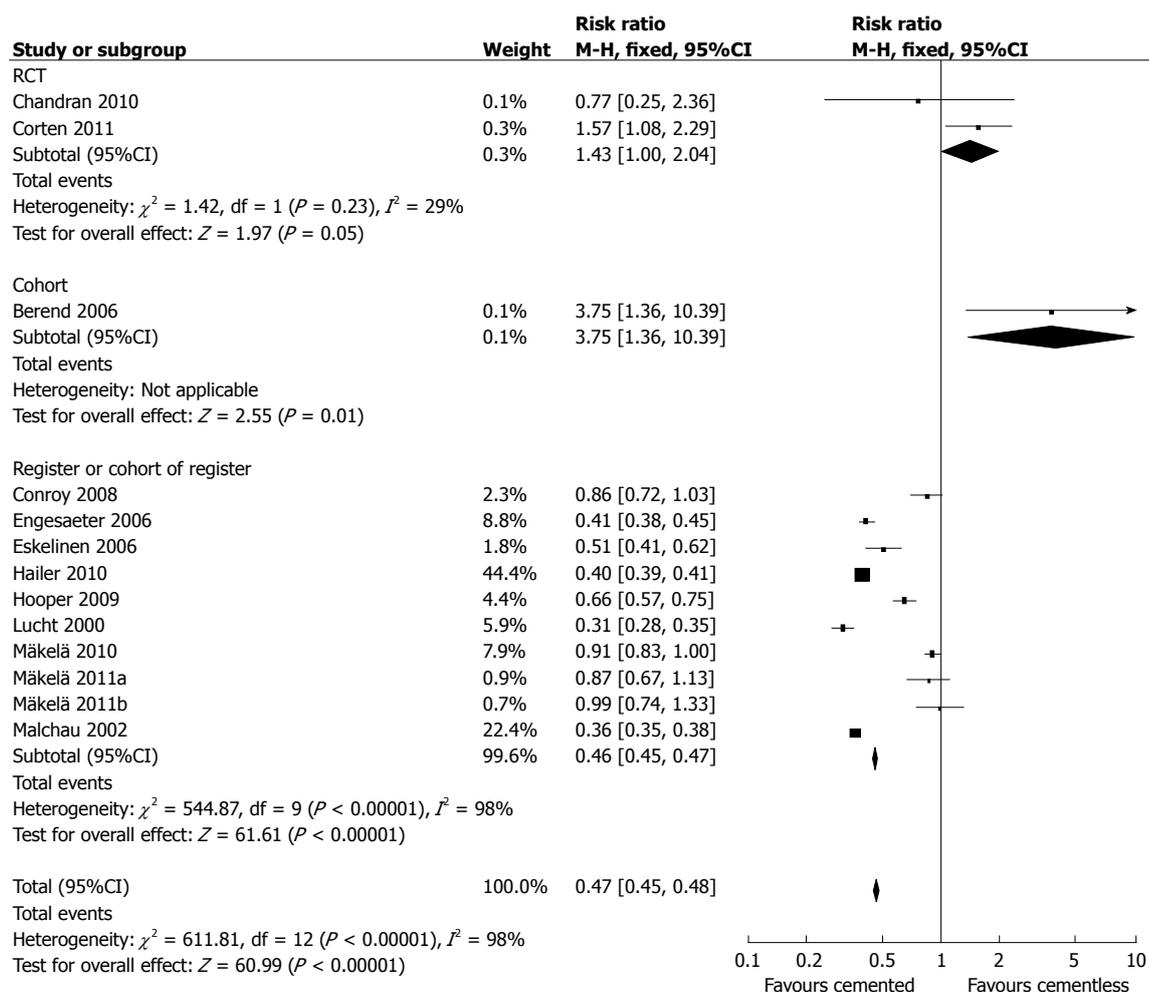


Figure 2 Forest plot of comparison: Cemented vs cementless: Revision of any component due to any reason.

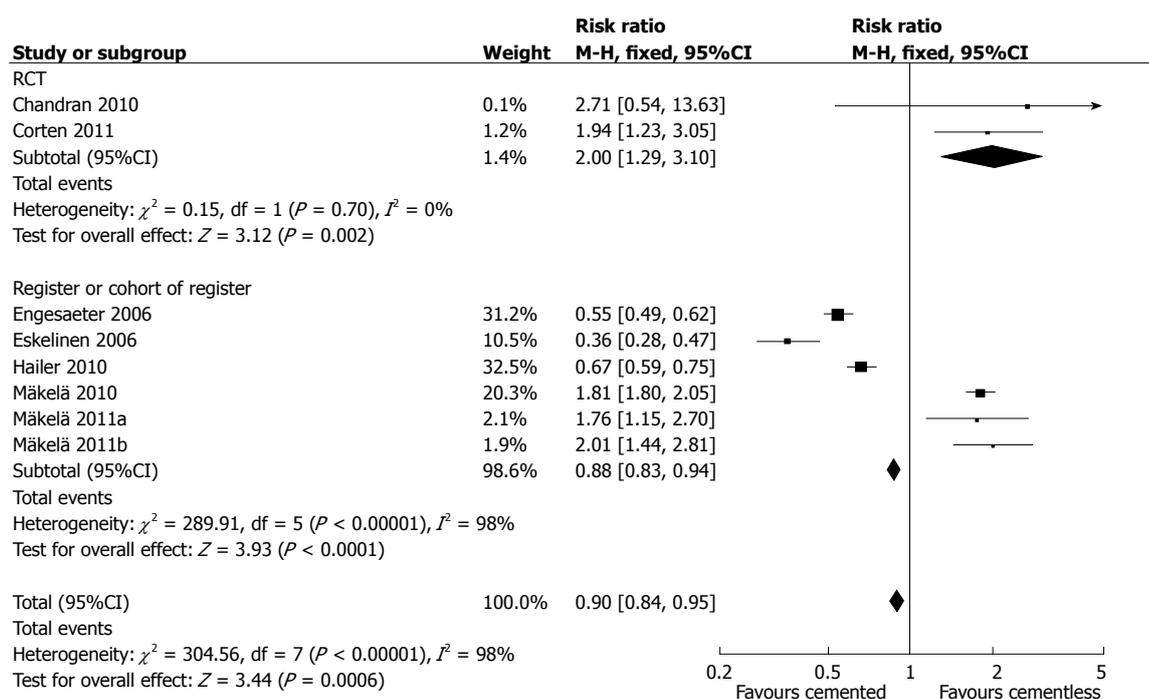


Figure 3 Forest plot of comparison: Cemented vs cementless: Revision of any component due to aseptic loosening.

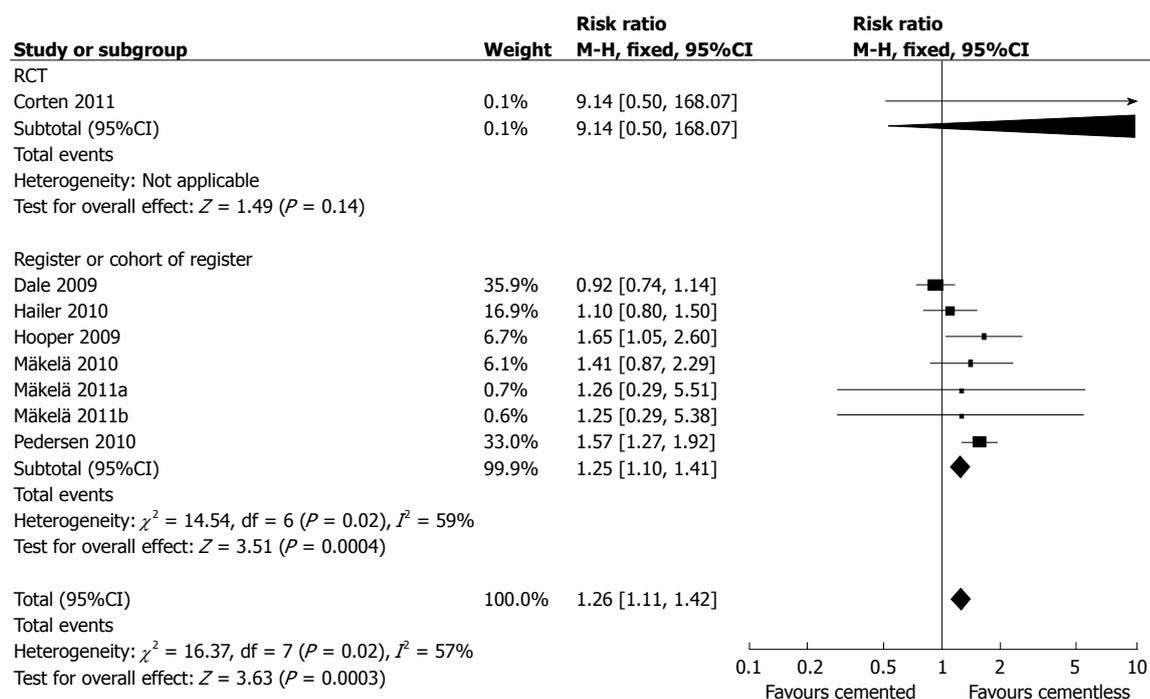


Figure 4 Forest plot of comparison: Cemented vs cementless: Revision of any component due to infection.

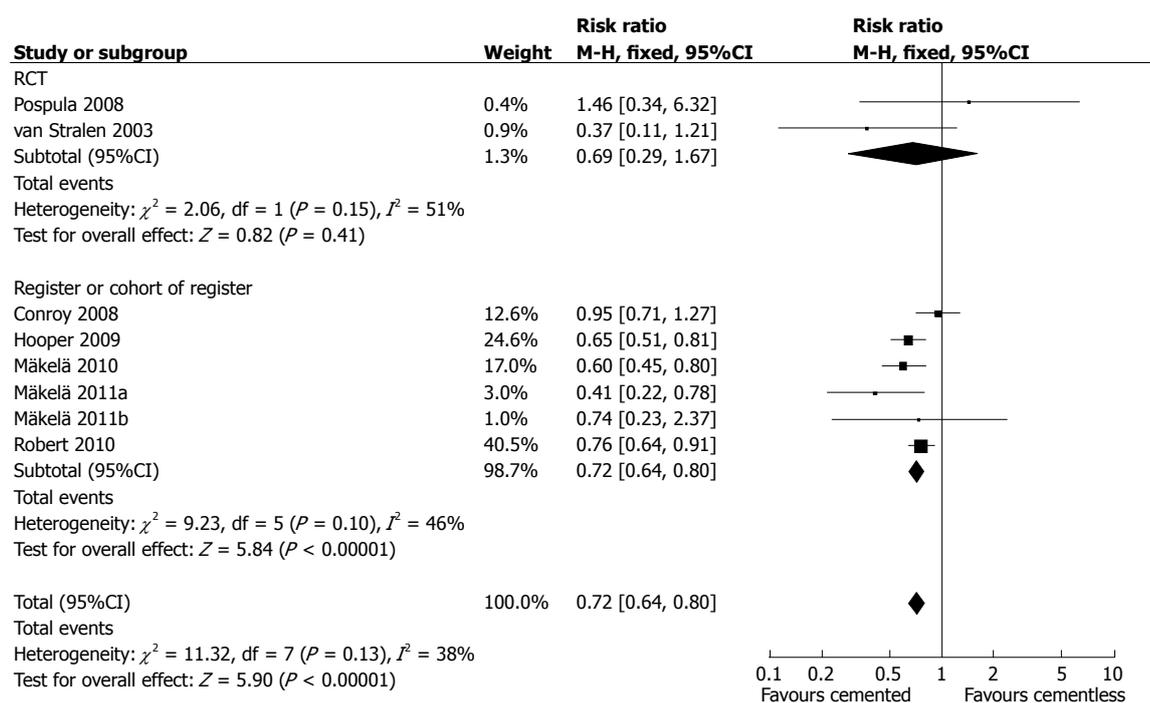


Figure 5 Forest plot of comparison: Cemented vs cementless: Dislocation of any component.

= 0.72; 95%CI: 0.64-0.80 respectively). Pooled RR was 0.72 (95%CI: 0.64-0.80) with heterogeneity of 38%.

Cemented vs hybrid THR

Revision of any component due to any reason:

Revision of any component due to any reason was addressed by two RCTs, one cohort, and three registers (Figure 6). Analysis of RCTs showed similar risk of revision of any component due to any reason while

analysis of registers favored cemented fixation (RR = 0.73; 95%CI: 0.47-1.13 and RR = 0.82; 95%CI: 0.76-0.89 respectively). Pooled all studies together, the RR was 0.82 (95%CI: 0.76-0.89) with a heterogeneity of 41%.

Revision of any component due to aseptic loosening: Only one RCT and one cohort provided information for evaluation of revision of any component

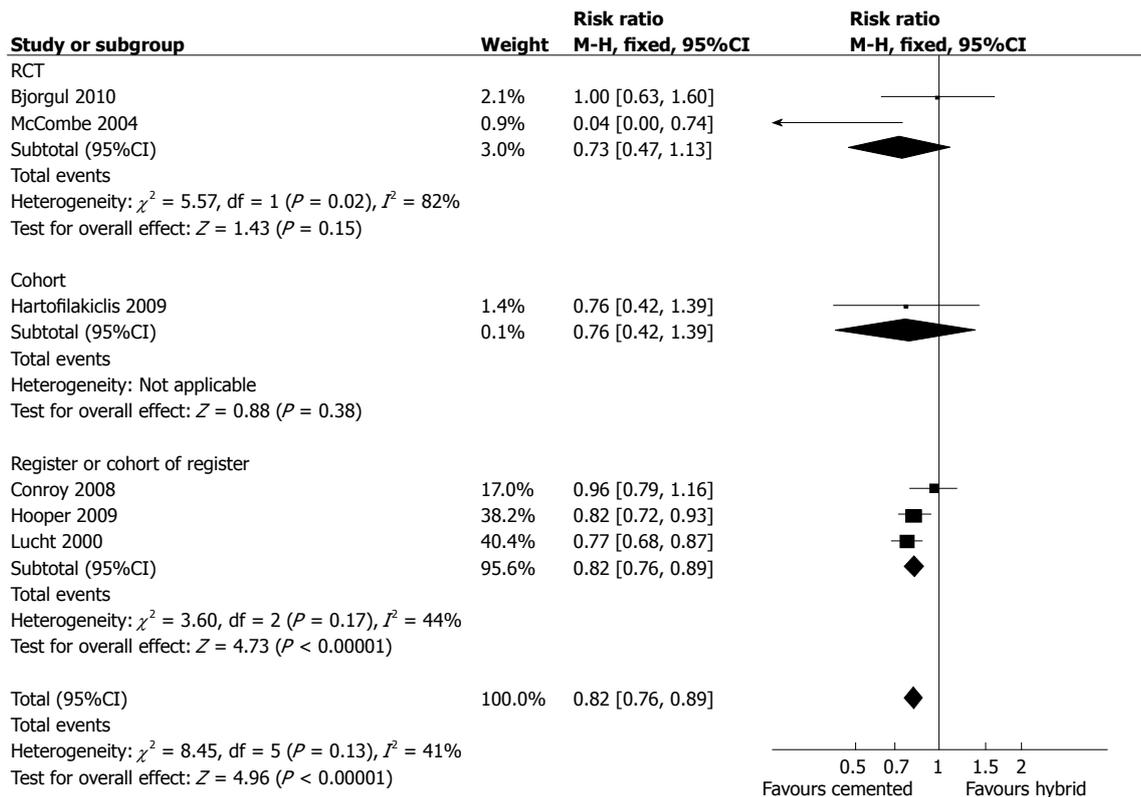


Figure 6 Forest plot of comparison: Cemented vs hybrid: Revision of any component due to any reason.

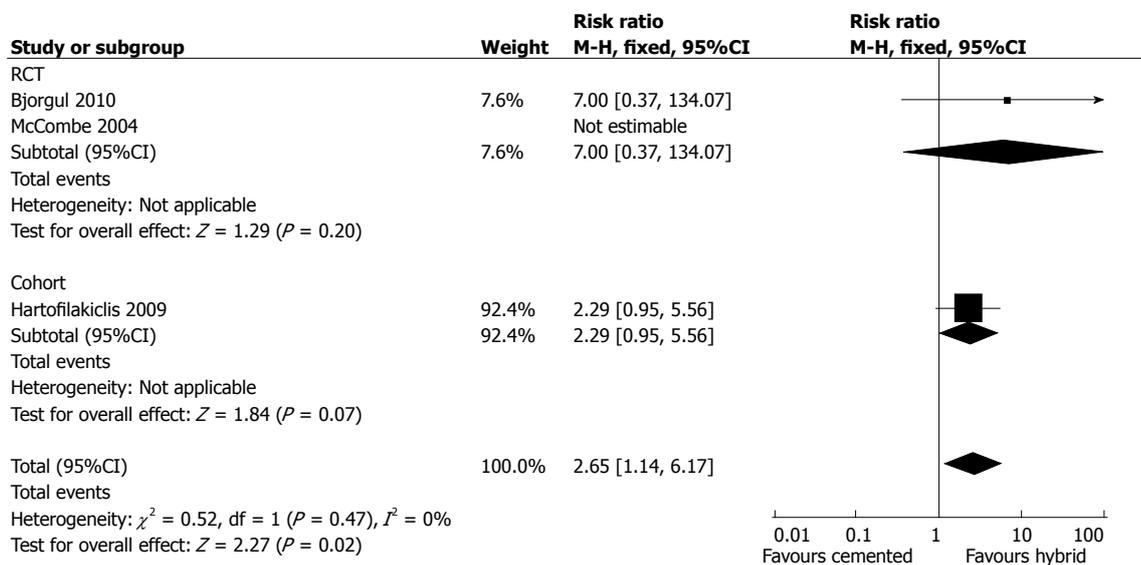


Figure 7 Forest plot of comparison: Cemented vs hybrid: Revision of any component due to aseptic loosening.

due to aseptic loosening (Figure 7). When both studies were pooled, the RR was 2.65 (95%CI: 1.14-6.17) and the heterogeneity was 0%.

Revision of any component due to infection: Two RCTs and one cohort and two registers reported revision of any component due to infection (Figure 8). However, one RCT and the cohort encountered zero-event in both arms, so only meta-analysis of registers could be

conducted, resulting in RR of 0.94 (95%CI: 0.80-1.11). If all types of study were pooled together, the RR was 0.92 (95%CI: 0.78-1.08) with heterogeneity of 42%.

Dislocation of any component: One RCT and two registers addressed dislocation of any component (Figure 9). Analysis of registers found that risk of dislocation of any component in cemented THR was lower than hybrid THR (RR = 0.11; 95%CI: 0.77-1.59). Pooled together,

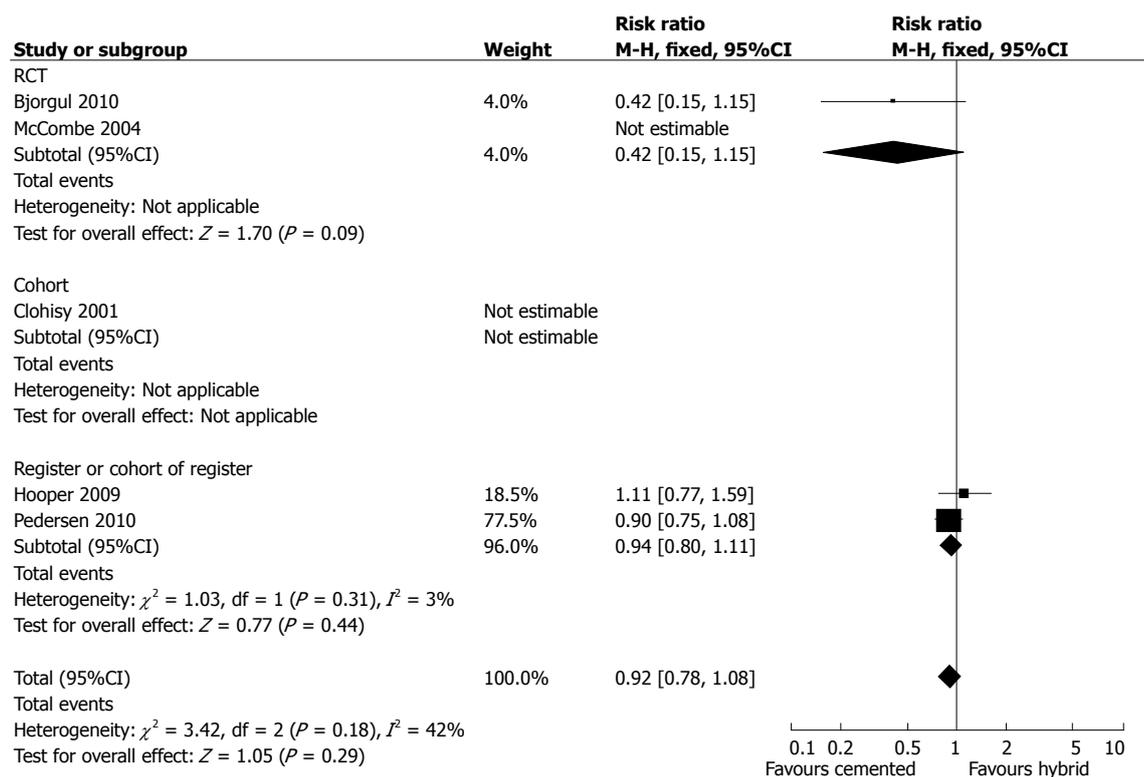


Figure 8 Forest plot of comparison: Cemented vs hybrid: Revision of any component due to infection.

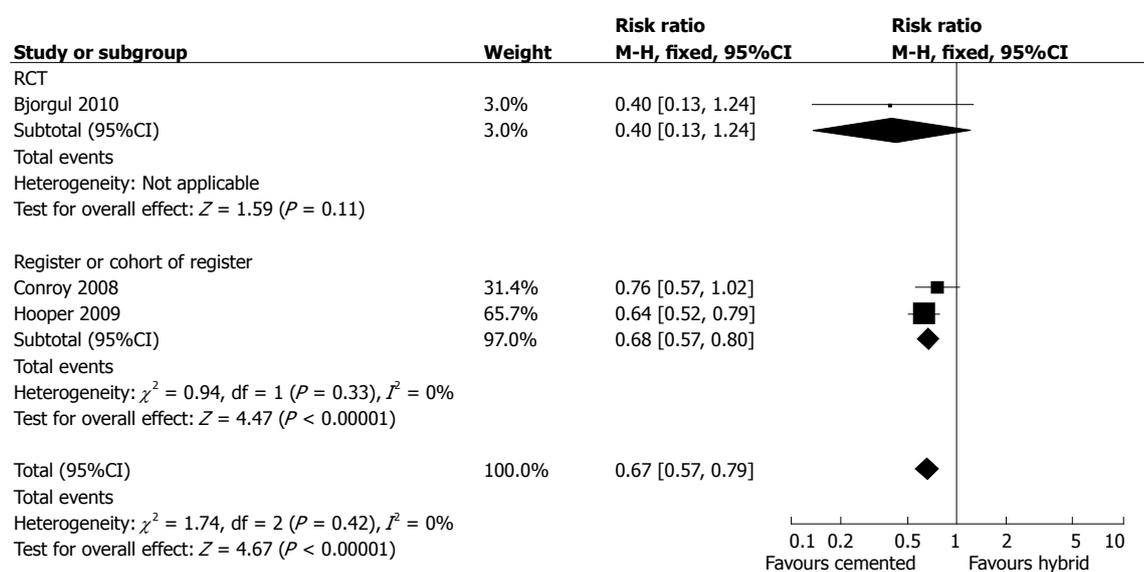


Figure 9 Forest plot of comparison: Cemented vs hybrid: Dislocation of any component.

the RR was 0.67 (95%CI: 0.57-0.79) with heterogeneity of 0%.

Cementless vs hybrid THR

Revision of any component due to any reason:

One RCT, four cohorts, and three registers investigated revision of any component due to any reason. Analysis of cohorts found similar risk while analysis of registers favored hybrid THR (Figure 10). Meta-regression reduced the heterogeneity into 23.7% but none of the factors

analyzed (age group, diagnosis, length of follow-up, starting year, publication type, and funding) showed significant influence.

Revision of any component due to aseptic loosening:

One RCT and three cohorts addressed risk of revision of any component due to aseptic loosening (Figure 11). However, one cohorts encountered zero-events in both arms so only two cohorts were eligible for further analysis, which revealed no difference (RR = 0.84;

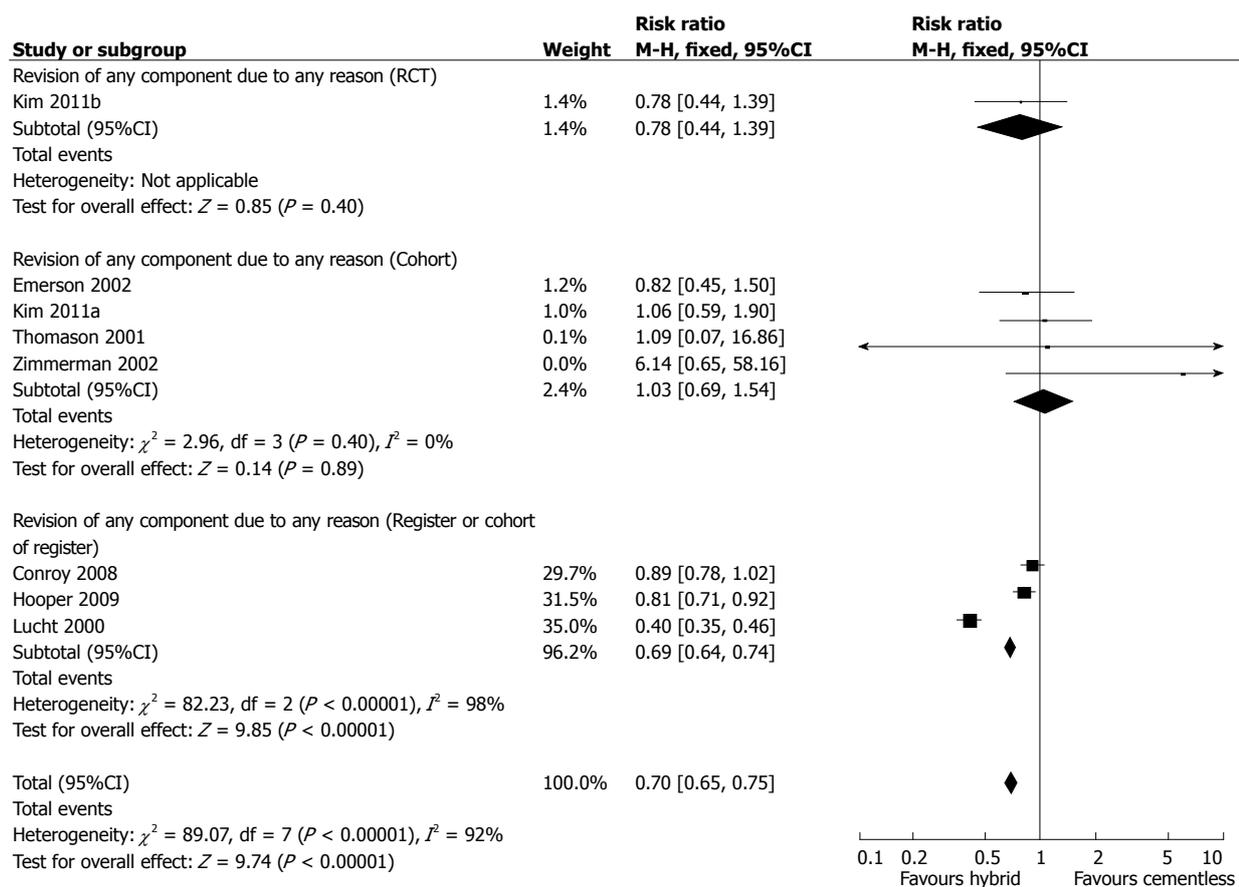


Figure 10 Forest plot of comparison: Cementless vs hybrid: Revision of any component due to any reason.

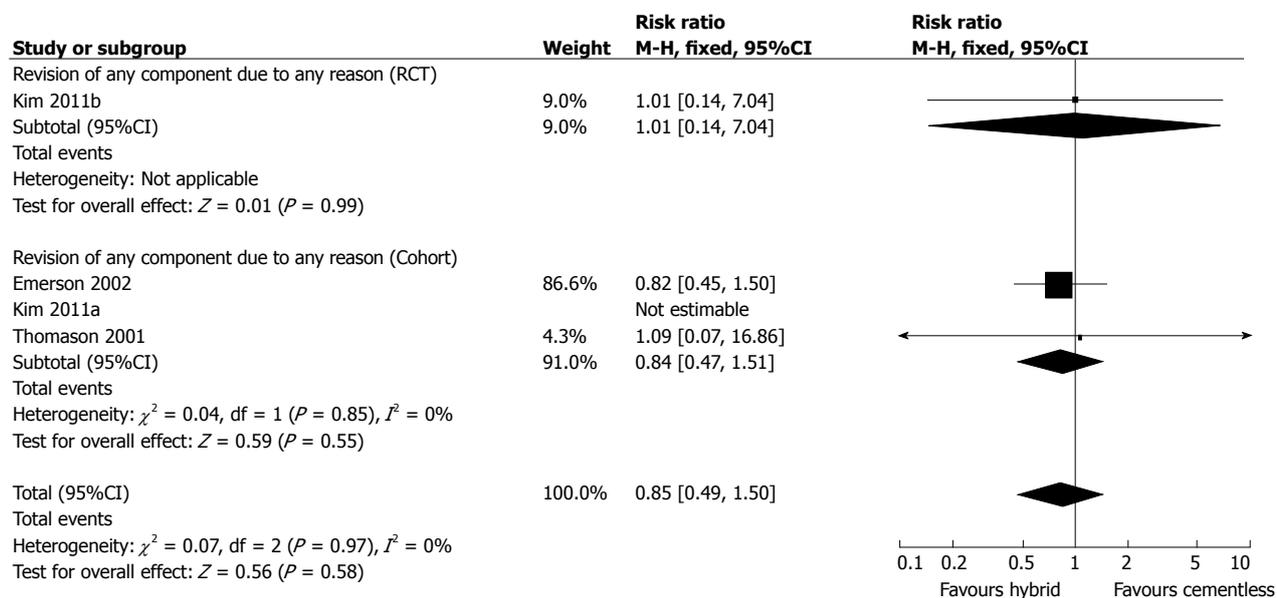


Figure 11 Forest plot of comparison: Cementless vs hybrid: Revision of any component due to infection.

95%CI: 0.47-1.51). Pooled all study types together; the RR was 0.85 (95%CI: 0.49-1.50) with heterogeneity of 0%.

Revision of any component due to infection: One

RCT, three cohorts, and two registers addressed revision of any component due to infection (Figure 12). However, two cohorts encountered zero events in both arm of studies so insufficient cohort was left for further analysis. Analysis of registers revealed RR of 1.69 (95%CI:

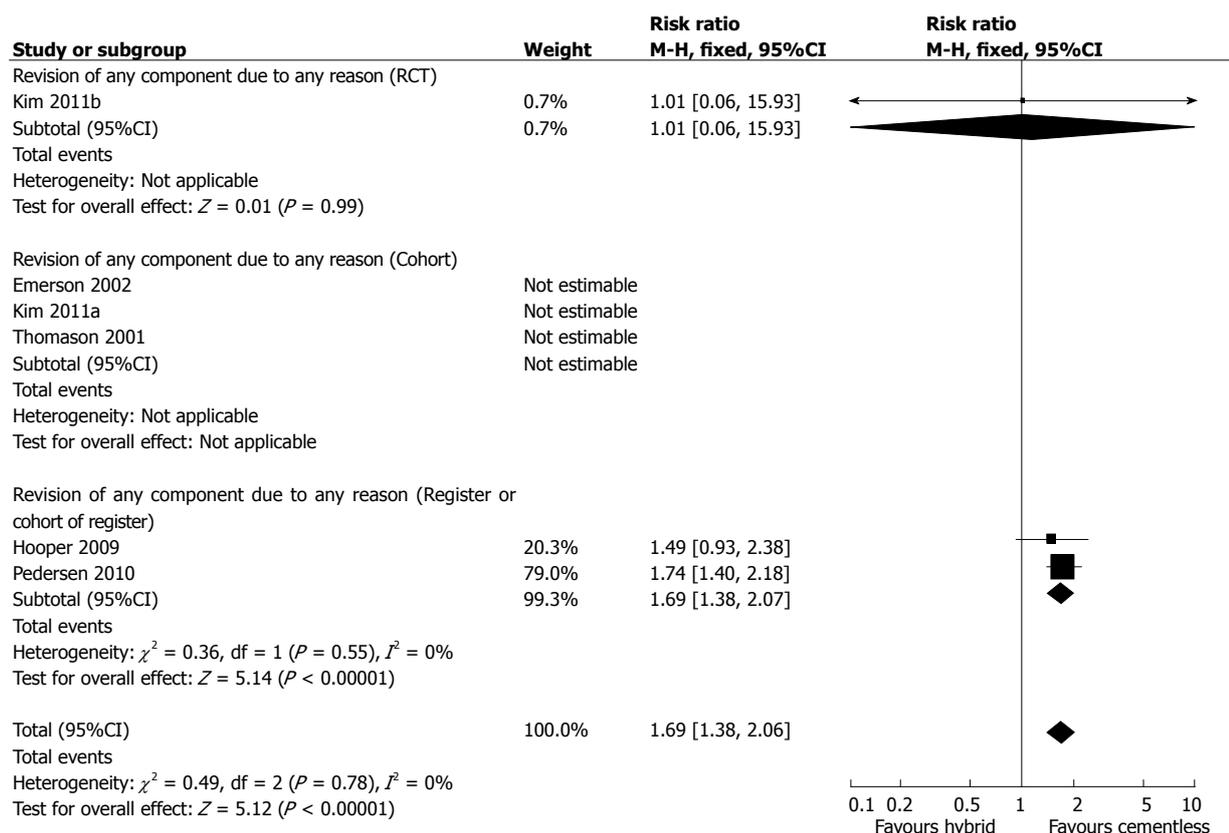


Figure 12 Forest plot of comparison: Cementless vs hybrid: Revision of any component due to infection.

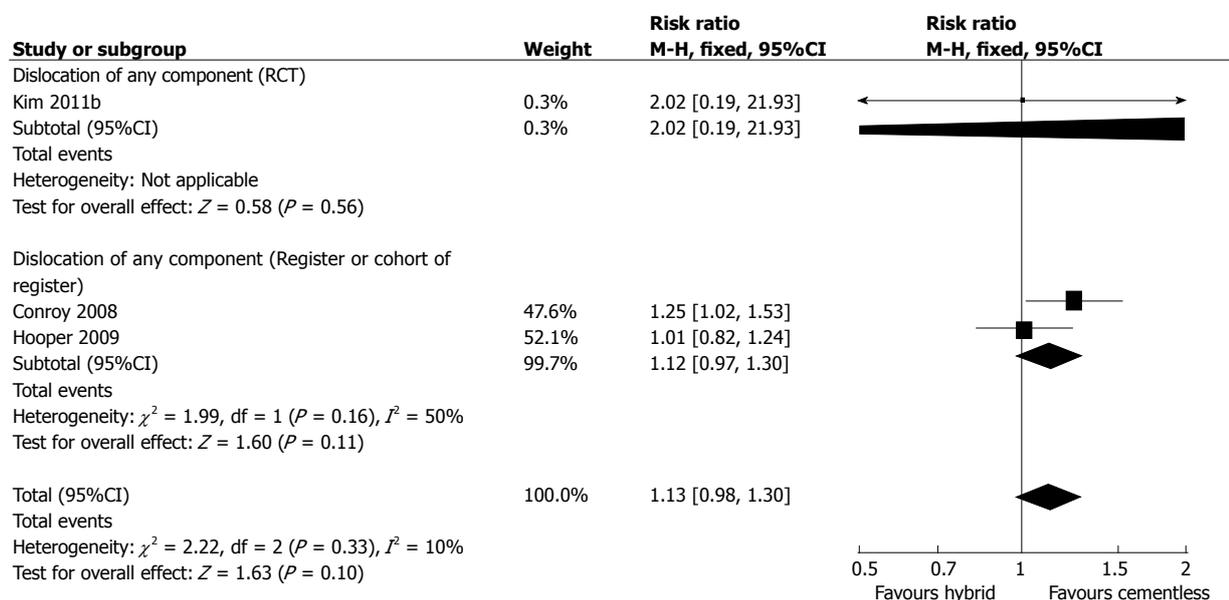


Figure 13 Forest plot of comparison: Cementless vs hybrid: Dislocation of any component.

1.38-2.07). If all available studies were put together, the RR was 1.69 (95%CI: 1.38-2.06) and the heterogeneity was 0%.

Dislocation of any component: One RCT and two cohorts evaluated risk of dislocation (Figure 13). Analysis of the registers resulted in insignificant difference

between any types of THR (RR = 1.12; 95%CI: 0.97-1.30). Pooled all study types together; the RR was 1.13 (95%CI: 0.98-1.30).

Analysis of publication bias: Figure 14 showed funnel plots based on risk of revision of any component due to any reason between cemented and cementless

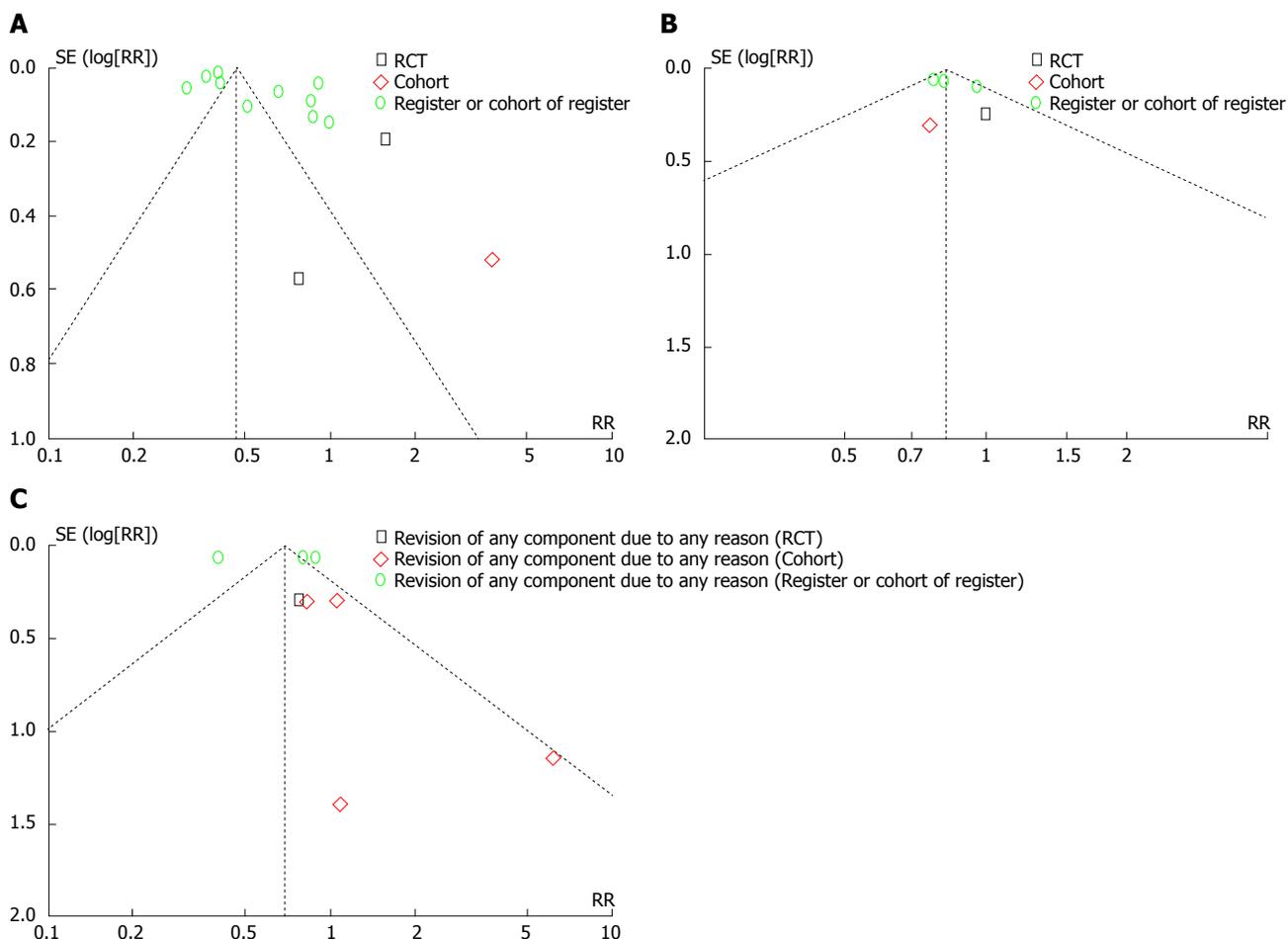


Figure 14 Funnel plot of comparison of revision of any component (A) cementless vs cementless; (B) cemented vs hybrid; (C) cementless vs hybrid.

(a), cemented and hybrid (b), and cementless and hybrid THR (c). Asymmetries were found in these plots suggesting the existence of bias.

Grading of the evidence: Most of the results were of low to very low level of evidence. The summaries of the grading were shown in Tables 2-4.

DISCUSSION

We summarized the evidence from 5 randomized clinical trials, 9 cohorts, and 13 registers or cohorts of register about total hip replacement and found that that cemented THR was superior to cementless THR and hybrid THR in terms of risk of revision due to any reason. Moreover, cemented THR was also more superior compared with cementless THR if revision due to aseptic loosening and revision due to dislocation were used as the endpoint but inferior if revision due to infection was used. Cemented THR was superior to hybrid THR in the risk of revision due to any reason and dislocation. Meanwhile cementless THR was most inferior compared to the others in risk of revision due to any reason.

In our knowledge, Morshed *et al.*^[9] performed the first metaanalysis reviewing the survival and outcome of cemented and uncemented fixation in total hip

replacement in 2007. Although cemented fixation seemed to outperform cementless fixation in large subsets of study population, there was no significant advantages were found for either type of fixation in terms of survival. There was an association between difference in survival and year of publication, with cementless fixation showing relative superiority over time. However, our recent analysis still suggested that cemented fixation continued to outperform uncemented fixation especially in large study populations (registers)^[24,26-33].

Recent metaanalysis by Abdulkarim *et al.*^[37] reviewed 9 RCTs that primarily comparing implants survival between cemented and cementless THR. In their study, no significant differences were found in implant survival especially as measured by the revision rate. By using RCT, which is the gold standard of clinical research, the quality of evidence in GRADE approach should be moderate or even high. However, the average follow up duration were only 4.3 years (2-8 years), which was relatively short to evaluate the implant survival.

In our study, an analysis of 2 RCTs comparing the survival of cemented and cementless implant was performed. As the duration of follow up ranged from 14-19 years, these RCTs would give a better evaluation in terms of implant survival. In this analysis, the relative risk of revision due to any revision was higher in cemented

Table 2 Summary of finding comparing cemented and cementless total hip replacement

	Illustrative comparative risks ⁷ (95%CI)		Relative effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cementless	Cemented				
Revision of any component due to any reason - RCT Follow-up: 14 to 19.5 yr	Study population 165 per 1000 Moderate	235 per 1000 (165 to 336)	RR 1.43 (1 to 2.04)	452 (2 studies)	++- low ^{1,2}	
Revision of any component due to any reason - Register or Cohort of register Follow-up: 0 to 24 yr	Study population 99 per 1000 Moderate	223 per 1000 (156 to 318) 46 per 1000 (45 to 47)	RR 0.46 (0.45 to 0.47)	518774 (10 studies)	+--- very low ^{2,3,4}	
Revision of any component due to any reason - All types of study Follow-up: 0 to 24 yr	Study population 99 per 1000 Moderate	46 per 1000 (44 to 47) 56 per 1000 (55 to 57)	RR 0.47 (0.45 to 0.48)	521757 (13 studies)	+--- very low ^{2,3,5}	
Revision of any component due to aseptic loosening - RCT Follow-up: 14 to 19.5 yr	Study population 104 per 1000 Moderate	208 per 1000 (134 to 322)	RR 2 (1.29 to 3.1)	452 (2 studies)	+++ moderate ²	
Revision of any component due to aseptic loosening - Register or Cohort of register Follow-up: 0 to 24 yr	Study population 47 per 1000 Moderate	194 per 1000 (125 to 301) 41 per 1000 (39 to 44)	RR 0.88 (0.83 to 0.94)	255779 (6 studies)	+--- very low ^{2,3,4}	
Revision of any component due to aseptic loosening - All types of study Follow-up: 0 to 24 yr	Study population 47 per 1000 Moderate	43 per 1000 (40 to 45) 43 per 1000 (40 to 46)	RR 0.9 (0.84 to 0.95)	256231 (8 studies)	+--- very low ^{2,3,5,6}	
Revision of any component due to infection - Register or Cohort of register Follow-up: 0 to 20 yr	Study population 5 per 1000 Moderate	6 per 1000 (5 to 7) 5 per 1000 (4 to 6)	RR 1.27 (1.04 to 1.55)	382433 (6 studies)	+--- very low ^{2,4}	
Revision of any component due to infection - All types of study Follow-up: 0 to 20 yr	Study population 5 per 1000 Moderate	6 per 1000 (5 to 7) 5 per 1000 (4 to 6)	RR 1.29 (1.06 to 1.57)	382683 (7 studies)	+--- very low ^{2,5}	
Dislocation of any component - Cohort Follow-up: 2.5 to 5 yr	Study population 30 per 1000 Moderate	21 per 1000 (9 to 50) 21 per 1000 (9 to 50)	RR 0.69 (0.29 to 1.67)	1066 (2 studies)	+--- very low ^{1,2,3}	
Dislocation of any component - Register or Cohort of register Follow-up: 5 to 15 yr	Study population 6 per 1000 Moderate	4 per 1000 (4 to 5) 9 per 1000 (8 to 10)	RR 0.69 (0.59 to 0.8)	254786 (6 studies)	+--- very low ^{3,4}	
Dislocation of any component - All types of study Follow-up: 2.5 to 15 yr	Study population 6 per 1000 Moderate	4 per 1000 (4 to 5) 10 per 1000 Ta(8 to 11)	RR 0.69 (0.6 to 0.79)	255852 (8 studies)	+--- very low ^{2,5}	

CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate. ¹95% confidence interval around the pooled or best estimate of effect includes both (1) no effect and (2) appreciable benefit or appreciable harm (> 25%); ²No explanation was provided; ³Unexplained heterogeneity; ⁴Indirect studies from registers; ⁵Overall result from all types of study; ⁶High heterogeneity, explained by meta-regression; ⁷The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

group with RR = 1.43 (1-2.04), which also meant that the cementless implant was superior. But it were pooled together with the cohort studies and registers, the results would be contradictive as it favored the cemented implant with RR = 0.47 (0.46-0.48).

Despite the tendencies of most registers towards cemented implant, there are some studies and even

some registries^[29,30,33] noted that uncemented implant survived better in the group of younger patients. Malchau *et al.*^[33] in their Swedish arthroplasty register, found that uncemented implants had better survival in patients with less than 55 years of age. Similar findings were reported by the Lucht *et al.*^[29] when they evaluated the Danish arthroplasty register. Eskelinen *et al.*^[26] in the Finnish

Table 3 Summary of finding table comparing cemented to hybrid total hip replacement

Outcomes	Illustrative comparative risks ⁶ (95%CI)		Relative effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Hybrid	Cemented				
Revision of any component due to any reason - RCT Follow-up: 6.5 to 14 yr	Study population 187 per 1000 Moderate	136 per 1000 (88 to 211) 129 per 1000 (83 to 200)	RR 0.73 (0.47 to 1.13)	402 (2 studies)	+--- very low ^{1,2,3}	
Revision of any component due to any reason - Register or Cohort of register Follow-up: 4 to 7 yr	Study population 30 per 1000 Moderate	24 per 1000 (23 to 26) 25 per 1000 (24 to 28)	RR 0.82 (0.76 to 0.89)	76746 (3 studies)	+--- very low ^{3,4}	
Revision of any component due to any reason - All types of study Follow-up: 4 to 15.4 yr	Study population 31 per 1000 Moderate	25 per 1000 (23 to 27) 85 per 1000 (79 to 93)	RR 0.82 (0.76 to 0.89)	77265 (6 studies)	+--- very low ^{3,5}	
Revision of any component due to aseptic loosening - All types of study Follow-up: 6.5 to 15.4 yr	Study population 23 per 1000 Moderate	62 per 1000 (27 to 145) 0 per 1000 (0 to 0)	RR 2.65 (1.14 to 6.17)	519 (3 studies)	+--- very low ^{3,5}	
Revision of any component due to infection - Register or Cohort of register Follow-up: 0 to 14 yr	Study population 7 per 1000 Moderate	0 per 1000 (0 to 0)	Not estimable	86389 (2 studies)	+--- very low ^{3,4}	
Revision of any component due to infection - All types of study Follow-up: 0 to 14 yr	Study population 7 per 1000 Moderate	7 per 1000 (5 to 10) 2 per 1000 (1 to 3)	RR 0.98 (0.7 to 1.38)	86881 (5 studies)	+--- very low ^{1,2,3,5}	
Dislocation of any component - Register of Cohort of register Follow-up: 5 to 7 yr	Study population 11 per 1000 Moderate	7 per 1000 (6 to 9) 7 per 1000 (6 to 9)	RR 0.68 (0.57 to 0.8)	60584 (2 studies)	+--- very low ^{3,4}	
Dislocation of any component - All types of study Follow-up: 5 to 14 yr	Study population 11 per 1000 Moderate	7 per 1000 (6 to 9) 9 per 1000 (8 to 11)	RR 0.67 (0.57 to 0.79)	60824 (3 studies)	+--- very low ^{3,5}	

CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate. ¹95% confidence interval around the pooled or best estimate of effect includes both (1) no effect and (2) appreciable benefit or appreciable harm (> 25%); ²No explanation was provided; ³Unexplained heterogeneity; ⁴Indirect studies from registers; ⁵Overall result from all types of study; ⁶The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).

arthroplasty register, reported that in age group under 55-years had higher revision rates for aseptic loosening in cemented group compared with proximally coated cementless femoral components. Further analysis of Finnish arthroplasty register in patients aged 55-year and older showed that uncemented femoral stem has better survival in the 55 to 74-year age group while there was no significant difference in 75-year and older patients^[30].

This series of studies might explain the reason why contradictive result occurred in our analysis. In their inclusion criteria, both RCTs used 75 years as the upper age limit without any lower age limit, and the average age in both RCTs was around 64 years^[12,13]. It was seemed that this fact might play a role in our result.

Hybrid THR was first introduced to address the

results of cemented THR in younger patients in whom acetabular failure was the main reason for revision. However, recent studies reported that hybrid THR was the most common THR types to be revised due to dislocation in the first 90 d and even after 90 d after the primary surgery^[28]. In their prospective multicenter study about primary total hip arthroplasty revision due to dislocation, Girard *et al*^[38] described that, from their revision series, cementless acetabular fixation and cemented femoral stem fixation were involved in a higher number of dislocation which are 63.8% and 53% respectively. However it was not mentioned about the reason why cementless acetabular fixation has a higher chance of dislocation compared to the cemented one. Although there are no supporting data, there was a hypothesis

Table 4 Summary of finding table comparing hybrid and cementless total hip replacement

Outcomes	Illustrative comparative risks ⁷ (95%CI)		Relative effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cementless	Hybrid				
Revision of any component due to any reason - Cohort Follow-up: 1 to 17.3 yr	Study population 105 per 1000 Moderate	108 per 1000 (72 to 161)	RR 1.03 (0.69 to 1.54)	706 (4 studies)	+--- very low ^{1,2}	
Revision of any component due to any reason - Register or Cohort of register Follow-up: 4 to 7 yr	Study population 33 per 1000 Moderate	109 per 1000 (73 to 163)	RR 0.69 (0.64 to 0.74)	81635 (3 studies)	+--- very low ^{2,3,4}	
Revision of any component due to any reason - All types of study Follow-up: 1 to 18.4 yr	Study population 34 per 1000 Moderate	24 per 1000 (22 to 26)	RR 0.7 (0.65 to 0.75)	82560 (8 studies)	+--- very low ^{2,5,6}	
Revision of any component due to aseptic loosening - Cohort Follow-up: 6.7 to 17.3 yr	Study population 76 per 1000 Moderate	64 per 1000 (36 to 115)	RR 0.84 (0.47 to 1.51)	447 (3 studies)	+--- very low ^{1,2}	
Revision of any component due to aseptic loosening - All types of study Follow-up: 6.7 to 17.3 yr	Study population 58 per 1000 Moderate	17 per 1000 (9 to 30)	RR 0.85 (0.49 to 1.5)	666 (4 studies)	+--- very low ^{1,2,6}	
Revision of any component due to infection - Register or Cohort of register Follow-up: 0 to 14 yr	Study population 4 per 1000 Moderate	0 per 1000 (0 to 0)	Not estimable	72197 (2 studies)	+--- very low ^{2,4}	
Revision of any component due to infection - All types of study Follow-up: 0 to 18.4 yr	Study population 4 per 1000 Moderate	6 per 1000 (4 to 10)	RR 1.47 (0.93 to 2.34)	72863 (5 studies)	+--- very low ^{1,2,6}	
Dislocation of any component - Register or Cohort of register Follow-up: 5 to 7 yr	Study population 9 per 1000 Moderate	10 per 1000 (9 to 11)	RR 1.12 (0.97 to 1.3)	75114 (2 studies)	+--- very low ^{1,2,4}	
Dislocation of any component - All types of study Follow-up: 5 to 18.4 yr	Study population 9 per 1000 Moderate	11 per 1000 (10 to 13)	RR 1.13 (0.98 to 1.3)	75333 (3 studies)	+--- very low ^{1,2,6}	

CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: We are very uncertain about the estimate. ¹95% confidence interval around the pooled or best estimate of effect includes both (1) no effect and (2) appreciable benefit or appreciable harm (> 25%); ²No explanation was provided; ³Unexplained heterogeneity; ⁴Indirect studies from registers; ⁵Overall result from all types of study; ⁶High heterogeneity, explained by meta-regression; ⁷The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

that positioning of acetabular component may be more accurate in cemented components^[23]. Although Parrate and Argenson^[39] didn't include cemented acetabular cup in their study, they showed that 57% cementless cup that inserted in conventional way and 20% navigated were outside of the defined safe zone (outliers). While cementing the acetabular component, few adjustments can be made during insertion and while waiting for the cement polymerization. On the other hand, cementless cup has less adjustability and may change their orientation from the most desired position during the final seating of the component. Despite all, from the economic perspective, hybrid prostheses lead to grater gain in mean postoperative quality of life and the most cost

effective alternative for most patients according to cost effectiveness analysis model by Pennington *et al.*^[40]

Clinical trials, cohorts, and register-based studies were included into our meta-analysis. Inclusion of register based studies had certain benefits and limitations^[30,36]. Register provided large number of samples for analysis and the population data corresponded to the actual population^[36]. Moreover, a poor result in a single center would not have major effect on the result of the study^[30]. Despite RCTs is considered the gold standard design for clinical research, one of its disadvantages is that strict inclusion and exclusion criteria might not reflect the condition of real population, as it often narrowed the samples to a highly selected group of patients that is operated by only a

few surgeons. However, the desired outcome was not the main purpose of the registry. Accuracy of the data might be limited due to inconsistencies or errors in data collection inputted to the register^[41]. Data available in clinical trials and cohorts might also have been included in the register and therefore were used twice in the analysis.

Various implant designs, surgical approaches and techniques (such as cementing technique), rehabilitation protocols, and activity levels were included in our study. Lack of data prevented us to analyze them separately in subgroup analysis or in meta-regression. Therefore, it was understandable that high heterogeneity existed in our study. We explored the heterogeneity to the greatest degree possible, in to a meta-regression, yet very high heterogeneity remained in some comparison.

Very high heterogeneity indicated that effect size of each study varied greatly^[42]. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working group recommended to lower the quality assessment in study with unexplained heterogeneity^[41]. Even though the result was obtain by a meta-analysis, interpreting the result must be careful.

In conclusion, despite some limitations in the selected studies especially the low quality assessment and heterogeneity, there was some tendency that cemented fixation was still superior than other types of fixation in terms of implant survival. Future high quality randomized clinical trials, preferably multicenter, to obtain larger sample size, considering all factors that may influent results, are required to give definite recommendations regarding the best type of total hip replacement.

COMMENTS

Background

Controversies still persisted on the optimal method of fixation for primary total hip replacement (THR). Previous meta-analysis found no difference between cemented and cementless implant, but since then, many larger studies with longer duration of follow-up had been conducted. In this meta-analysis, more recent studies were enrolled to determine whether cemented, cementless, or hybrid implant was superior to the other.

Research frontiers

Implant survival analysis in different type of THR fixation is still a controversial debate. Worldwide researches are still focused on which type of implant that suits best on patients to provide better care to the patients.

Innovations and breakthroughs

Despite some limitations in the selected studies especially the low quality assessment and heterogeneity, their study presented a metaanalysis of studies with a long duration of follow up, which would give a better perspective in terms of implant survival. There was some tendency that cemented fixation was still superior than other types of fixation.

Applications

There was some tendency that cemented fixation was still superior to other types of fixation.

Peer-review

It is well presented, well-structured and extensively build up and therefore useful for the readers.

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Novel technique for a symptomatic subscapularis herniation through a scapular defect

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Abstract

Fractures of the scapula are rare and have been reported to account for only 1% of all fractures and 3%-5% of upper extremity fractures. Several studies have reported successful outcomes with non-operative treatment of scapula fractures. Although non-operative treatments are successful in a very high percentage of patients, very few cases of non-union of scapular body fractures have been reported. In our review of the literature, we found two case reports of scapular body fractures developed into non-unions. In both of these cases, open reduction and internal fixation with reconstruction plates and bone graft was successful at eliminating pain and restoring function. This is a case report of a patient with a symptomatic, extra-articular scapular body defect from a non-union that was treated successfully with an acellular dermal extracellular matrix and bone graft using a novel technique

Key words: Scapular fractures; Mesh repair; Non-union; Bone graft; Acellular dermal extracellular matrix

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Core tip: Scapular fracture complicated by non-union requiring surgical intervention is extremely rare and seldom reported in the literature. This study demonstrates successful surgical treatment of a symptomatic scapular body defect using a novel technique that has never been described for this condition.

Grau L, Chen K, Alhandi AA, Goldberg B. Novel technique for a symptomatic subscapularis herniation through a scapular defect. *World J Orthop* 2017; 8(2): 208-211 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i2/208.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i2.208>

INTRODUCTION

Several studies have reported successful outcomes with non-operative treatment of scapula fractures^[1-3]. In reviewing the literature, we found only two case reports of scapular body fractures that developed into non-unions^[4,5]. In both of these cases, open reduction and internal fixation with reconstruction plates and bone graft was successful at eliminating pain and restoring function. This is a case report of a patient with symptomatic, extra-articular scapular body defect from a non-union, which was treated successfully with acellular dermal extracellular matrix and bone graft using a novel technique.

CASE REPORT

Presentation

A 52-year-old female sustained a right scapular body and right clavicle fracture in a motorcycle accident 14 mo prior to presenting to our clinic. She was treated non-operatively for the scapular body fracture and with open reduction and internal fixation of the clavicle fracture at an outside hospital. The patient complained that she continued to have constant, posterior shoulder pain along her right scapula after the accident. She came to our clinic because her pain was preventing her from sleeping at night and affecting her activities of daily living. A computed tomography (CT) scan showed a 4 cm × 2 cm elliptical defect of the inferior scapular body with herniation of the subscapularis muscle through the defect (Figures 1 and 2).

Physical exam

On physical exam the patient had tenderness to palpation over the inferior aspect of the scapular body on her right side. Her range of motion was intact with forward flexion of 180 degrees, abduction of 180 degrees, internal rotation of 90 degrees and external rotation of 55 degrees. She was neurologically intact in the axillary, median and ulnar nerve distributions. Her strength was 5/5 in all planes of motion in her upper extremity.

Surgery

After the nonunion site was marked (Figure 3), an oblique 10 cm incision was made just inferior to the scapular spine running from medial to lateral (Figure 4). A portion of the deltoid was incised in a longitudinal manner to help expose the scapular spine. The infraspinatus muscle was peeled off to expose the nonunion site that was approximately 4 cm in length and 2 cm in width (Figure 5). A herniation of the subscapularis muscle through the defect was noted.

Several drill holes around the edge of the defect were made circumferentially with K-wires and two #2 FiberWires were passed through each of these holes. An Arthroflex jacket (Arthrex, Naples, Florida), which is an acellular dermal extracellular matrix, was sewn into the undersurface of the scapula using #2 FiberWires. Approximately 7 cc of Graft-on bone product was placed on top of the jacket into the defect. The jacket

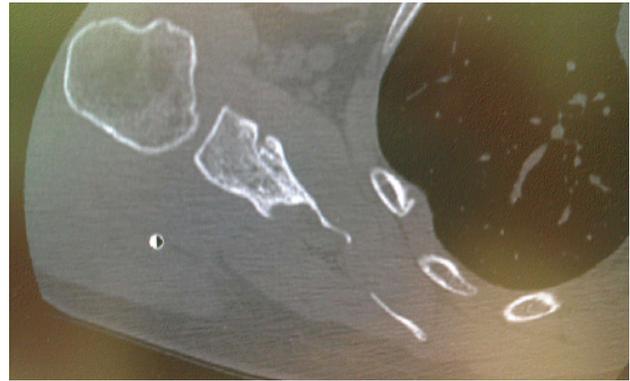


Figure 1 Axial computed tomography showing defect of scapular body.



Figure 2 Coronal computed tomography showing defect of scapular body.

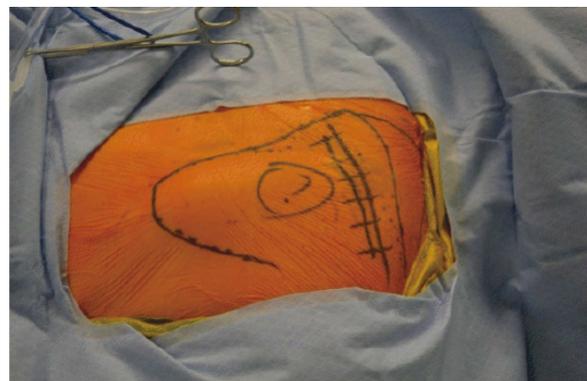


Figure 3 Borders of scapula, scapular spine, incision site (dashed line) and area over defect were marked.

was then folded onto the Grafton and sewn onto the posterior aspect of the scapular creating a pouch and barrier between the anterior and posterior aspects of the scapula (Figure 6). The infraspinatus was then attached back to its origin using 0 Vicryl and repair the deltoid muscle was performed with 0 Vicryl sutures in a figure of eight fashion. The dermis and epidermis was closed in standard fashion and dressings were applied. There were no complications postoperatively.

Outcome

At 2 wk follow up, the patient could sleep through the

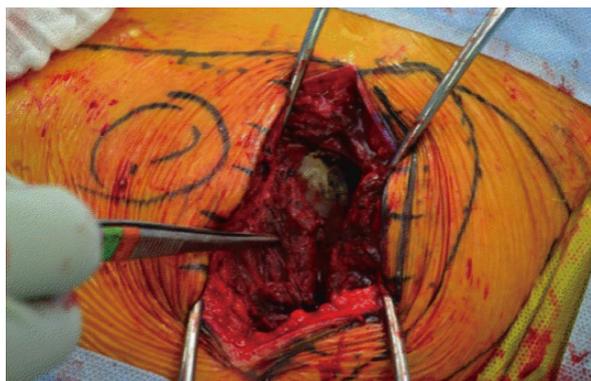


Figure 4 The 10 cm incision made just inferior to scapula spine, running from medial to lateral.



Figure 5 The 4 cm x 2 cm scapular defect exposed.

night, which she could not do prior to the operation. At her two month follow up visit the patient no longer complained of any right shoulder pain. She was also able to get back to doing activities such working out and riding her motorcycle. Her range of motion, strength, and sensation of the right shoulder were fully intact.

DISCUSSION

In our review of the literature, we found two case reports on scapular nonunion, Gupta *et al*^[5] and Ferraz *et al*^[4] both had excellent results with open reduction and internal fixation using reconstruction plates and bone graft. In both cases the patients had a fracture pattern that was unstable and causing functional limitations. Ferraz *et al*^[4] reported that their patient had pain and decreased range of motion of the shoulder joint secondary to intra-articular involvement of the fracture and cartilage damage. In the case reported by Gupta *et al*^[5] the patient had a transverse comminuted fracture with displacement and overlap of the fracture fragments that was causing winging with forward flexion and decreased range of motion.

Non-union is rare in patients treated conservatively for scapular body fractures and it is perhaps even rarer for these to be symptomatic. Persistent pain following injury requires further work up and possible surgical

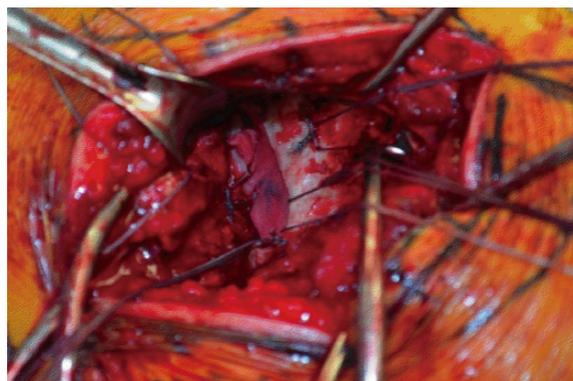


Figure 6 The dermal jacket is sewn into the defect.

intervention.

Herniation of the subscapularis muscle through the scapular defect was likely the cause of our patient's pain. This could be seen on the pre-operative CT scan (Figures 1 and 2). The patient had excellent preoperative function because the defect was not unstable and the scapula remained functioning as a unit and there was no involvement of the joint. For these reasons the authors believed that mechanical stabilization with plates and screws was not necessary. Similar to mesh that is used for intestinal herniation in general surgery the use of the extracellular dermal matrix with bone graft was successful at preventing herniation of the subscapularis, which was likely the patient's source of pain. This was confirmed by the success of our surgery in providing relief for the patient as early as 2 wk after the procedure and at later follow-up. We believe this to be rare case of scapular nonunion with a unique etiology for pain that was treated with a novel technique.

COMMENTS

Case characteristics

A 52-year-old women, 14 mo status post non-operative treatment of scapular fracture, presented with constant pain that interrupted her sleep and daily activities.

Clinical diagnosis

Intact range of motion and neurovascular exam, with tenderness to palpation over the inferior aspect of the scapular body on her right side.

Differential diagnosis

Subscapularis herniation, painful scapula non-union, rotator cuff pathology, and scapula dyskinesia.

Laboratory diagnosis

Within normal limits.

Imaging diagnosis

Computed tomography scan showed a 4 cm x 2 cm elliptical defect of the inferior scapular body with herniation of the subscapularis muscle through the defect.

Pathological diagnosis

Pathological samples were not taken.

Treatment

Surgical intervention by acellular dermal extracellular matrix and bone graft.

Related reports

Other reports in the literature have mentioned decreased range of motion associated with the injury. The lack of decreased range of motion does not exclude the injury.

Term explanation

Scapular fracture healed in non-union are not a common result of non-operative treatment.

Experiences and lessons

The use of the extracellular dermal matrix with bone graft was successful at preventing herniation of the subscapularis and alleviating the patient's symptoms.

Peer-review

It is a well-written case.

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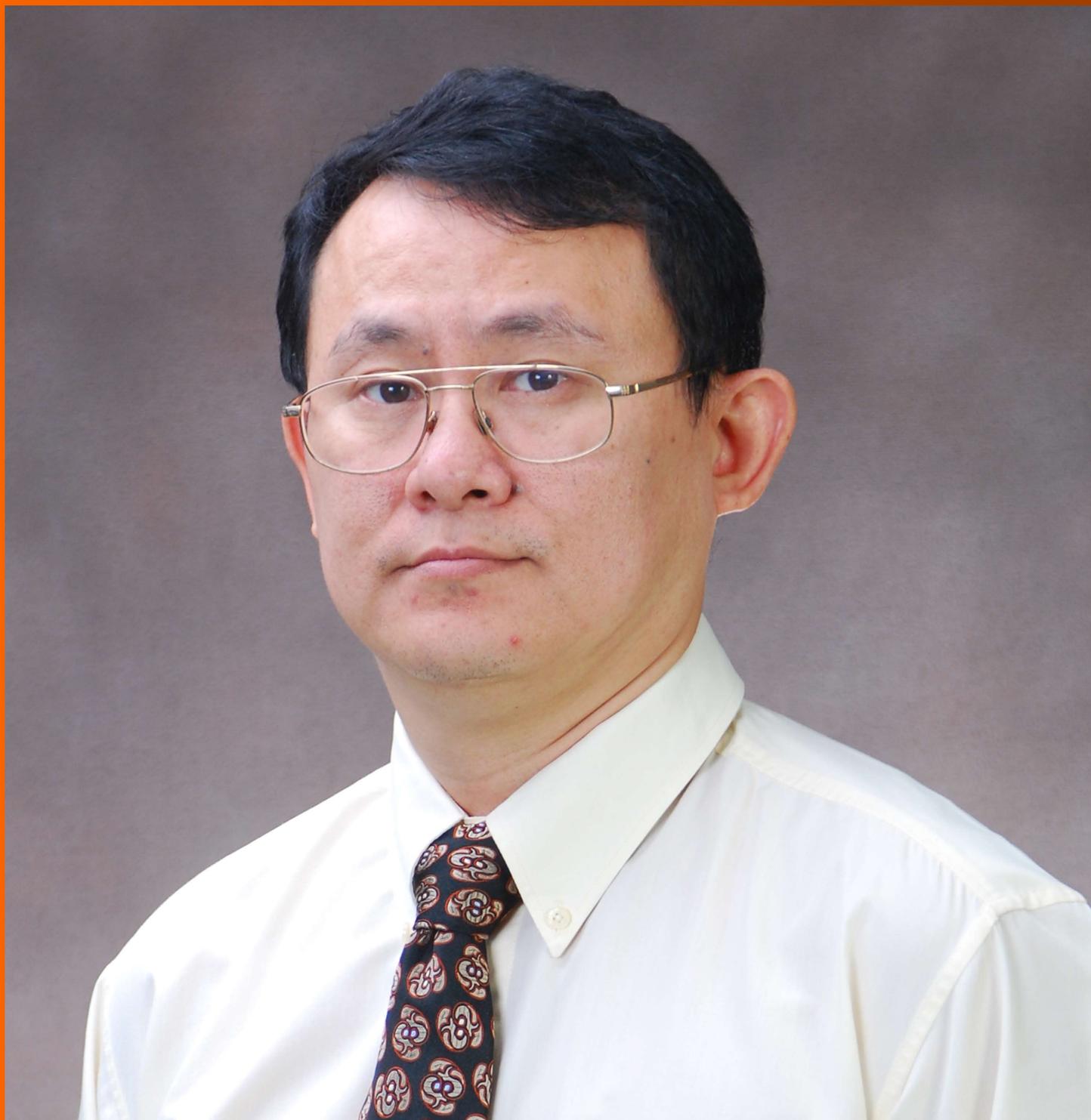
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Anterior cruciate ligament reconstruction and knee osteoarthritis

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Abstract

Anterior cruciate ligament (ACL) injury is a traumatic event that can lead to significant functional impairment and inability to participate in high-level sports-related activities. ACL reconstruction is considered the treatment

of choice for symptomatic ACL-deficient patients and can assist in full functional recovery. Furthermore, ACL reconstruction restores ligamentous stability to normal, and, therefore, can potentially fully reinstate kinematics of the knee joint. As a consequence, the natural history of ACL injury could be potentially reversed *via* ACL reconstruction. Evidence from the literature is controversial regarding the effectiveness of ACL reconstruction in preventing the development of knee cartilage degeneration. This editorial aims to present recent high-level evidence in an attempt to answer whether ACL injury inevitably leads to osteoarthritis and whether ACL reconstruction can prevent this development or not.

Key words: Anterior cruciate ligament; Osteoarthritis; Anterior cruciate ligament reconstruction; Prevention of osteoarthritis; Meniscus tear; Anterior cruciate ligament tear

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Core tip: This editorial aims to present recent evidence in an attempt to answer the following questions: (1) does anterior cruciate ligament (ACL) injury inevitably leads to osteoarthritis (OA)? (2) can ACL reconstruction prevent cartilage degeneration and to what extent is this possible? and (3) what are the risk factors for OA development after ACL injury?

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Anterior cruciate ligament (ACL) tear is a devastating injury with both short and long term consequences. Short-term knee functional impairment is successfully

addressed with ACL reconstruction and rehabilitation that allows patients to return to previous sports activities. However, the long-term consequences of ACL injury and the role of ACL reconstruction towards fully restoring knee biomechanics and potentially preventing cartilage degeneration post-traumatically is surrounded with controversy. The aim of this editorial is to discuss the recent literature for the long-term effects of ACL reconstruction, in an attempt to seek answers on whether ACL reconstruction can prevent development of osteoarthritis (OA).

ACL RECONSTRUCTION AND OA

ACL deficiency leads to anteroposterior and rotational instability as well as functional impairment, as evidenced by subjective and objective knee functional scores. The role of instability as a predisposing factor for cartilage degeneration was highlighted early^[1]. Using regression analysis, a prospective analysis of 292 patients with knee injury, revealed a linear correlation between radiographic scores and maximum displacement measurements^[1].

ACL reconstruction is the treatment of choice for symptomatic ACL deficient knees. Undeniably, ACL reconstruction restores knee stability, knee kinematics are also reinstated, and functional scores can be also equivalent to ACL-intact knees^[2,3]. As a result, if knee instability and its resultant abnormal forces to cartilage was the sole factor for future OA development, ACL reconstructed knees would theoretically have similar incidence of OA compared to ACL uninjured knees.

ACL tear was reported to be associated with a higher risk for knee OA regardless reconstruction. A meta-analysis of six studies evaluating progression of OA after ACL injury showed that ACL-reconstructed knees had a relative risk of 3.62 vs uninjured knees (206 out of 395 vs 62 out of 395) in OA development, indicating that ACL reconstruction cannot fully prevent OA. Non-operative treated ACL-deficient knees showed a relative risk of 4.98 (40 out of 120 vs 8 out of 120), suggesting that ACL reconstruction can act preventively for OA compared to non-operative treatment^[4]. A relative risk of 3.89 for ACL-injured knees existed towards OA (240 out of 465) compared to contralateral knees (73 out of 507)^[4]. These data suggest that ACL reconstruction can prevent OA development to a certain degree. The presence of a higher risk for OA compared to the uninjured knee, demonstrates that ACL reconstruction cannot fully eliminate the increased risk of OA progression.

Some studies demonstrated that ACL reconstruction not only cannot fully prevent development of OA, but, in certain occasions, ACL reconstruction may be associated with a higher prevalence of knee OA. Specifically, a retrospective cohort study at 11 years post ACL injury showed that only 25% of conservatively treated knees developed OA vs 42% in ACL reconstructed knees^[5]. Similarly, another report demonstrated that patients that underwent ACL reconstruction had a higher incidence of knee OA^[1]. Furthermore, a more severe

degree of OA using radiographic criteria was shown after ACL reconstruction compared to ACL-injured knees. Specifically, the relative risk of progression to severe OA in ACL-injured knees using Kellgren and Lawrence grade III or IV was found to be 3.84 compared to the controls^[4]. In contrast, the relative risk in ACL-reconstructed knees was 4.71^[4]. These findings are typically attributed to the higher incidence of meniscus injury in these patients^[1,4]. However, most studies that compare the degree of cartilage degeneration between patients undergoing ACL reconstruction and patients with non-operative treatment showed either reduction in the risk of OA development or no difference in risk^[4]. The phenomena that can potentially lead to increased OA prevalence after ACL reconstruction are poorly understood. Further research that can identify additional risk factors that play a major role in OA development - apart from knee stability - is of paramount importance.

THE ROLE OF COMBINED MENISCUS AND CARTILAGE INJURIES IN OA DEVELOPMENT

A key factor that contributes to the development of OA is the presence of combined injuries, *i.e.*, the presence of meniscal or chondral injury combined with ACL tear. Specifically, patients suffering from a combined injury had a significantly higher chance to develop radiographic knee OA (Kellgren and Lawrence grade 2 or higher) compared to subjects with isolated ACL injuries^[6]. Indeed, 80% of the ACL reconstructed knees with associated meniscal or chondral injuries developed knee OA after 10-15 years vs only 62% of subjects with isolated ACL reconstructed injuries^[6]. In the same cohort study, the percentage of subjects that developed knee OA at the contralateral uninjured knee was 15%^[6]. The importance of menisci and cartilage status at the time of the ACL reconstruction was confirmed in another study with 7.5 years follow-up that demonstrated that IKDC radiographic score was abnormal in only 3% of patients with intact menisci and cartilage, while an abnormal IKDC score was obtained in 32% of patients that had both menisci damaged as well as cartilage lesions at the time of the initial surgery^[7]. Similar results were highlighted by a systematic review that reported a prevalence of knee OA after isolated ACL injury ranging between 0% to 13%. In contrast, when a meniscal injury was present, the prevalence of OA increased between 21% to 48%, highlighting the significant role of meniscal injuries to subsequent osteoarthritis^[8]. Unquestionably, the presence of a meniscal or chondral injury at the time of initial ACL tear is considered the most important predictor for the development of subsequent OA. Figure 1 describes the degree of contribution of ACL and associated injuries in the percentage of OA development.

The major role of meniscus and cartilage lesions at the time of surgery in the future development of OA was shown clearly by the findings of a recent study with long

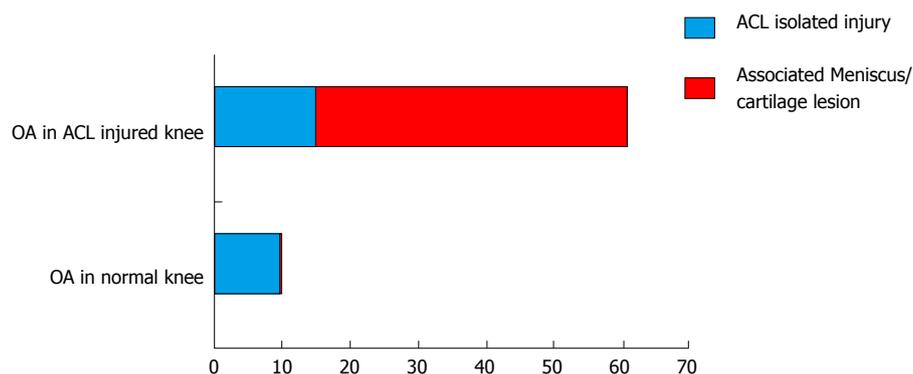


Figure 1 Percentage of patients developing osteoarthritis after an isolated anterior cruciate ligament injury and after anterior cruciate ligament plus associated injuries in comparison to osteoarthritis development to a non-injured knee. ACL: Anterior cruciate ligament; OA: Osteoarthritis.

term follow-up that excluded patients with concomitant injuries at the initial surgery at its assessment. Specifically, it was shown that, 20 years after ACL reconstruction, in 122 patients, 80% of those treated with patellar tendon graft and 87% of those treated with hamstrings tendon graft, respectively, had normal or nearly normal IKDC scores. Considering that the mean age of patients during the 20-year follow-up assessment was approximately 50 years of age, the prevalence of 20% and 13%, respectively, for OA presence in that age group can be considered comparable to that of normal population^[9].

PATHOGENESIS AND RISK FACTORS FOR OA AFTER ACL INJURY

One theory that aims to explain the increased incidence of OA in ACL injured knees without associated injuries is the theory of the initial impact. According to this theory, acute impact trauma to the articular cartilage initiates a degeneration process that can progress to osteoarthritis over the next years after the event. During ACL injury, pro-inflammatory cytokines, such as interleukin-6, interleukin-8, tumor necrosis factor-alpha, and keratan sulfate are increased and can remain elevated even three months after the injury^[10-12]. These changes, as well as changes in gene expression post impact injury could trigger cartilage catabolism and potentially initiate the process of cartilage degeneration^[11,13]. An indirect sign that supports this theory is the significant cartilage thickening seen in MRIs 5 years following an ACL tear, that can be attributed to abnormal swelling due to disruption of cartilaginous matrix integrity^[14]. However, the exact role of cartilage thickness change after ACL injury is yet to be determined.

A recent prospective case-controlled study that measured MRI T2 relaxation times, cartilage oligomeric matrix protein (COMP) - an indicator of cartilage breakdown-, and C-reactive protein levels attempted to shed more light in the phenomena occurring after ACL injury that may be associated with OA development^[15]. Specifically, it was shown that the cartilage at the lateral knee compartment of ACL-injured patients with

associated bone marrow edema exhibited prolonged T2 relaxation times, suggesting that the bone marrow edema may represent areas of initial cartilage injury that could potentially predispose to cartilage degeneration^[15]. This study also demonstrated that cartilage that was not directly impacted may also be the subject of future degeneration due to changes in joint homeostasis, as shown by the elevated levels of serum COMP and the prolonged T2 relaxation times in areas where no bone marrow edema was present. At 1-year post ACL reconstruction, T2 relaxation time remained prolonged in certain areas, indicating that the alterations seen in cartilaginous matrix may persist^[15]. A cohort study with yearly follow-up assessment for 11 years showed that cartilage degradation as a result of the initial impact typically accelerates after 5 years from the injury^[16]. These recent data suggest that at the time of ACL injury a degradation process of the cartilaginous matrix initiates, either as the result of direct impact or due to alterations in joint homeostasis after the impact injury to the joint.

A second theory for the high incidence of OA after ACL injury involves chronic derangement of local joint-loading patterns that introduce high shear and compressive forces on the menisci and cartilage that lead to irreversible changes to cartilage homeostasis regardless of restoration of ligamentous stability^[17]. Specifically, ACL deficiency leads to increase in contact forces at the cartilage and alteration of knee joint kinematics^[18,19]. Furthermore, increased anterior tibial translation can increase stress at both menisci and this explains the high incidence of meniscal tears in ACL-deficient knees^[5,20,21]. These secondary injuries could be responsible for subsequent cartilage degeneration in the ACL-deficient knee.

The type of graft used in ACL reconstruction was recently considered that could play a role in future OA development. A recent study evaluating PT and HT grafts at 20 years post ACL reconstruction confirmed previous suggestions for OA development. Specifically, it was demonstrated that further surgery subsequently to ACL reconstruction as well as the use of patellar tendon as a graft increased the odds ratio of abnormal radiographic appearance of the knee by 2.6 and 2.4,

Table 1 Risk factors for osteoarthritis development after anterior cruciate ligament injury

Associated injuries at the time of ACL injury
Meniscus tear
Cartilage lesion
Demographic characteristics
Advanced age
High BMI
Reconstruction related factors
Patellar tendon graft
Loss of knee extension
Laxity in Lachman test
> 6 mo interval between injury and reconstruction
Poor performance at the single-legged hop test 1 yr postoperatively

ACL: Anterior cruciate ligament; BMI: Body mass index.

respectively. PT grafts were associated with radiographic OA in 61% of patients vs only 41% in HT grafts^[9]. In contrast, other reports did not confirm this difference^[22]. Additional high-level studies are necessary to further evaluate whether the use of patellar tendon predisposes towards OA progression and to further recognize potential pathogenetic mechanisms of this association.

Identification of factors that are associated with the development of knee OA after ACL injury is clinically important (Table 1). Apart from meniscal and chondral injury at the time of ACL reconstruction, advanced age and high BMI have also been suggested as risk factors for OA development after ACL reconstruction. Every 10 years of age was proposed that add 1.7 odds ratio risk towards OA, while other studies report age greater than 25 years at the time of ACL reconstruction as a predisposing factor^[5,23]. Every increment of BMI was associated with a 1.2 odds ratio for progression to OA^[5]. Other predisposing factors suggested were an interval of more than 6 mo between injury and reconstruction, loss of knee extension, and poor performance at the single-legged hop test 1 year postoperatively^[23,24]. A greater degree of laxity, as documented with Lachman test, was also associated with OA development^[25], which re-introduces the question how successfully can ACL reconstruction address anteroposterior and rotation instability post ACL tear^[26,27]. The recent interest in the anterolateral structures of the knee and their contribution in rotational knee stability led to techniques that combine ACL reconstruction with lateral extra-articular tenodesis^[28,29]. It would be interesting to evaluate long-term results of these procedures towards the development of OA.

Interestingly, ACL-reconstructed patients traditionally performed significantly better compared to non-operated patients in both subjective and objective scores and demonstrated significantly less laxity at KT-1000^[4]. This performance resulted in maintaining a higher participation in high risk pivoting activities and sports involvement. As a consequence, it may difficult to compare the development of OA between patients that fully participate in sports and return to their pre-injury

level of activity with patients that cannot fully participate in sports. Furthermore, in a study that evaluated performance on return in elite football players after ACL reconstruction, it was found that there was a significant descent in mean performance compared to controls^[30]. Therefore, ACL-reconstruction may contribute to restoration of most functional scores, but a minor deficit - that is obvious only in elite athletes - may still persist. This deficit could be associated with OA progression. For these patients, anterolateral ligament augmentation was recently suggested as a significant contributor to full restoration of function in these athletes^[31].

Lastly, the importance of rehabilitation programs after ACL reconstruction has been highlighted over the last few years and certain controversies have been resolved. Specifically, evidence suggests that accelerated rehabilitation protocols that introduce sequential phases are associated with better outcomes^[32]. Rehabilitation in phase 1 typically aims towards pain and oedema reduction, and regaining of range of motion. Phase 2 usually introduces progressive improvement of quadriceps and hamstring strength. The next phase adds improvement in neuromuscular control to the above^[32,33]. When strength and endurance are maximized, specific exercises that aim to fulfill return to sports criteria are introduced. The criteria used for return to sports are still subject of controversy; however, recent data suggest that functional test assessment, such as single-leg hop test, and muscle strength criteria, such as percentage of isokinetic strength should be introduced^[32,34,35]. The importance of maintaining an advanced level of physical activity is critical, as it appears to benefit both physical and mental health^[36,37]. In the future, this can be extremely important as new biological treatments for early osteoarthritis become available and, therefore, interventions that can confront the initial phenomena post ACL injury and prevent at the progression to osteoarthritis would be available^[38].

CONCLUSION

ACL tear is associated with an increased risk for OA development. This risk increases remarkably when an associated meniscal or chondral lesion is present. ACL reconstruction potentially restores knee stability and appears to reduce the risk of OA, but it cannot fully eliminate the increased risk. The initial impact of injury at the time of ACL tear could explain the association between OA and ACL tear, but additional research is needed to understand the exact pathogenesis of post-ACL injury OA. Identification of risk factors that can further increase the risk of knee OA is important in an attempt to control the natural history of cartilage degeneration after ACL tear.

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Fix and replace: An emerging paradigm for treating acetabular fractures in older patients

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Abstract

Acetabular fractures in older patients are challenging to manage. The "fix and replace" construct may present a new paradigm for the management of these injuries. We present the current challenge of acetabular fractures

in older patients. We present this in the context of the current literature. This invited editorial presents early results from our centre and the ongoing challenges are discussed.

Key words: Acetabular fracture; Total hip arthroplasty; Trauma

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Core tip: Acetabular fractures in older patients are challenging to manage. The "fix and replace" construct may present a new paradigm for the management of these injuries.

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Acetabular fractures in older patients pose a challenge for both patients and clinicians providing care. These fractures and the circumstances in which they occur require multidisciplinary management from both medical and surgical specialties, and new ways of managing these injuries in this patient cohort are required. The annual incidence of acetabular fractures is estimated at 2000 per year in the United Kingdom with 72.5% of these occurring in older patients (patients greater than 65 years of age)^[1,2]. With an ageing population, the incidence is increasing with one study demonstrating a 2.4 fold increase between 1980 and 2007^[3]. Furthermore, outcomes have historically been poor - with up to 30% of patients who are managed non-operatively having an unacceptable functional result^[4] and mortality is high (25% in one study^[5]). For patients managed with open

Table 1 Fix and replace cohort; early results (*n* = 19)

Characteristic	Details
Age	Average 77 yr (range 63-94)
Gender	9 females 10 males
Pre-morbid mobility	9 independently mobile 10 mobile with walking aid
Mechanism of injury	12 fall from standing height 3 road traffic collision 2 fall from height 1 seizure resulting in fall 1 unknown
Mobility day 1 post op	11 not mobile out of bed 6 sat out 2 unknown
Number of days to mobilise post up	Average 2.5 d (range 1-11)

reduction and internal fixation, results in older patients are significantly poorer compared to younger patients with up to 50% of older patients requiring an early total hip replacement^[6]. Overall, the quality of evidence is poor and limited to retrospective cohort reviews. As a result there is no clear consensus or guidelines on how best to manage these challenging injuries. As the incidence of these fractures in older patients is increasing, and outcomes of treatment uncertain or poor, better evidence and new strategies of treatment are required to improve the management of these injuries in this patient cohort.

Acetabular fractures in older patients may be viewed to be a similar injury to hip fractures (neck of femur) where the treatment aims to restore hip function to allow immediate weight bearing. As hip fractures represent a major fracture burden in older patients, a well developed conceptual framework has been established in the United Kingdom including a level one evidence-based treatment pathway (Orthopaedic Blue Book), national guidelines (NICE Guideline 2011)^[7] and an associated best practice tariff. Fundamental pillars in this treatment pathway include multi-disciplinary team (MDT) care, timely surgery and full weight bearing post operatively (BOAST Guideline 1 Version 2). The hip fracture framework - and the financial incentives associated with it - have significantly improved outcomes post hip fracture with year on year reductions in mortality^[8]. There was a hip fracture paradigm shift; one is now needed for fractures on the other side of the hip joint - the acetabular fracture. The hip fracture framework - MDT care, early surgery and early full weight bearing - can be equally applied to acetabular fractures in older patients.

To achieve the aim of immediate mobilization post fracture, a surgical paradigm shift is also required from the prolonged immobilisation associated with non-operative treatment or operative fixation alone to surgical treatment that enables immediate weight bearing. A paper from two decades ago stated, "Hip arthroplasty for acute treatment of acetabular fractures is rarely indicated"^[9]. Our conceptual framework has changed since then. Acetabular fractures in the elderly have a particular injury pattern: A separate quadrilateral-plate

component and roof impaction in the anterior column fractures with medialisation of the femoral head, and comminution and marginal impaction in posterior-wall/column fractures^[3]. Surgical fixation methods must take this in to account and total hip arthroplasty (THA) is an important component of the surgical armamentarium in these fractures. THA aids in the goal of early full weight bearing. Non-weight bearing or restricted weight bearing is difficult or impossible for older patients. Particularly in the frail and cognitively impaired, restricted weight bearing significantly increases medical complications and prolongs dependence on care. They are often observed to slowly decline, both physically and psychologically; and usually do not recover to their pre-fracture function, with overall loss of quality of life. A management strategy is required that allows early, unrestricted weight bearing.

Is the "fix and replace" construct a new surgical paradigm in the management of the elderly acetabular fracture? There is room for early optimism. Rickman *et al*^[10] in the United Kingdom reported on a cohort in 2014. Their surgical technique included plate stabilization of both acetabular columns plus simultaneous THA using a tantalum socket and a cemented femoral stem. All 24 patients mobilized with full weight bearing by day 7 postoperatively. Complications included: Superficial wound infection, symptomatic deep venous thrombosis and one in-hospital death from myocardial infarction. A more recent international report^[10] reiterates the challenges posed by this group of patients. Their cohort of 18 patients included younger patients (average 66 years, range 35-81) but with excellent Harris Hip Scores at almost 2 years average follow-up.

Early results from our centre are promising. Our current "fix and replace" cohort includes 19 patients (14 with a minimum of 3 mo follow-up). The age range is from 63 to 94 with 9 females and 10 males. Initial data from our cohort is summarized in Table 1. Cognitive impairment is not a contraindication in our institution. Anecdotally these patients seem to benefit the most with their full weight bearing status post operatively. They are generically unable to comply with anything less. In our series, 9 (47%) were independently mobile prior to admission and the most common mechanism of injury was a fall from a standing height. Our surgical approach includes open reduction and internal fixation of the anterior fracture component (through a modified Stoppa approach) followed by posterior column reconstruction with a THA or hip arthroplasty revision (in 4 cases) (through a posterior or Kocher Lanchenbeck approach). Open reduction internal fixation of both acetabular columns is achieved with standard reconstruction acetabular plates (Synthes), occasionally supplemented by suprapectineal plates (Stryker) to buttress quadrilateral plate comminution and prevent medial migration of the cup. For acetabular cup reconstruction, we use a trabecular metal shell (TMARS, Zimmer Biomet) to address any bone defects and enable further fracture fixation with screw fixation in both columns. A cup is then cemented into the shell (either polyethylene lipped liner or a dual mobility

cup) in appropriate alignment to optimise hip stability. A cemented femoral stem is then used. The cost of these implants is approximately £6000 per case.

The mean time to get out of bed (with assistance) was 2.5 d. This is a significant improvement on the alternative of usually a minimum of 2 wk bed rest and another 6 wk of restricted weight bearing status with non-operative management. Despite efforts aiming for early mobilization, most patients (58%) did not get out of bed on the first post-operative day. The mean post operative Oxford Hip Score was 31, at a minimum of 3 mo.

Medical complications in this cohort included: A urinary tract infection, a lower respiratory tract infection, acute kidney injury, malignant neuroleptic syndrome in a patient with Parkinson's disease and a non-fatal pulmonary embolus. Two groups of patients posed a particular challenge: Patients with neurological conditions such as Parkinson's disease and patients with periprosthetic fractures (the "fix and revise" cohort). There were 6 hip dislocations in 5 patients (2 in the "fix and revise" group, 2 in the Parkinson's group and 1 Parkinson's patient with a "fix and revise"). Of these dislocations, 2 underwent a closed reduction; there were 3 stem revisions (one with subsequent Girdlestone after a repeat dislocation) and one Girdlestone in a patient with severe Parkinson's disease. The dislocations that required open reduction and revision were in the group with severe Parkinson's disease, and/or periprosthetic fractures. Dislocation rates and subsequent complications are known to be high in this group^[11-13]. There were two deaths in the cohort-one due to an out of hospital cardiac arrest 20 mo post surgery and one due to pneumonia 8 mo post-surgery.

The early results of this cohort highlight the potential gains with this strategy (early mobilization compared to non-operative management) but also concerns related to length of surgery and cost of treatment. Complications have been medical as well as directly related to surgery and continuous service evaluation allows medical and surgical care to be adapted as our protocol develops.

Despite the early promising potential, questions remain. There are concerns about the length of surgery and the physiological reserve required to withstand this. Are the complications that can arise from this complex surgery surmountable? Do the benefits of early mobilization outweigh the potential risks of sciatic nerve injury, periprosthetic infection, haemorrhage (including potential catastrophic bleeding from the friable elderly presacral plexus), hip dislocation, periprosthetic fracture or failure of the construct? Who in this cohort benefits from the "fix and replace" construct? What are our goals beyond early weight bearing?

Which is better: Non-operative management, operative management with open reduction and internal fixation alone or operative management with open reduction and internal fixation and THA? There is no agreed consensus^[5,13].

A 2014 systematic review presents pooled data from 8 studies demonstrating that satisfactory surgical fixation had only been achieved in 45.3% of patients and 23.1% of patients had significant pain and reduced function necessitating THA. When surgical fixation alone and surgical fixation with THA was compared, there was no increase in complications compared to patients who underwent surgical fixation alone^[5]. The paper highlights that there is a paucity of high quality data to draw robust conclusions. Clinical trials are now needed to provide high quality evidence that address the above described challenges and ultimately determine the optimum management of acetabular fractures in older patients. The new "fix and replace" paradigm may help provide the answer.

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Development of an internally braced prosthesis for total talus replacement

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Author contributions: Regauer M had the primary idea of an internally braced prosthesis for total talus replacement, designed the research project, performed the research project including the cadaver surgery and was responsible for acquisition of data, writing the paper and design of illustrations and figures; Lange M and Baumbach S contributed relevant literature and helped to design the illustrations and figures; Soldan K and Peyerl S were responsible for the design, technical development and final production of the first prototype of the internally braced prosthesis; Böcker W and Polzer H revised the article critically for important intellectual content and were responsible for the final approval of the version to be published.

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Abstract

Total loss of talus due to trauma or avascular necrosis, for example, still remains to be a major challenge in foot and ankle surgery with severely limited treatment options. Implantation of a custom made total talar prosthesis has shown promising results so far. Most important factors for long time success are degree of congruence of articular surfaces and ligamentous stability of the ankle. Therefore, our aim was to develop an optimized custom made prosthesis for total talus replacement providing a high level of primary stability. A custom made hemiprosthesis was developed using computed tomography and magnetic resonance imaging data of the affected and contralateral talus considering the principles and technology for the development of the S.T.A.R. prosthesis (Stryker). Additionally, four eyelets for fixation of artificial ligaments were added at the correspondent footprints of the most important ligaments. Two modifications can be provided according to the clinical requirements: A tri-articular hemiprosthesis or a bi-articular hemiprosthesis combined with the tibial component of the S.T.A.R. total ankle replacement system. A feasibility study was performed using a fresh frozen human cadaver. Maximum range of motion of the ankle was measured and ligamentous stability was evaluated by use of standard X-rays after application of varus, valgus or sagittal stress with 150

N. Correct implantation of the prosthesis was technically possible *via* an anterior approach to the ankle and using standard instruments. Malleolar osteotomies were not required. Maximum ankle dorsiflexion and plantarflexion were measured as 22-0-28 degrees. Maximum anterior displacement of the talus was 6 mm, maximum varus tilt 3 degrees and maximum valgus tilt 2 degrees. Application of an internally braced prosthesis for total talus replacement in humans is technically feasible and might be a reasonable procedure in carefully selected cases with no better alternatives left.

Key words: Ankle; Avascular necrosis; Total loss of talus; Prosthesis; Hemiprosthesis; InternalBrace; Talus replacement

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Core tip: Implantation of a total talar prosthesis has shown promising results so far. The aim was to develop an optimized prosthesis providing a high level of primary stability. A custom made hemiprosthesis was developed using computed tomography and magnetic resonance imaging data. Four eyelets for fixation of artificial ligaments were added at the footprints of important ligaments. Correct implantation of the prosthesis in a cadaver model was possible *via* an anterior approach. Maximum ankle dorsiflexion and plantarflexion were measured as 22-0-28 degrees. Maximum anterior displacement of the talus was 6 mm, maximum varus tilt 3 degrees and maximum valgus tilt 2 degrees.

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INTRODUCTION

Total loss of talus due to trauma^[1-5] or avascular necrosis^[6-9], for example, still remains to be a major challenge in foot and ankle surgery with severely limited treatment options^[2,4,5,8,9]. Furthermore, collapse of the talar body as a complication of total ankle arthroplasty^[10], talectomy in infection and septic talus necrosis^[11] or severe bone defects due to tumor resection^[12] may result in the need for total talar replacement, especially in younger and active patients (Figure 1).

Because arthrodesis of the ankle or the complete rearfoot as well as tibio-calcaneal fusion after talectomy can produce severe disability of the ankle and the foot, different study groups have already developed a prosthesis to replace the talar body^[13-16] or even the complete talus^[10,17-20]. Lampert *et al*^[12] and Ketz *et al*^[21] combined a custom total talar prosthesis with the tibial component of a standard total ankle prosthesis, and



Figure 1 Magnetic resonance imaging of a 32-year-old male patient showing complete avascular necrosis of the talus.

Giannini *et al*^[22] recently reported on a custom-made total talonavicular replacement in a professional rock-climber.

Implantation of a custom made talar body^[13-16] or total talar prosthesis^[10,17-20] in humans has already shown promising results so far. In 1997 Hamroongroj *et al*^[16] was the first to report on a series of 16 patients treated by use of a quite primitive talar body prosthesis which has been implanted by a medial transmalleolar approach. Eight of nine patients who were evaluated 11 to 15 years postoperatively had a satisfactory result, which is quite comparable to the results reported after standard total ankle replacement at that period of time. The exceptional patient in this series had an unsatisfactory result because the prosthetic stem had sunk into the talar neck and needed revision surgery 13 years after the index operation^[16]. Total talar replacement with a prosthesis was first performed in Japan in 1999. Several subsequent prosthetic design revisions have resulted in improved outcomes after prosthesis implantation^[14]. Taniguchi *et al*^[14] reported favorable results in eight of 14 patients after a mean follow-up period of 83 mo using a second-generation prosthesis which only partially replaced the talar body. As mentioned in their report, the third-generation prosthesis completely replacing the talus is currently recommended and has been associated with much better outcomes than the second-generation prosthesis^[14]. Tsukamoto *et al*^[10] first reported treatment of talar collapse after total ankle arthroplasty in a patient with rheumatoid arthritis by talar replacement with a third-generation prosthesis. However, this type of prosthesis still had a subtalar stem for fixation to the calcaneus by use of bone cement. Magnan *et al*^[13] extended this procedure using a total talar prosthesis and combined it with the standard S.T.A.R. total ankle arthroplasty system (Waldemar Link, Hamburg, Germany) in a 45-year-old professional male skier and rock-climber. Stevens *et al*^[17] even reported on a 14-year-old girl who underwent total talar replacement after an open talar dislocation. And again it was Hamroongroj to report on the largest series of 33 patients with by far the longest follow-up period of 10-36 years after implantation of a talar body prosthesis^[15]. In this series published in 2014,

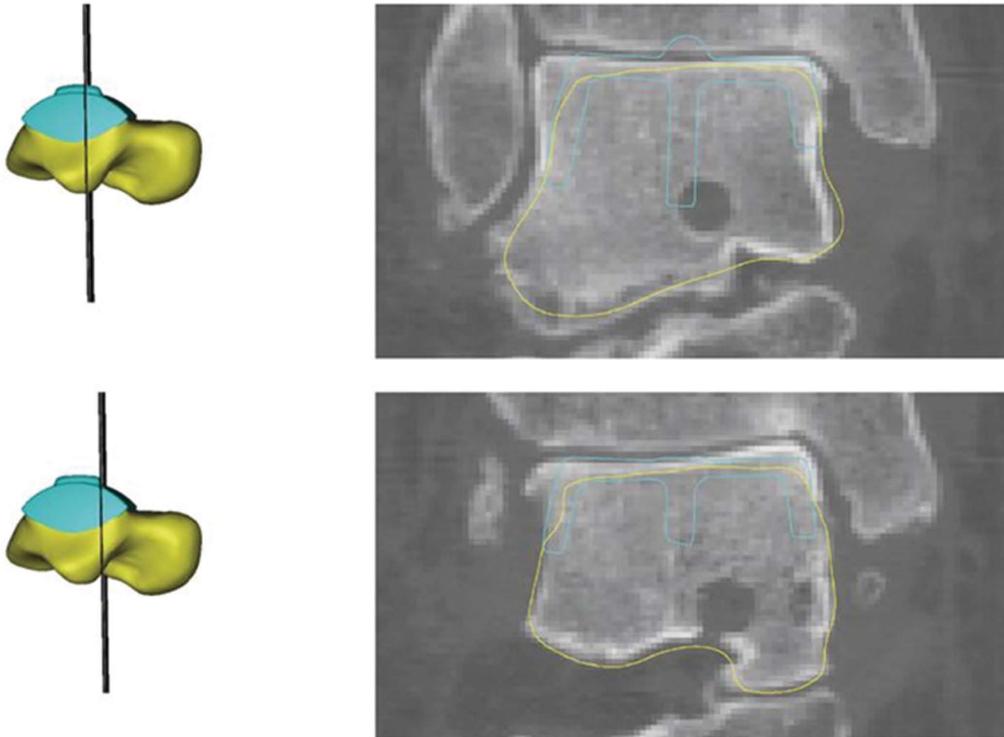


Figure 2 A customized hemiprosthesis was developed using computed tomography and magnetic resonance imaging data of the affected and contralateral talus considering the option of integrating the S.T.A.R. prosthesis (Stryker) into the design.

28 of the 33 prostheses were still in place at the time of final follow-up while five had failed prior to five years.

Advantages of total talar replacement include preservation of joint mobility, a relatively short period of restricted weight bearing, rapid pain relief and preservation of limb length^[18]. A native talus is well-seated within the ankle, fitted firmly between the tibia, the fibula, tarsal navicular, and the calcaneus. It has no muscular attachments and over 60% of its surface is covered with articular cartilage^[17]. Therefore, stability of the talus or a total talus prosthesis, respectively, depends on the integrity of the main ligaments and on the adjacent bones that build up the ankle mortise and the subtalar joint as well as on the anatomical shape of the talus itself^[16].

For example, early prosthesis failure occurred as a result of size mismatch in two patients in the large series reported by Hamroongroj *et al.*^[15]. And according to Ando *et al.* the procedure of total talar replacement carries at least a theoretical risk of anterior instability of the prosthesis, because the anterior talofibular ligament (ATFL) and deep deltoid ligaments are divided during the procedure^[16]. To address this problem of ligamentous stabilization, Stevens proposed the addition of porous coating at the main ligamentous attachment sites of the ATFL and the deltoid ligament to provide improved stability^[17].

According to this, most important factors for long time survival of a prosthesis for total talus replacement are degree of congruence of articular surfaces and ligamentous stability of the ankle and subtalar joint.

Therefore, to further improve the idea of total talus

replacement, our aim was to develop an optimized custom made prosthesis for total talus replacement providing maximum possible congruence of the articular surfaces and a maximum high level of primary stability immediately after implantation. We introduced the use of preoperative magnetic resonance imaging (MRI) data and an internal bracing technique we had been using successfully for augmentation of severe ligamentous injuries of the foot and ankle since several years^[22,23]. The primary aim of this so called InternalBrace™ technique is reconstruction or repair of vital tissue rather than replacement with non-vital tendon transplants. The InternalBrace™ acts as a corner stone or check-rein to stability allowing physiological and limiting pathologic motion. Thereby this method applies the classical AO principles to soft tissues.

DEVELOPMENT OF AN INTERNALLY BRACED TALAR PROSTHESIS

A custom made hemiprosthesis was developed considering the relevant anatomical principles and the technology for the development of the S.T.A.R. total ankle prosthesis (Stryker)^[24-28].

As we believed that a computed tomography (CT) might underestimate the real dimensions of the talus to be replaced, we added an MRI and calculated the mean dimensions of the talus between CT and MRI data to approximate the real dimensions of the talus as accurately as possible (Figures 2 and 3). Most other authors only used X-rays and CT scans for designing the



Figure 3 Components of the customized hemiprosthesis for combination with the S.T.A.R. prosthesis (Stryker).



Figure 4 Eyelets for fixation of artificial ligaments (FiberTape®, Arthrex) were added at the corresponding footprints of the main ankle ligaments. View from lateral on the eyelet (black arrow) for the artificial anterior talofibular ligament.

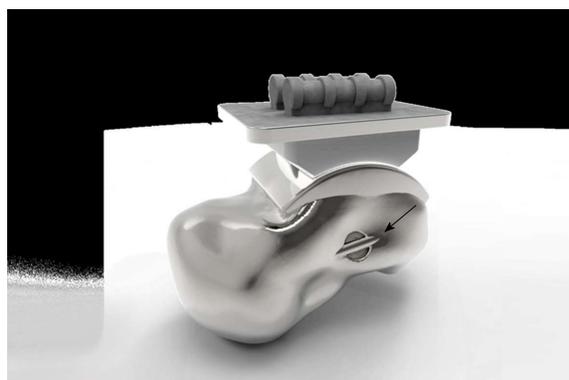


Figure 6 View from medial on the eyelet (black arrow) for fixation of the artificial deltoid ligament.



Figure 5 View from anterior on the eyelet (black arrow) for the artificial anterior talofibular ligament.



Figure 7 In the view from posterior the eyelets are not visible.

prosthesis^[10,15-18].

In cases where the index talus has been severely destructed the prosthesis can be designed alternatively using the mirror image of the CT and MRI data from the contralateral ankle.

Additionally, four eyelets for fixation of artificial ligaments (Figures 4-8) were added at the correspondent footprints of the ATFL, the deltoid ligament and the interosseous talocalcaneal ligament (ITCL). We used artificial ligaments called FiberTape® (Arthrex, Naples, United States) for performing the InternalBrace™ technique at surgery (Figures 9-13).

Two modifications can be provided according to the clinical requirements: A tri-articular hemiprosthesis in



Figure 8 View from plantar on the eyelets (black arrows) for the artificial interosseous talocalcaneal ligament.

case of completely intact surrounding articular surfaces or a bi-articular hemiprosthesis combined with the tibial component of the S.T.A.R. total ankle replacement system

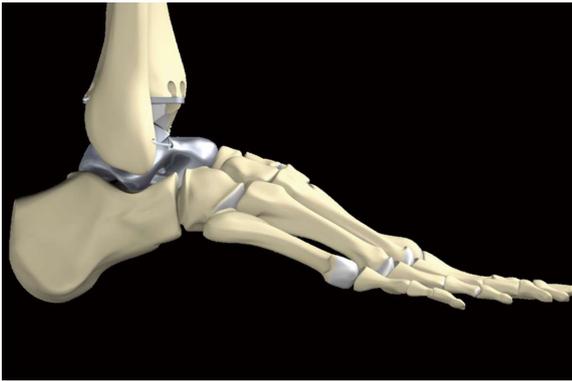


Figure 9 Anterolateral stabilization of the customized hemiprosthesis by use of an InternalBrace™ in the anatomic course of the anterior talofibular ligament viewed from lateral.

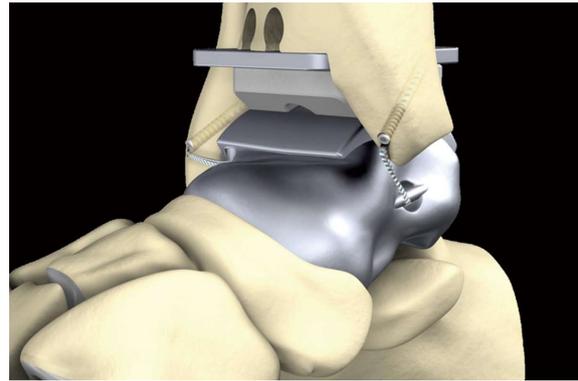


Figure 12 Anterolateral and anteromedial stabilization of the customized hemiprosthesis by use of an InternalBrace™ in the anatomic courses of the anterior talofibular ligament and the deltoid ligament viewed from anteromedial.

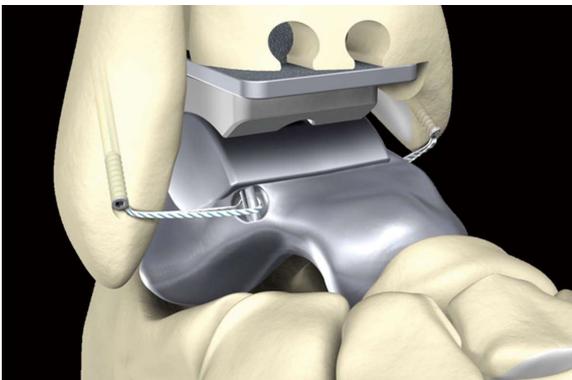


Figure 10 Anterolateral and anteromedial stabilization of the customized hemiprosthesis by use of an InternalBrace™ in the anatomic courses of the anterior talofibular ligament and the deltoid ligament viewed from anterolateral.



Figure 13 Anteromedial stabilization of the customized hemiprosthesis by use of an InternalBrace™ in the anatomic courses of the deltoid ligament viewed from posteromedial.

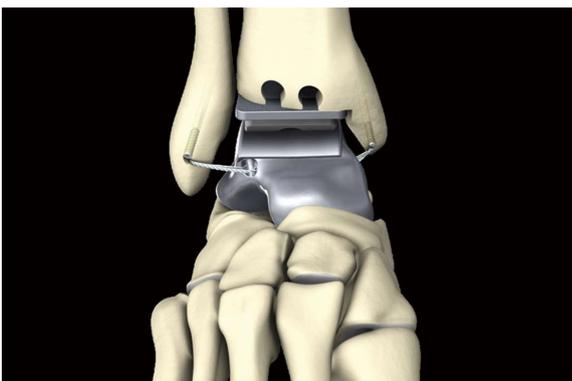


Figure 11 Anterolateral and anteromedial stabilization of the customized hemiprosthesis by use of an InternalBrace™ in the anatomic courses of the anterior talofibular ligament and the deltoid ligament viewed from anterior.

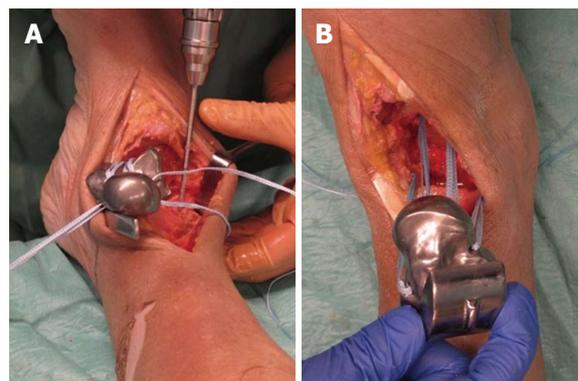


Figure 14 A feasibility study was performed using a fresh frozen male human cadaver. A: Preparing of the bone tunnels at the anatomic footprints of the native ligaments for fixation of the artificial ligaments; B: All four artificial ligaments were shuttled through the bone tunnels before insertion of the prosthesis.

in case of additional damage to the articular surface of the tibial pylon (Figure 3).

SURGICAL TECHNIQUE

A feasibility study was performed using a 36-year-old male fresh frozen whole leg human cadaver. In the supine

position, a straight skin incision was made according to a standard anterior approach to the ankle joint for total ankle arthroplasty (Figure 14). After opening the anterior capsule of the ankle joint, the talus was divided into five main parts by use of a chisel and completely resected. Then the bone tunnels were prepared at the anatomic



Figure 15 Prosthesis and through the bone tunnels before insertion of the prosthesis. A: The prosthesis was inserted from anterior while steady tensioning the four artificial ligaments; B: View from anterior on the pre-tensioned anterior talofibular ligament.

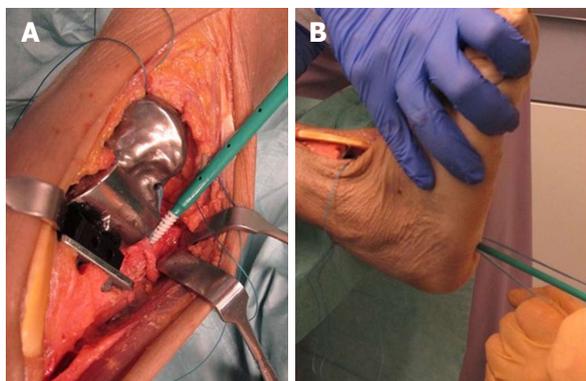


Figure 16 Aperture fixation of the correctly pre-tensioned artificial ligaments at the anatomic footprints with an interference screw (SwiveLock® 4.75 mm, Arthrex, Naples, United States). A: Direct aperture fixation of the anterior talofibular ligament at the distal fibula; B: Retrograde indirect aperture fixation of the interosseous talocalcaneal ligament at the calcaneus performed percutaneously from plantar.

footprints of the native ligaments for fixation of the artificial ligaments (Figure 14). All four artificial ligaments for replacement of the ATFL, the deltoid ligament and the ITCL were shuttled through the eyelets of the prosthesis and through the bone tunnels before insertion of the prosthesis (Figure 14). Then the prosthesis was inserted from anterior while steady tensioning the four artificial ligaments (Figure 15). Figure 15B shows a view from anterior on the pre-tensioned ATFL.

After insertion of the tibial component and the inlay of the S.T.A.R. total ankle prosthesis we performed an aperture fixation of the correctly pre-tensioned artificial ligaments at the anatomic footprints with an interference screw (SwiveLock® 4.75 mm, Arthrex, Naples, United States). Direct aperture fixation of the artificial ATFL and the deltoid ligament was performed at the distal fibula (Figure 16A) and the medial malleolus, respectively, and retrograde indirect aperture fixation of the ITCL at the calcaneus was performed percutaneously from plantar (Figure 16B).

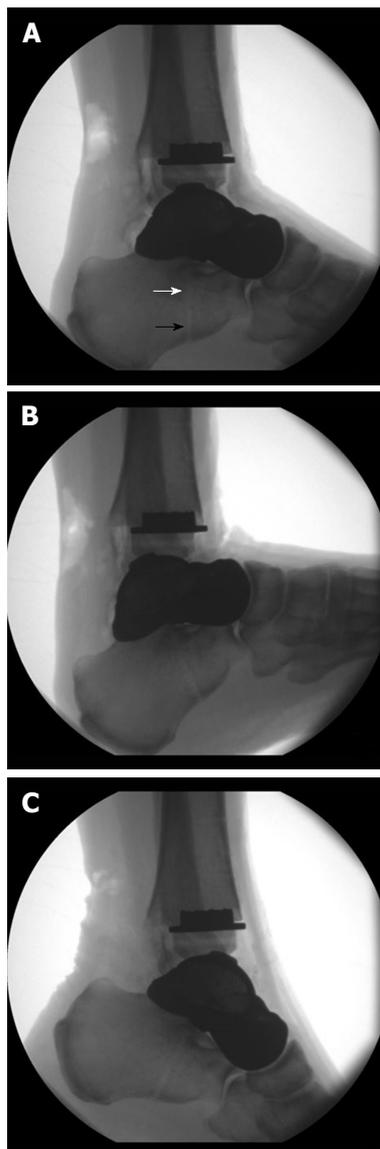


Figure 17 Radiographic examination of the maximum range of motion of the ankle joint after internally bracing of the customized hemiprosthesis. A: Neutral position; B: Maximum dorsiflexion 22°; C: Maximum plantarflexion 28°. Note the visible bone tunnel in the calcaneus (black arrow) with the interference screw inside the proximal part of the tunnel (white arrow) to prevent tunnel widening by indirect aperture fixation at the subtalar joint performed percutaneously from plantar.

FEASIBILITY STUDY

Correct implantation of the internally braced total talar prosthesis was technically possible *via* a standard anterior approach to the ankle and using standard instruments. Malleolar osteotomies were not required.

Radiographic examination of the maximum range of motion of the ankle joint after internally bracing of the customized hemiprosthesis was performed. Figure 17 shows neutral position (Figure 17A), maximum dorsiflexion of 22° (Figure 17B), and maximum plantarflexion of 28° (Figure 17C). Note the visible bone tunnel in the calcaneus (black arrow) with the interference screw inside the proximal part of the tunnel (white arrow) to

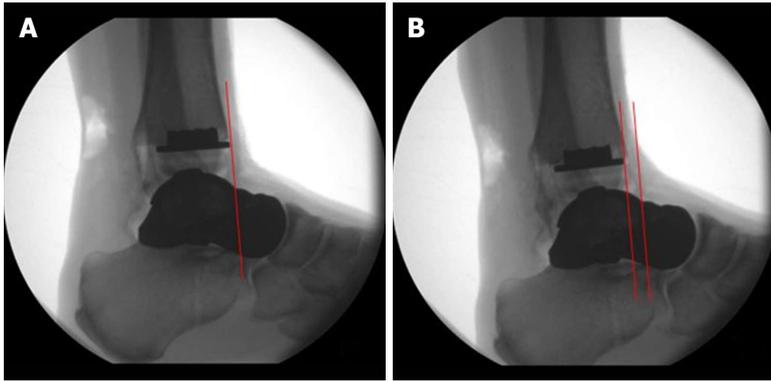


Figure 18 Maximum anterior displacement of the talus was 6 mm (B) compared to the neutral position (A).

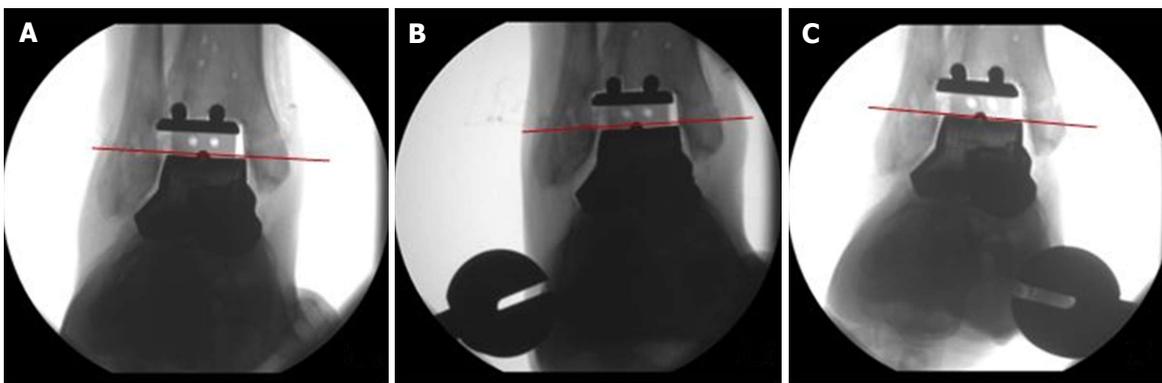


Figure 19 Compared to the neutral position (A) maximum varus tilt was 3° (B) and maximum valgus tilt was 2° (C).

prevent tunnel widening by indirect aperture fixation at the subtalar joint performed percutaneously from plantar.

Primary ligamentous stability of the internally braced total talar prosthesis was evaluated by use of standard X-rays after application of varus, valgus or sagittal stress with 150 N: maximum anterior displacement of the talus was 6 mm (Figure 18), maximum varus tilt 3 degrees and maximum valgus tilt 2 degrees (Figure 19) resembling quite physiological ankle function.

ON THE HORIZON

Application of an improved internally braced custom made prosthesis for total talus replacement in humans is technically feasible, and first experimental results show a very high primary stability of the implanted prosthesis. Based on our results the described procedure might be a reasonable treatment option in carefully selected cases with no better alternatives left. Due to the quite low frequency of adequate cases, multicentric evaluation seems to be necessary to provide high quality scientific data of outcome results and possible complications after implantation of an internally braced prosthesis for total talus replacement.

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Prevention and management of post-instability glenohumeral arthropathy

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Abstract

Post-instability arthropathy may commonly develop in high-risk patients with a history of recurrent glenohumeral instability, both with and without surgical stabilization. Classically related to anterior shoulder instability, the incidence and rates of arthritic progression may vary widely. Radiographic arthritic changes may be present in up to two-thirds of patients after primary Bankart repair and 30% after Latarjet procedure, with increasing rates associated with recurrent dislocation history, prominent implant position, non-anatomic reconstruction, and/or lateralized bone graft placement. However, the presence radiographic arthrosis does not predict poor patient-reported function. After exhausting conservative measures, both joint-preserving and arthroplasty surgical options may be considered depending on a combination of patient-specific and anatomic factors. Arthroscopic procedures are optimally indicated for individuals with focal disease and may yield superior symptomatic relief when combined with treatment of combined shoulder pathology. For more advanced secondary arthropathy, total shoulder arthroplasty remains the most reliable option, although the clinical outcomes, wear characteristics, and implant survivorship remains a concern among active, young patients.

Key words: Arthropathy; Glenohumeral; Dislocation; Latarjet; Instability

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Core tip: Non-anatomic stabilization procedures may result in overconstraint or incongruence of the glenohumeral

joint with resultant instability arthropathy. Proud suture anchors can create a traumatic wear pattern resulting in an iatrogenic arthropathy. Secondary arthropathy may occur in up to two-thirds of patients after Bankart repair and 30% after coracoid transfer at mid- to long-term follow-up, although clinical outcomes may vary. When conservative measures have failed, various arthroscopic procedures may be considered to address mechanical symptoms and other pain generators. Total shoulder arthroplasty remains the most reliable option for advanced instability arthropathy, although concern exists above survivorship in patients under 50 years.

Waterman BR, Kilcoyne KG, Parada SA, Eichinger JK. Prevention and management of post-instability glenohumeral arthropathy. *World J Orthop* 2017; 8(3): 229-241 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i3/229.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i3.229>

INTRODUCTION

Glenohumeral instability is a frequent problem encountered within high-risk patient populations^[1,2], and it poses important short- and long-term implications for shoulder function. While numerous previous studies have focused on the ideal management, risk stratification, and/or surgical technique for addressing patients with shoulder instability, few have examined the natural history of instability events as it relates to secondary arthrosis. The presence of concomitant shoulder instability and premature degenerative wear creates a difficult clinical scenario, and optimal treatment requires a fundamental knowledge of underlying anatomy and current, evolving treatment options.

With the largest range of motion of any articulation and minimal osseous constraint, the glenohumeral joint is largely stabilized by rotator cuff compression and its inherent concavity, which is deepened by its circumferential labral attachment. In addition to the anterior and posterior inferior labrum, the inferior glenohumeral ligament (IGHL) complex provides vital restraint to humeral translation. The anterior band of the IGHL limits anterior instability in elevated positions of abduction and external rotation, whereas the posterior band acts in forward flexion and internal rotation. Additionally, the rotator interval, which contains the coracohumeral, middle glenohumeral, and superior glenohumeral ligaments, has been a focal area of research. However, its contributions to inferior and anteroposterior glenohumeral restraint remains a continuing source of debate^[3,4].

Shoulder instability is classically defined by the directionality of excessive glenohumeral translation in association with a provocative examination. However, this must be differentiated from patients with asymptomatic laxity, particularly those with multidirectional involvement. Anterior instability accounts for the vast majority of patients with shoulder dislocations, with a reported

incidence rate ranging from 0.08 to 0.24 patients per 1000 person-years in civilian populations^[5-7]. Within a higher risk military demographic, the incidence may rise to nearly 3% per year when subluxation events are also considered^[1]. Conversely, posterior instability has historically accounted for only a smaller fraction of all unstable shoulders, with approximately 2% to 10% reported^[8-10]. More recent series indicate that isolated posterior instability may comprise over a quarter of patients with shoulder stabilization, and approximately 20% of additional patients will undergo surgery for combined or bidirectional instability^[11]. Especially within young active patients, circumferential labral pathology may also be common with isolated or recurrent anterior shoulder instability^[12,13], so there must be a high index of suspicion in the evaluation of these at-risk individuals.

MANAGEMENT OF GLENOHUMERAL INSTABILITY

Initial management

The initial management of an acute shoulder dislocation includes reduction of the glenohumeral joint followed by a period of immobilization in a sling with rest, ice, and anti-inflammatory medications. After the acute phase, initiation of passive range of motion and guided physical therapy can begin. Traditionally, patients were placed in a sling, which typically puts the shoulder into internal rotation. Duration in a sling varies according to the treating physician, and can range from very brief initial sling use to 2-3 wk of immobilization in variable positions^[14].

The indications for surgical management include recurrent instability following a trial of nonoperative treatment, ongoing pain and dysfunction from recurring subluxations, or selected, higher patient demographics with shoulder instability. There has also been focus on primary surgical stabilization in the young first-time dislocator, especially among young athletes and military servicemembers. A study in West Point cadets demonstrated the importance of age as a predictor for redislocation, with patients less than 20 years old having a 92% rate of redislocation with non-operative treatment^[15]. Similarly, a retrospective review of young athletes, predominantly rugby players with average age of 21 years, demonstrated that 94.5% of the patients treated non-operatively sustained recurrent dislocation vs only one patient (3.5%) in the operative group^[16].

In another prospective randomized controlled trial in active duty service members, Bottoni *et al.*^[17] compared 14 patients treated with four weeks of immobilization with 10 patients treated initially with acute arthroscopic Bankart repair. Of the 12 patients in the non-operative group available for follow-up, 9 (75%) developed recurrent instability. Comparatively, only one patient (11.1%) in the operative group developed recurrent instability. As a result, the authors advocated acute arthroscopic stabilization for young, high risk patients with a first-time anterior

dislocation in order to reduce the rate of recurrent instability and worsening secondary pathology, including glenohumeral arthropathy.

Open vs arthroscopic

Bankart repair and capsulorrhaphy were traditionally performed *via* an open deltopectoral approach, and historically considered the gold standard for repair. However, over the past three decades, clinical outcomes with an arthroscopic technique have improved dramatically, and many surgeons view this as an equivalent procedure to the classic open Bankart procedure. Variations of the open approach largely differ according to management of the subscapularis, with complete and partial tendon takedown described, as well as horizontal splitting techniques^[18,19]. With the evolution of contemporary suture anchor technology, the arthroscopic Bankart repair has become increasingly more common, and advocates highlight its enhanced cosmesis, avoidance of surgical site morbidity (*i.e.*, subscapularis compromise), ability to treat all associated intra-articular pathology, and improved external rotation. This debate has continued in the existent literature, and most studies have preferentially focused on recurrence rates and patient outcomes scores among comparative series. In a 2004 meta-analysis, the documented recurrence rate (subluxation or dislocation) for arthroscopic repair was 20%, whereas use of an open technique demonstrated a significantly lower rate (10%) of subsequent instability^[20]. Additionally, the authors found that a higher proportion of patients in the open group had a good or excellent Rowe score postoperatively. However, this study encompassed older techniques for arthroscopic labral repair, including trans-glenoid sutures and bioabsorbable suture tacks, which may introduce selection bias. A subsequent prospective randomized controlled trial of open vs arthroscopic Bankart repairs with modern suture anchor technique demonstrated a significantly lower recurrence rate at two years in the open group (11%) compared with the arthroscopic group (23%)^[21]. Furthermore, the authors found age less than 25, male gender and presence of a Hill-Sachs lesions as risk factors for recurrent instability. Conversely, a large scale study from the United States military demonstrated that open anterior stabilization had nearly two-fold higher rate of short-term revision surgery than those with arthroscopic procedures after multivariate analysis, although this failed to control for degree of occult bone loss.

Augmentation

Variations of the original Bankart repair have been introduced over the years in an attempt to further mitigate rates of recurrent instability. These methods have included a number of different bone and soft tissue transfers used in the setting of bony deficiency and/or irreparable soft tissue damage. Historically, the Magnuson-Stack procedure was a non-anatomic transfer of the subscapularis from its native insertion on the lesser tuberosity to the greater tuberosity in an attempt to increase tension and improve stability^[22,23]. Similarly, the Putti-Platt procedure provided

a longitudinal, "pants over vest" shortening of the subscapularis and underlying capsule in order to tighten the anterior soft tissue restraints^[24]. However, clinical outcomes with both of these non-anatomic procedures significantly disrupted the length-tension relationship of the subscapularis, leading to anterior overtensioning, loss of external rotation, and premature glenohumeral arthritis^[25-28].

Alternatively, Latarjet described a technique of transfer of the coracoid process to the anterior inferior glenoid as a bony augmentation^[29]. A slightly different type of coracoid transplantation procedure was described by Helfet and named in honor of his mentor, Walter Bristow^[30]. The Latarjet has become increasingly popular as an option for the treatment of glenoid or bipolar bone loss, which is a significant predictor of recurrent instability after arthroscopic repair^[31]. Modifications to the initial description were made by Young *et al.*^[32], which included fixation with two screws, repairing the anterior capsule to the coracoacromial ligament retained on the coracoid graft and placing the graft through a split in the subscapularis to provide a "sling" effect of the conjoined tendon. Further adaptations, such as the congruent arc technique, have also been proposed. In this circumstance, the inferior aspect of the coracoid, as opposed to the lateral surface described in the original technique, is rotated to match the contour of the glenoid neck and extend the potential articular surface^[33,34].

Other alternatives may be considered for complex shoulder instability with critical bone loss or engaging bipolar lesions. Potential graft sources for anterior glenoid reconstruction may include autograft or allograft iliac crest, allograft distal tibia, allograft glenoid, and/or local distal clavicular autograft^[35-37]. All of these procedures are predicated on the goal of extending the articular surface of the glenoid without providing a bony constraint to anterior humeral translation^[38]. On the humeral side, the "remplissage" procedure provides a capsulotenodesis of the posterior capsule and infraspinatus tendon into the Hill-Sachs lesion to prevent its engagement with the glenoid^[39]. This non-anatomic, arthroscopic procedure can be combined with a labral repair to provide stability even in the setting of glenoid bone loss^[40].

POST-INSTABILITY ARTHROPATHY

In an attempt to describe and characterize the natural history of the development of dislocation arthropathy after a primary shoulder dislocation, Hovelius *et al.*^[41] followed 257 shoulders initially treated with non-operative management at long-term follow-up. At 25-year follow-up, 227 shoulders met criteria for inclusion. Of those, 29% had developed mild arthropathy, 9% moderate, and 17% severe, and less than half (44%) were classified as normal. Risk factors for development of secondary arthropathy included age greater than 25 at time of initial dislocation, high energy mechanism of injury during sporting activity, and history of alcohol abuse. When evaluating the same patient cohort requiring subsequent

stabilization surgery, Hovelius *et al*^[42] concluded that approximately two-thirds of patients under the age of 25 with surgery for first-time anterior dislocation developed at least mild arthropathy by final follow-up.

In addition to assessing the long term results of primary dislocations treated with initial non-operative management, the rates of secondary arthropathy have also been quantified for other methods of treating anterior shoulder stabilizations. To this end, Hovelius *et al*^[43] performed a retrospective comparative analysis of 26 shoulders with open Bankart repair and 30 shoulders with Bristow-Latarjet procedure at greater than 15-year follow-up. Of the shoulders that underwent Bankart repair, 16 (61.5%) went on to develop arthropathy (14 mild, 2 moderate), as compared to 9 (30%) shoulders in the Latarjet group (5 mild, 3 moderate, 1 severe). Interestingly, all patients who developed moderate or severe arthropathy, from either treatment group, reported being very satisfied with their outcome. This may reflect a disconnect between radiographic outcomes and patient-reported function after symptomatic instability has resolved, and this has been documented in other prior series as well^[27,44].

In a separate long term study assessing both the clinical and radiographic outcomes after Latarjet procedure performed for recurrent instability, Allain *et al*^[45] found that none of the 58 shoulders had recurrent dislocation at 10-23 years postoperatively, although 6 had apprehension, and 1 had intermittent subluxations. However, only 22 shoulders (38%) demonstrated no evidence of glenohumeral osteoarthritis. Thirty-four shoulders (59%) had radiographic evidence of osteoarthritis, with the majority (25 shoulders) being grade 1 with no detrimental effects on upper extremity function. Two additional patients had severe, grade 4 changes with eccentric wear present, and there was a significant correlation between degree of secondary arthropathy and functional scores on both Constant and Rowe outcome measures. Recurrent dislocation, as opposed to subluxation, was significantly associated with a higher rate of secondary arthrosis, whereas number of shoulder dislocations and time to surgery were not significant predictors.

With failed primary stabilization procedures, patients with revision surgery may also be at heightened risk for instability arthropathy due to attritional bone loss and increasing injury complexity. Tauber *et al*^[46] investigated the reasons for failure after index stabilization surgery, but also assessed for the subsequent development and/or progression of arthritic changes after revision surgery. The authors found no significant difference in the progression of arthritis between bony glenoid augmentation procedures and soft tissue repairs at time of revision surgery, although only 14 of 41 (34%) had no radiographic signs of arthritis at the time of revision surgery. At mean 49 mo follow-up, only 5 shoulders (12%) continued to demonstrate no evidence of glenohumeral arthritis. The authors suggest that once the development of arthritis has been initiated, subsequent surgery for revision anterior stabilization

may not mitigate the onset or progression of secondary arthropathy.

The notion that the natural history of dislocation arthropathy is unchanged by surgical stabilization is echoed in a more recent study by Hovelius' group^[47]. At 33-35 years from transfer of the coracoid for shoulder stabilization, 31 shoulders were available for follow-up. Of these shoulder, 39% were normal, 27% had mild OA, 23% moderate and 11% severe. These findings were similar to their previous study (outlined above) on the long term outcome of shoulder dislocations treated non operatively^[41]. Interestingly, the majority of patients remained as satisfied with their outcomes at long-term follow-up as they were at 2-4 years from surgery, and only one patient required re-operation for recurrent instability.

Despite these long-term nature of these studies, most investigations do not control or evaluate for the role of surgical technique or patient-specific factors on the development of dislocation arthropathy^[34,41,43,45,47]. It is well established that the overtensioning of the capsular and/or subscapularis, as in the historical non-anatomic procedures, may overconstrain the glenohumeral joint and contribute to premature onset of arthritis with asymmetric, anterior glenoid wear. Additionally, non-absorbable or metallic implants, prominent anchor placement, and/or malpositioned arthroscopic knots can abrade the articular surface of the humeral head, thus increasing the risk for the arthritic change (Figure 1). Most series also emphasize that lateral placement of coracoid bone graft can hasten the development of dislocation arthropathy, or at least significantly increase the rate of secondary chondral damage^[45,48]. While some authors theorize that intra-articular coracoid graft placement (*i.e.*, capsule repaired to the lateral vs medial edge of the graft used) may increase the chances of humeral head abrasion^[48,49], there is no clear data correlating this technique with clinical or radiographic endpoints.

CONSERVATIVE TREATMENT

Periarticular injections

Injections for management of shoulder arthropathy are considered a treatment alternative as they represent a less invasive treatment method to surgery. Although there are several types of injections, the efficacy of these injections is not well articulated in the existent literature.

Diagnostic injections may also have utility when clinical examination alone does not yield a clear diagnosis or primary source of pathology. While also offering potential therapeutic value, diagnostic injections can be performed with short acting local anesthetics, particularly xylocaine or lidocaine, into the specific areas of interest, such as the biceps sheath and acromioclavicular joint. Particularly given the association between infusion pain pumps and irreversible chondrolysis^[50], longer acting medications (*e.g.*, bupivacaine) should be avoided over shorter acting agents due to greater potential for chondrotoxicity^[51-56].

Cortisone injections are also frequently used for



Figure 1 Anteroposterior (A) and lateral (B) X-rays of a 39-year-old male with dislocation arthropathy status post instability procedure with metal anchors.

the nonoperative treatment of glenohumeral arthritis; however, their efficacy has not been well studied and the majority of scientific evidence is based on limited case series^[57-59]. Corticosteroids interrupt the inflammatory cascade and typically result in a transient decrease in secondary pain. Unfortunately, the efficacy and duration of symptomatic relief is not known and often patient-dependent, typically ranging from weeks and months. Therefore, a limitation of cortisone injections is lack of consistent durability. Additional concerns exist regarding the potential systemic side effects and increased risk of infection when performed within 3 mo of an arthroplasty procedure^[60].

While used less frequently, injectable non-steroidal anti-inflammatory drugs (NSAIDs), such as Ketorolac, may result in fewer side effects and may have similar efficacy to cortisone^[61]. As with cortisone, NSAIDs may also lack effect durability and represent a temporizing treatment option. Further research is required to better ascertain the role and relative efficacy of local NSAID injections in young patients with post-instability arthritis.

Viscosupplementation/hyaluronic acid injections and orthobiologics: Viscosupplementation, while FDA-approved for knee osteoarthritis, is considered off-label for use in the shoulder. A prior meta-analysis performed evaluating the use of hyaluronic acid (HA) injections in the shoulder for a variety of disorders, including osteoarthritis, revealed an absence of evidence for clinically significant improvement^[62]. More recently, a subsequent meta-analysis of 8 studies evaluating osteoarthritis of the glenohumeral joint, including two randomized prospective trials, suggested a lack of convincing evidence for the efficacy of HA injections^[63-67].

Given the lack of definitive efficacy, reimbursement for HA injections is limited. Theoretically it should behave in the shoulder similar to the knee as both are synovial joints. Recently, scientific support for viscosupplementation in the knee was challenged by guidelines published by the American Academy of Orthopaedic Surgeons (AAOS), making application in general less likely to be supported by third party payers. Nevertheless, its safety profile and ease of administration make it a safe and reasonable

alternative to more invasive treatment options.

Further innovations in orthobiologics represent the vanguard of nonoperative treatment for many musculoskeletal conditions, although clinical trials are lacking. Specifically, platelet-rich plasma (PRP) or stem cell injections may have potential as viable treatment option for glenohumeral arthritis, but no literature currently exists to support their use. Recent literature indicates that there may be benefit for PRP injections in the setting of knee arthritis^[68]. Biologic alternative injections that modulate cartilage repair processes and regulate inflammatory mediators are a principle area of current research but no definitive treatment options have been developed to date.

Physical therapy

Little to no literature exists regarding the use of physical therapy as a form of treatment for glenohumeral osteoarthritis. A recent clinical practice guideline from the AAOS stated that there was “no evidence for or against” the use of physical therapy or other modalities such as “massage, joint mobilization, joint manipulation, exercise, phonophoresis, iontophoresis, ultrasound, laser, acupuncture, and/or electrical stimulation”^[69]. Given the low risks associated and limited alternatives, physical therapy may be a reasonable consideration in patients desiring non-surgical management. However, it may also exacerbate symptoms related to painful, advanced arthritis. If restoration of motion or dynamic control of residual instability are among the primary goals, then a physical therapist or self-directed home exercise program may provide value among available treatment options^[70].

Oral medication

A variety of oral analgesics are available for treatment of osteoarthritis including NSAIDs, oral corticosteroids, acetaminophen, topical analgesics, and various non-regulated supplements such as chondroitin sulfate, vitamins, and herbal supplements. Non-narcotic analgesics are routinely recommended for the treatment of pain associated with glenohumeral arthritis, but as with other conservative interventions, there is no specific evidence documenting their effectiveness. Nonetheless,

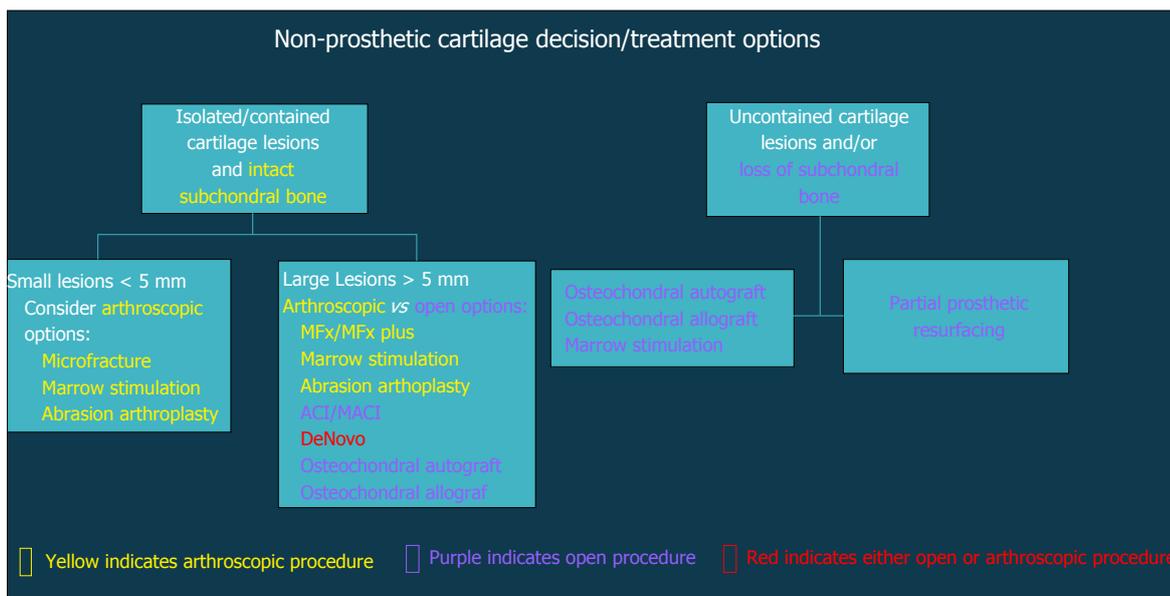


Figure 2 Flow-chart demonstrating decision algorithm for non-prosthetic cartilage treatment options.

these medications are considered a first-line alternative to more invasive interventions, must be balanced with the potential side effects. Specifically, NSAIDs may be contraindicated for patients with known kidney disorders, gastritis or a history of peptic ulcer disease, hypertension, coronary artery diseases, and/or other medical problems that impair drug metabolism.

SURGICAL MANAGEMENT

Treatment decision making

When conservative treatment fails to ameliorate symptoms in patients with instability arthropathy, a multitude of potential surgical options exist. Ultimately, treatment should be decided through a shared decision-making process and tailored to their unique anatomic factors, physiological age, comorbidities, and functional demands. In contrast to patients with osteoarthritis, individuals with early arthropathy due to glenohumeral instability are often younger, more active, and involved in both athletics or intense occupational duties. Accordingly, the potential clinical benefits of a given procedure must be balanced with its efficacy, durability, and impact on future surgical treatment.

Relevant clinical variables such as size or extent of glenohumeral chondral lesion(s), residual instability, concomitant motion loss, and presence of associated pathology.

Patients with altered glenohumeral kinematics must be identified and addressed alone or in conjunction with an additional surgical procedure (Figure 2). When post-instability arthropathy has developed due to over-tensioning of either the anterior or posterior capsule, an arthroscopic capsular release may be considered restore normal kinematics should be performed in these patients. Furthermore, loss of appropriate rotator

cuff function, particularly the subscapularis, can result in shoulder dysfunction and must also be addressed accordingly. Finally, patients with a collagen disorder (*e.g.*, Ehlers Danlos) represent a particularly difficult population to manage. Given that many of these patients will have had several prior surgeries, reconstructive options will be limited in the setting of post-instability arthropathy, including continuing conservative care, arthroscopic debridement, or potentially, arthrodesis.

In general, surgical strategies for post-instability arthropathy are contingent on the degree and severity of the associated articular cartilage lesions. Variable arthroscopic and open procedures may be indicated for localized disease and/or focal defects of the glenohumeral joint (Figure 3). However, when the articular involvement is more advanced and secondary arthritis has developed (Figure 4), arthroplasty options may be preferentially considered in the absence of marked rotator cuff disease, significant neurologic deficits, and/or structural glenohumeral bone loss with residual instability.

Non-arthroplasty options

Glenohumeral debridement: Arthroscopic debridement of the glenohumeral joint (Figure 5) has been reported as having variable, if not modest success among several case series^[71-73]. While most of these studies do not detail the precise surgical interventions, simple removal of symptomatic loose bodies or foreign bodies (*e.g.*, prominent suture material), debridement of hypertrophic synovitis, and/or capsular release may have a positive short-term effect on most patients^[74].

Adjunctive procedures: The addition of adjunctive procedures has not been extensively evaluated, although treatment of biceps-labral complex, rotator cuff, acromioclavicular, or subacromial pathology may also yield

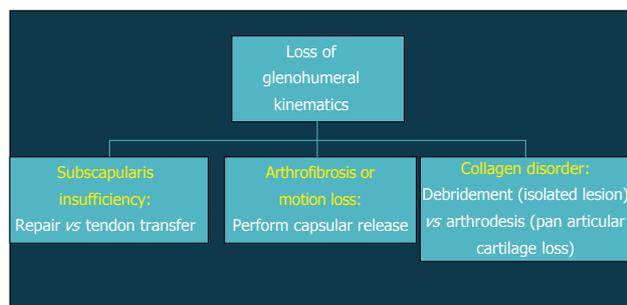


Figure 3 Flow-chart depicting treatment options after loss of glenohumeral kinematics.

partial, symptomatic relief. Skelley *et al*^[75] revealed worse surgical results when arthroscopic glenohumeral debridement and capsular release was performed strictly without any additional procedures. As a result, the authors suggest that isolated arthroscopic debridement and capsular release when done without any other concomitant procedures may not provide lasting enough benefit to justify its use.

More recently, the Comprehensive Arthroscopic Management (CAM) procedure was described by Millet *et al*^[76] for younger, active patients early glenohumeral arthritis. The CAM procedure differs from previous arthroscopic debridement in that it also features an extensive capsular release, humeral osteoplasty with inferior osteophyte removal, axillary neurolysis, and a biceps tenodesis, when appropriate. Retrospective, short term follow-up of 30 shoulders in 29 patients with an average age of 52 years (range 33 to 68 years) revealed 85% survivorship at 2 years with statistically significant improvement in pain and functional scores. Worse preoperative functional scores and joint space measurements less than 2 mm were more likely experience clinical failure and require subsequent shoulder arthroplasty. By contrast, patients with worse pre-operative motion experienced greater postoperative satisfaction, suggesting that the CAM procedure may be ideally suited for those patients affected by with motion loss due to impinging osteophytes or capsular tightness. In a separate analysis, the authors further evaluated the CAM procedure with a Markov decision model and discovered that arthroscopic management was the preferred strategy for patients younger than 47 years, whereas TSA was optimal for patients over 66 years and both treatment strategies may be considered between 47-66 years^[77].

Chondral restoration: Isolated glenohumeral chondral lesions without global or diffuse cartilage involvement may be considered for a restorative procedure. Identification of symptomatic cartilage lesions can be a challenge, as coexistent pathology may be frequently be present and difficult to independently distinguish. As previously mentioned, diagnostic injections may help identify focal areas of pathology masquerading as glenohumeral disease^[78].

Microfracture or other marrow stimulation techniques

have been employed with clinical success in the knee, although only three small case series have been evaluated its role in the glenohumeral joint^[79-81]. The merits of this procedure include that it can be performed arthroscopically without the surgical morbidity associated with an open approach. However, the utility of isolated microfracture is probably limited, and its durability of this procedure is in question due to failure rates approaching 20%^[80]. Additionally, some authors have expressed concerns about the potentially harmful effects that of subchondral bone particularly in the glenoid may be harmful^[82]. Newer modifications incorporating marrow stimulation with orthobiologics are also emerging, but these techniques have not yet been described in the shoulder^[83].

Osteochondral autograft transfer (OATS) or osteochondral allograft transplantation have demonstrated narrow indications in the shoulder, mostly for humeral-based lesions (Figure 6), although the literature is notably limited. Due to the concave geometry of the glenoid vault, centrally located glenoid lesions may be able to accommodate osteochondral transfer, although remains technically challenging^[84]. Only one known series has evaluated the surgical outcomes of 8 patients with OATS from the lateral femoral condyle for Outbridge grade IV lesions of the shoulder (7 humeral, 1 glenoid). All patients experienced improvement in both function and pain postoperatively, but two patients experienced mild, persistent shoulder limitations and one patient with donor site knee pain requiring arthroscopic debridement^[85]. In a systematic review of 35 patients with osteochondral allografts of the humeral head at mean 57 mo follow-up, Saltzman *et al*^[86] showed significant improvements in range of motion and American Shoulder and Elbow Society scores. Of note, however, 8.7% demonstrated graft necrosis, 26.7% of patients underwent reoperation, and 35.7% developed secondary arthritic changes. The authors also acknowledged that the majority of grafts were derived from frozen allografts, thereby limiting chondrocyte viability vis-à-vis fresh osteochondral allografts.

Arthroplasty options

Arthroplasty options exist for post-instability arthropathy that incorporates a prosthesis of the humeral head, the glenoid, or both. Survivorship as a concept for surgical treatment is the period of time free from revision surgery. Another way to describe survivorship is durability of outcome or durability of patient satisfaction. Recent literature has highlighted the discrepancy of implant survival with patient satisfaction in shoulder arthroplasty in patients under the age of 50 years^[87].

Partial resurfacing/biologic resurfacing/hemiarthroplasty: Partial humeral head resurfacing with a prosthesis has been suggested as an option for patients with isolated or unipolar humeral disease. Concomitant pathology as well as prior surgical procedures have been found to decrease outcomes and could be considered a contraindication to this procedure^[88]. Soft-

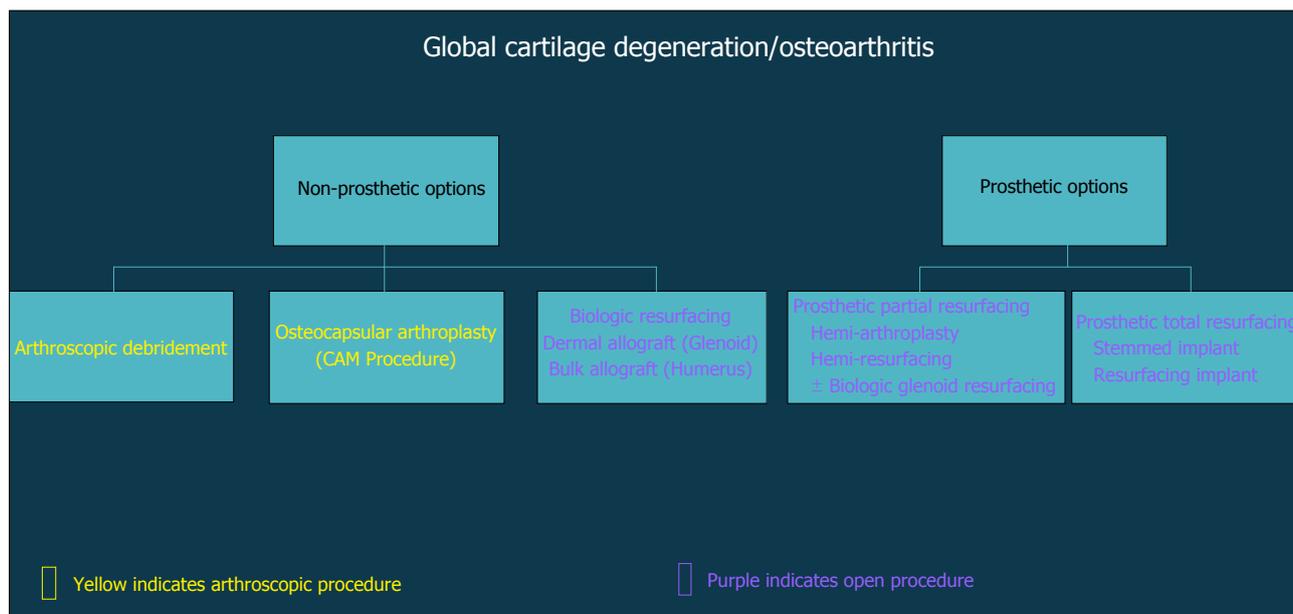


Figure 4 Flow-chart demonstrating decision algorithm for non-prosthetic vs prosthetic treatment options that include arthroscopic and open procedures.

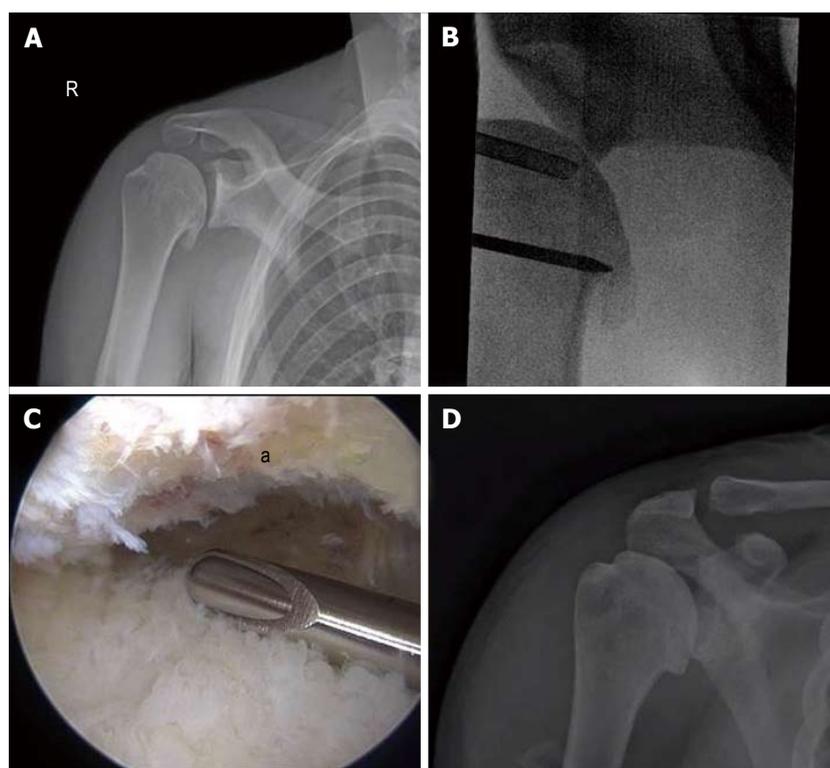


Figure 5 Comprehensive arthroscopy management of glenohumeral arthropathy. A: Images from a 37-year-old male with instability arthropathy demonstrating preoperative anteroposterior radiograph with large inferior humeral head osteophyte and loss of glenohumeral joint space; B: Intra-operative fluoroscopy localization of extent of inferior humeral head osteophyte; C: Intra-operative arthroscopic image viewing from posterior portal, demonstrating inferior humeral neck (a) status post debridement of osteophyte, the arthroscopic shaver is on the inferior capsule; D: Post-operative anteroposterior radiograph demonstrating debridement of osteophyte and biceps tenodesis with a biocomposite screw.

tissue interpositional arthroplasty procedures involve humeral head arthroplasty and then securing soft-tissue to cover the arthritic glenoid in an effort to improve upon the outcomes of humeral hemiarthroplasty (HA) alone. Unfortunately, multiple authors have reported

unacceptably poor outcomes following this procedure^[89-91]. Another option that can be performed with humeral HA is the “ream-and-run” technique popularized by Gilmer *et al*^[92]. This technique provides concentric glenoid reaming with an over-sized reamer with a goal of creating a

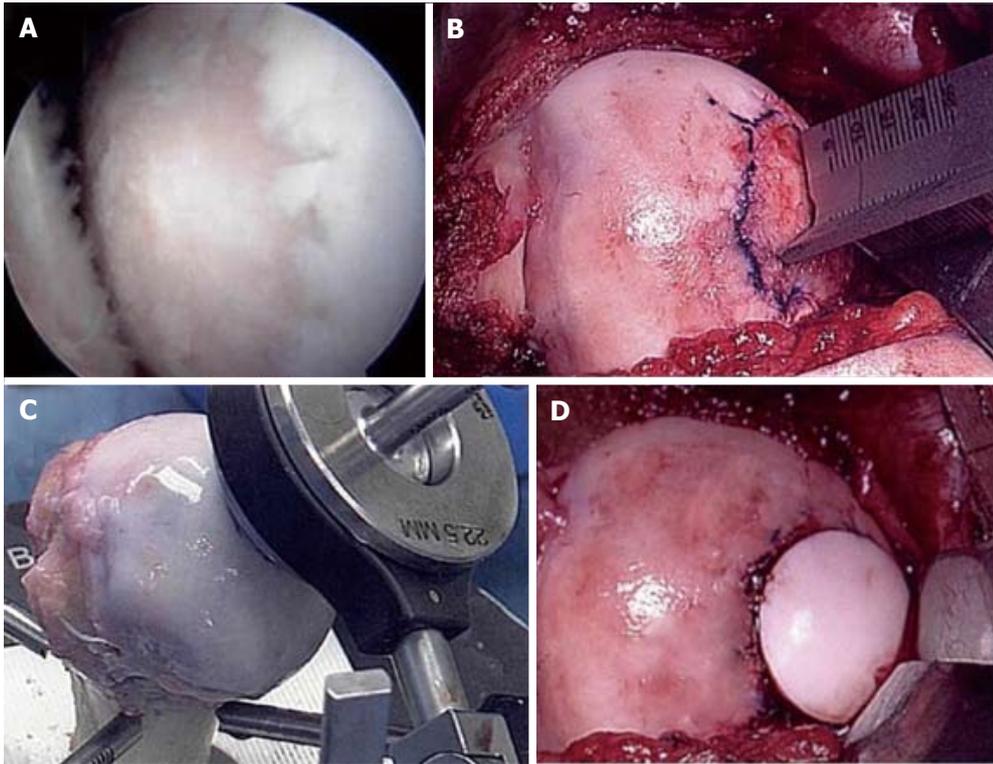


Figure 6 Fresh osteochondral allograft transplantation. A: Intra-operative arthroscopic image of central humeral articular lesion while viewing from a posterior portal in a 39-year-old patient; B: After an open approach, preparation of the central lesion; C: Harvesting a corresponding osteochondral plug from a size-matched, fresh allograft humerus; D: Status post insertion of the osteochondral plug into the defect.

smooth concavity for articulation. This has been shown by the author to be a viable alternative to TSA in the young patient^[93,94], although published series from other institutions are limited^[95]. In the previous studies, the ream-and-run technique utilized in the arthritic shoulder in patients 55 years old or less led to a significant improvement in the Simple Shoulder Test as well as minimal medial glenoid erosion.

HA has been promulgated as an option which theoretically would allow patients to pursue more aggressive/demanding activities and avoid the risk of glenoid component loosening. However, concerns for the durability of pain relief is a concern with glenoid wear over time^[96].

Total shoulder arthroplasty: Total shoulder arthroplasty (TSA) outperforms HA both functionally and in terms of implant survivorship both in the short term and long-term follow-up^[97-100]. Despite initial concerns over the possibility of glenoid loosening, recent studies have shown that patients have a significantly increased return to sports after TSA compared to HA^[101,102]. Large meta-analysis of pooled data has also demonstrated that TSA provides greater pain improvement and increased range of motion compared to HA in young patients with glenohumeral arthritis^[103]. Certainly, the young patient with arthritis is very difficult to treat with any arthroplasty modality, and outcomes in this population are worse than standard arthroplasty patients^[87,104]. Concern over a future

revision procedure can influence the surgeon's choice of the initial arthroplasty procedure, as surgeons worry about medializing glenoid wear with a HA or aseptic glenoid loosening with a TSA. There remains a higher risk of revision surgery in the population of patients under 60 receiving a HA compared to a TSA^[104].

TSA is by no means an operation without complications and adverse effects in this young patient population. In our own experience of treating a young, active military population with instability arthropathy, we have found a high rate of complications to include component failure, neurologic injury, adhesive capsulitis and venous thrombosis. In our series of 26 TSAs in a predominantly male cohort with a mean age of 45.8 years (range, 35-54 years), we experienced 9 patients with 12 complications (46.2%) leading to a 23.1% reoperation rate at an average of 3.5 years follow-up. Nine patients (37.5%) were unable to continue their high-demand activities and underwent a medical discharge for persistent shoulder disability^[105].

CONCLUSION

So-called instability (or dislocation) arthropathy may develop in high-risk patients with a history of recurrent glenohumeral instability, both with and without surgical stabilization. The incidence and rates of arthritic progression may vary widely, with radiographic changes present in up to two out of three patients after primary

Bankart repair. However, the presence of secondary arthrosis does not predict poor patient-reported function. When oral medication, periarticular injections, and physical therapy have failed, surgical options will depend on patient-specific factors, anticipated upper extremity demands, size and extent of articular involvement, and other anatomic factors. A variety of arthroscopic and open non-arthroplasty procedures are available as temporizing measures, and data regarding the efficacy of chondral restoration options are currently limited. Total shoulder arthroplasty remains the most reliable option for the treatment of post-instability arthropathy, although the clinical outcomes, wear characteristics, and implant survivorship remains a concern among active, young patients. Further investigations are warranted to evaluate the comparative efficacy of management options in this challenging, young patient demographic with early arthritis.

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Lower limb stress fractures in sport: Optimising their management and outcome

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common, comprising up to 10% of all of sporting injuries. Around 90% of such injuries are located in the lower limb. This article aims to define the optimal management of lower limb stress fractures in the athlete, with a view to maximise return rates and minimise return times to sport. Treatment planning of this condition is specific to the location of the injury. However, there remains a clear division of stress fractures by "high" and "low" risk. "Low risk" stress fractures are those with a low probability of fracture propagation, delayed union, or non-union, and so can be managed reliably with rest and exercise limitation. These include stress fractures of the Postero-Medial Tibial Diaphysis, Metatarsal Shafts, Distal Fibula, Medial Femoral Neck, Femoral Shaft and Calcaneus. "High risk" stress fractures, in contrast, have increased rates of fracture propagation, displacement, delayed and non-union, and so require immediate cessation of activity, with orthopaedic referral, to assess the need for surgical intervention. These include stress fractures of the Anterior Tibial Diaphysis, Fifth Metatarsal Base, Medial Malleolus, Lateral Femoral Neck, Tarsal Navicular and Great Toe Sesamoids. In order to establish the optimal methods for managing these injuries, we present and review the current evidence which guides the treatment of stress fractures in athletes. From this, we note an increased role for surgical management of certain high risk stress fractures to improve return times and rates to sport. Following this, key recommendations are provided for the management of the common stress fracture types seen in the athlete. Five case reports are also presented to illustrate the application of sport-focussed lower limb stress fracture treatment in the clinical setting.

Key words: Fractures; Lower; Limb; Sport; Management; Stress

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Abstract

Stress fractures in sport are becoming increasing more

Core tip: This editorial article offers a current perspective on the treatment of lower limb stress fractures in the

athlete. The authors focus on the most common “high risk” (Anterior Tibial Diaphysis, Fifth Metatarsal Base, Medial Malleolus, Lateral Femoral Neck, Tarsal Navicular, Great Toe Sesamoid) and “low risk” stress fractures (Postero-Medial Tibial Diaphysis, Metatarsal Shafts, Distal Fibula, Medial Femoral Neck, Femoral Shaft, Calcaneus), highlighting the optimal treatment methods for each, and assessing the most recent evidence which directs this. The value of preventative interventions is also discussed. Finally, five case reports are presented to demonstrate the evidence-based treatment process in clinical practice.

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INTRODUCTION

Stress fractures represent one of the more serious injuries in sport^[1]. Following such injuries, return times to sport are often prolonged, and failure to return to sport, chance of re-injury and persisting morbidity are all distinct possibilities^[2-8]. As a group, stress fractures comprise just over 10% of all sport-related injuries, with this figure as high as 30% within certain sports, such as running^[1,9-12]. The incidence of these injuries is around 1% within recreational athletes, and around 20% within elite level athletes^[1,9-12]. Around 90% of these injuries are located within the lower limb^[12,13]. Given the financial implications of sport within modern society, both with the substantial revenues associated with professional sport, as well as the economic implications associated with injuries to amateur athletes, the effect of such injuries is considerable^[1].

The significance of this injury depends on the location and nature of the fracture^[1]: The tibial diaphysis is the commonest reported location and comprises up to three quarters of all stress fractures^[2]; other common sites include the metatarsals, the femoral neck, the tarsal navicular, the fibula, the medial malleolus and the calcaneus^[1,14,15]. Until the 1980's, much of the stress fracture research had focussed on military cohorts, overlooking cohorts of sporting individuals^[9,10]. Since then, there has been increasing attention paid to the epidemiology, management and outcome of these injuries in sporting individuals, along with optimisation of rehabilitation techniques and promotion of injury prevention^[1]. However the optimal management plans for many stress fracture locations have still to be determined^[1].

At present, there forms a clear division of stress fractures by those which are deemed “high risk”, with a predilection for fracture propagation, delayed union, or non-union^[14]; and those which are deemed “low risk”,

with reliable healing patterns and resolution of symptoms when managed accordingly^[15]. Low risk fractures can often be investigated with radiographs alone, and are virtually always managed successfully through conservative management, with rest, activity modification and rehabilitation^[15]. High risk fractures often require specialised imaging to better define and quantify the injury, particularly when first line imaging is equivocal; these injuries also may require surgical management, depending on the location of the injury and the response to initial conservative management^[14]. As a consequence of this, return to sport is often more challenging with high risk injuries, and this proves particularly demanding with the high level professional athlete^[4,7,14]. For individual fracture types, the severity of the injury can be graded from the extent of the radiological changes, using either generic (Fredericson *et al.*^[16] or Arendt *et al.*^[17]) or site-specific (Saxena *et al.*^[18] or Torg *et al.*^[19]) classifications^[1,20]; such classifications can further guide management planning as well as provide prognostic information regarding return times to sport^[1,20].

The management strategies of these injuries is constantly developing, and at present, the optimal treatment modality for many stress fracture locations remains unestablished^[1]. Even with similar injuries, management and return to sport times can vary for different sport, with prolonged rehabilitation often required to return to repetitive loading sports such as long distance running and jumping^[1,5]. Regular review of the emerging research in this area, in conjunction with pre-existing treatment protocols, is necessary to determine the best way to manage such athletes, and maximise return to sport^[1]. In addition to this, given the overuse nature of such injuries, often demonstrating prodromal symptoms and resulting from the presence of risk factors, primary prevention programmes provide the best way of managing such injuries^[21,22]. Ongoing research in this field provides continued resources which can benefit both the athlete and the sports medic to fully maximise the potential of such a practice^[21,22].

From the clinical perspective, when defining the optimal method for managing each fracture type, seven major areas require addressing: (1) is the fracture High Risk or Low Risk? (2) what is the optimal imaging modality for the fracture? (3) should this fracture be managed conservatively or surgically? (4) if managed surgically, what is the best technique to employ? (5) if managed conservatively, what is the optimal rehabilitation schedule? (6) how quickly can sporting activities be resumed? and (7) are there any preventative programmes available for this fracture type?

This framework ensures that optimal treatment planning and outcome can be achieved for each individual athlete^[1]. In this editorial, we aim to determine the optimal evidence-based management strategies for the most common “high” and “low” risk sport-related lower limb stress fractures, by reviewing the available literature in this field. With this, we also aim to discuss the areas that require further clarification to provide optimal care for the athlete, as well as to assess the emerging

evidence for preventative strategy programmes that can avert such injuries from developing. To illustrate this treatment process in clinical practice, five case reports assessing the management of sport-related lower limb stress fractures are presented at the end of the article.

HIGH RISK SPORT-RELATED LOWER LIMB STRESS FRACTURES

High risk stress fractures are those which have an increased risk of fracture propagation, delayed union, or non-union^[14]. This is normally because they are located on the tension side of the bone, or because they develop in an area with limited vascularity. The most common high risk stress fractures are those of the Anterior Tibial Diaphysis, the Fifth Metatarsal Base, the Medial Malleolus, the Lateral Femoral Neck, the Tarsal Navicular and the Sesamoids of the Great Toe^[1,14,15,23].

Anterior tibial diaphysis

Common in running athletes, anterior tibial diaphyseal stress fractures (TDSFs) are visualised on radiographs as the "dreaded black line" on the anterior mid tibial cortex^[1,2,14,24]. However, radiographic changes can be absent in up to 85% of cases^[25]; with persisting symptoms and negative radiographs, the recommended second line imaging investigation is now magnetic resonance imaging (MRI) scan^[24].

The severity of the fracture can be graded by presence of changes on each of the MRI sequences, using either the Fredericson^[16] or the Arendt^[17] Scale (Table 1). A higher grade of Fredericson Scale has been shown to be associated with an increased return to running time for TDSFs^[16]. When both cortices of the tibia are involved, with completed fracture lines, this injury needs to be managed as an acute fracture^[1,2,14].

Current treatment protocols advocate a trial of 3 to 6 mo of conservative management, as initial treatment of these injuries^[1,2,14]. Fredericson Grade 1 to 3 injuries are managed with crutch-assisted weightbearing until resolution of pain; bracing serves as a potential adjunct to reduce symptoms^[16]. For Grade 4 injuries, initially casting is recommended for a period of 6 wk^[16].

If symptoms persist following attempted conservative management, surgical intervention should be advised^[1,2,14]. The available surgical techniques include tibial intra-medullary (IM) Nailing, compression plating, or drilling of the stress fracture with bone grafting^[2]. A recent systematic review by Robertson *et al.*^[21] found that intra-medullary nailing and compression plating provided the highest return rates and lowest return times of all the surgical treatments available; as such these are the preferred surgical techniques for this injury.

This review also found that conservative management of these injuries resulted in decreased return rates to sport compared to surgical management; return to sports rates were 71% for conservative management and 96% for surgical management^[2]. Thus, clinicians must remain

aware of the benefit of early surgical management in the high level athlete who fails to respond to conservative management^[2]. Reported return times to sports for this injury included 7 mo for conservative management and 7 mo for surgical management^[2].

For completed fractures, current protocols advocate conservative management (casting) for those which are undisplaced, and surgical management for those which are displaced, normally with an IM Nail^[1,2,14]. Reported return times for these injuries included 11.5 mo for conservative management and 7 mo for surgical management, with return rates of 67% for conservative management and 100% for surgical management^[2].

For conservative management, recommended rehabilitation techniques advise activity cessation, with avoidance of heavy loading of the tibia, limited weight-bearing with crutches for between 3 to 6 mo^[1,2,14]. During this time, bracing of the lower limb can be helpful to reduce symptoms^[1,2,14]. Following this, progression of weightbearing and return to loading activities can be allowed as pain permits^[1,2,14]. For surgical management, recommended rehabilitation techniques comprise commencement of a progressive weight-bearing programme, within the first week post-operatively, under the care of physiotherapy, with return to full loading activities between 6 and 8 wk post-operatively^[1,2,14]. With both conservative and surgical management, full level sport should not be commenced until there is clear evidence of clinical and radiological union^[1,2,14].

Validated prevention interventions for this injury type include the use of shock absorbing insoles as well as the optimisation of athlete fitness prior to the commencement of vigorous exercise^[21,22,26].

Fifth metatarsal base

Common in soccer, american football and basketball players, these injuries appear on plain radiographs as a sclerotic or radiolucent line at the proximal aspect of the fifth metatarsal^[1,14,23,24]. However, radiographic changes can be absent in up to 69% of patients^[25]. In such cases, the second line imaging investigation is now MRI scan^[24]. Computed tomography (CT) scan can be of value in assessing fracture union if conservative management is attempted^[24]. These injuries are graded using the Torg Classification^[19] (Table 1), which provides a helpful guide to direct treatment^[13,27].

Torg 1 injuries can be managed either surgically or conservatively^[13,27]. Surgical techniques comprise either percutaneous intramedullary cannulated screw fixation or modified tension band wire; screw fixation is the recommended modality as this has the higher volume of evidence at present^[4,23]. Conservative management comprises non-weightbearing in a below knee cast or moon boot for 6 wk followed by partial weightbearing for a further 6 wk^[27].

There is a growing trend for surgical management of such injuries in high level athletes and athletes in high intensity repetitive loading sports (running, jumping),

Table 1 Classification systems for lower limb stress fractures

	Arendt scale ^[17] (MRI based)	Federicson scale ^[16] (MRI based)	Saxena classification ^[18] (CT based)	Torg classification ^[19] (radiograph based)
Location of use	Generic	Generic	Navicular	5 th Metatarsal Base
Grade 1	STIR signal change	periosteal edema - bone marrow normal	Dorsal cortex involved	Acute fracture line, no intramedullary sclerosis or periosteal reaction
Grade 2	STIR and T2 change	periosteal and bone marrow edema - T2 change only	Dorsal cortex and body involved	Widened fracture line with intramedullary sclerosis and periosteal reaction
Grade 3	STIR, T1 and T2 change - no fracture line present	periosteal and bone marrow edema - T1 and T2 change - no fracture line	Dorsal and Volar cortices involved	Widened fracture line with complete intramedullary sclerosis and periosteal reaction
Grade 4	STIR, T1 and T2 change - fracture line present	periosteal and bone marrow edema - STIR, T1 and T2 change - fracture line	-	-

MRI: Magnetic resonance imaging; CT: Computed tomography; STIR: Short tau inversion recovery.

with a recent systematic review from Mallee *et al.*^[4] showing proven benefit of surgical management, in terms of return times and rates to sport. Reported return rates following surgical management ranged from 75% to 100%^[27-31], with return times of 13.8 wk^[28]. Return rates for conservative management ranged from 33% to 100%^[27,28], with return times 19.2 wk^[28]. Conservative management however remains a realistic option for the low level athlete.

As conservative management remains a recognised acceptable alternative to surgery, all athletes being advised to undertake surgical treatment should be fully informed of the available treatment options^[5,14,23]. The risks and benefits for both surgical and conservative should be fully explained: For conservative management the main benefit being the avoidance of surgery, while the main risk being the development of non-union; for surgical management, the main benefit being an improved return rate and time to sport, while the main risk being that of infection and structural damage^[5,14,23].

Torg 2 (delayed union) and Torg 3 (non-union) injuries are advised to be managed with surgical intervention, in the form of internal fixation and bone grafting, to facilitate union^[5,14,23]. A higher Torg grading and a plantar gap greater than 1 mm are predictive of a prolonged return times to sport^[4,29].

For surgical management, current rehabilitation recommendations advise 3 wk non-weightbearing in a short leg cast, followed by progressive weightbearing over the following 3 to 6 wk in protective footwear^[5,14,23]. An over accelerated rehabilitation must be avoided as this significantly increases the chances of treatment failure^[5,14,23]. For conservative management, current rehabilitation recommendations advise 6 wk non weight-bearing in a cast or boot, followed by 6 wk partial weightbearing in a functional splint, and then by a graduated return to sport under the guidance of the physiotherapists^[5,14,23]. With both forms of treatment, full level sport should only be commenced once there is clear evidence of clinical and radiological union^[5,14,23]. There are no validated prevention interventions for this fracture

type at present^[21,22].

Medial malleolus

Common in athletes involved in running and jumping sports, radiographs form the first line imaging of this condition, but can be negative in up to 55% of cases^[25]. With persisting symptoms and no clear radiographic changes, the second line imaging investigation is now MRI scan^[24].

Current management protocols direct treatment based on fracture displacement and the level of the athlete^[1,5,6,14,23]. All displaced fractures should be treated with surgical reduction and fixation to aid fracture union, reduce post-injury symptoms and facilitate return to sport^[1,5,6,14,23]. Undisplaced fractures in the low level athlete are recommended for conservative management, minimal weightbearing with crutches in a short leg cast or moon-boot for 6 to 8 wk^[1,5,6,14,23]. Undisplaced fractures in the high level athlete and in athletes who participate in high intensity repetitive loading sports (such as running and jumping) are, however, now recommended for the surgical fixation, as this has been shown to reduce return to sport times, compared to conservative management^[1,5,6,14,23]. A recent systematic review by Irion *et al.*^[6] found similar return to sport rates for surgical vs conservative management of these injuries (both 100%), but the mean return to sport time was three times higher with conservative management (2.4 wk for surgical management vs 7.6 wk for conservative management).

Surgical techniques include cannulated cancellous screw fixation or modified tension band wire technique^[1,5,6,14,23]. The preferred surgical technique is screw fixation, as this has the stronger evidence-base^[1,5,6,14,23]. Any athlete undergoing surgical management, when conservative management form a reasonable alternative, should be fully informed of the benefits and risks of both treatments, particularly outlining the surgical risks involved, which include infection, bleeding, structural damage and requirement for revisional surgery^[1,5,6,14,23].

Recommended rehabilitation for surgical management

comprises 1 to 3 wk limited weightbearing in a cast or moonboot, while that for conservative comprises 6 to 8 wk limited weightbearing in a cast or moonboot^[1,5,6,14,23]. This is then followed by a progressive strengthening, range of motion and proprioception programme under the care of the physiotherapist, with a graduated return to sport^[1,5,6,14,23]. For both forms of management, return to full level sport should only be performed when there is clear evidence of clinical and radiological union^[1,5,6,14,23]. There are no validated prevention interventions for this fracture type at present^[21,22].

Lateral (tension side) femoral neck

Most commonly seen in marathon and long distance runners, plain radiographs form the initial imaging investigation for lateral-sided (tension) femoral neck stress fracture (FNSFs)^[1,5,8,14,24]; however radiographic changes can be absent in up to 80% of cases^[25]. When radiographs are negative, and the history and exam findings are suggestive of the diagnosis, the second line imaging investigation is MRI Scan^[24]. The severity of these fractures can be graded using the Arendt^[17] or Fredericson^[16] Classification; however this type of FNSF is managed universally with surgical fixation, so such gradings have no significant influence on treatment planning^[1,5,8,14,24].

Current management protocols advocate urgent surgical fixation of this fracture type, to prevent fracture displacement and its associated risks of avascular necrosis (AVN) of the femoral head^[1,5,8,14,24]. Surgical fixation is ideally performed with a Dynamic Hip Screw (DHS) (with or without a de-rotation screw) as compared to multiple cannulated screws (MCS), as the DHS confers more stability of fixation for the unstable shear-pattern of these fractures^[1,5,8,14,32-34]. There is limited data for return to sport rates and times for lateral femoral neck fractures, as the majority of studies reported are case reports or series^[1,5,8,14]. In a recent systematic review by Neubauer *et al.*^[8], which recorded all published FNSFs in runners, 28 out of 48 patients were noted to return running. Displaced fractures had significantly lower return rates (6/18), than non-displaced fractures (22/30)^[8]; this has been noted by previous authors^[35]. Reported return to sport times varied from 3 to 12 mo^[8].

Recommended rehabilitation techniques advise toe-touch weight-bearing with crutches for 6 wk, followed by partial weight-bearing with crutches for a further 6 wk^[1,5,8,14,36]. Hydrotherapy and upper limb exercises can be commenced 2 wk post-surgery^[36]. Following this, weight-bearing is permitted as tolerated, with commencement of physiotherapy to focus on hip and lower limb muscle strengthening and range of motion exercises, facilitating a graduated return to sport^[1,5,8,14,36]. Full level sport should only be commenced once there is clear evidence of clinical and radiological union^[1,5,8,14,36]. Clinical and radiographic follow-up should be maintained for a minimum of 2 years to ensure delayed post-treatment AVN does not ensue^[1,5,8,14,36].

Validated prevention interventions include education programmes to promote physiological optimisation prior to engaging in rigorous activity, as well performing progressive training regimes (limit training volume increases to 10%,) and limiting training volumes within recommended targets (around 160 km over a 12 wk when starting)^[8,37-39].

Navicular

Common in sprinting athletes, these are visualised on plain radiographs as a sclerotic or radiolucent line extending from the superior tension side of the navicular^[1,3,5,14,23]. However, radiographic changes can be absent in up to 40% of cases^[25]. Thus, with persisting symptoms and negative radiographs, the second line imaging investigation is either CT or MRI Scan^[24]. CT Scanning allows visualisation and quantification of the fracture line, which is useful for management planning^[24]. This enables these injuries to be classified by the Saxena Classification^[18] (Table 1). This can guide management planning, as well as well provide prognostic information regarding return to sport, with a higher Saxena Grade correlating with a prolonged return to sport^[4]. MRI scanning provides a comprehensive picture of the stress injury as well as visualising the surrounding soft tissue structures^[24].

Current management protocols are guided by the extent of the fracture line (Saxena Classification) and displacement of the fracture^[1,3,5,14,18,23]. At present, for partial undisplaced fractures (Saxena Grade 1 and 2), conservative management with short leg cast and non-weight-bearing for 6 wk is recommended^[1,3,5,14,18,23]. In a systematic review by Torg *et al.*^[3], such treatment was found to offer superior results over other treatment modalities, with return to sports rates of 96% and return times on mean of 4.9 mo. For displaced or completed fractures (Saxena Grade 3), surgical management, with reduction with internal fixation, is recommended^[1,3,5,14,18,23]. Reported return times following surgical management range from 16.4 wk to 5.2 mo, with return to sport rates of 82%^[3,4]. The available surgical techniques include screw fixation or fracture site drilling, both with or without bone graft^[3,4,18,40]. The preferred technique at present is screw fixation, as this offer improved return times and rates to sport^[3,4,40].

To note, developing evidence suggests that surgical management of all navicular stress fractures may offer improved return to sport times for high level athletes^[4]; however, such evidence fails to stratify outcome by severity of fracture or Saxena Classification, and, as such, further well designed randomised controls are necessary to confirm this^[1,3,5,14,18,23].

Recommended rehabilitation techniques both for conservative and surgical management consist of non-weightbearing in a below knee cast or moon boot for 4 to 6 wk, followed by progressive partial weight bearing for a further 6 wk until painfree^[1,3,5,14,18,23]. This is then followed by a graduated return to sporting activities

under the supervision of the physiotherapists. For both forms of management, return to full level sport should only be performed when there is clear evidence of clinical and radiological union.

Validated prevention interventions include physiological optimisation programmes for the athlete before embarking upon rigorous physical activity as well as performing progressive training regimes and limiting training volumes within recommended targets^[37].

Sesamoids (great toe)

Commonly seen in sports which involve repeated, forced dorsiflexion of the great toe (dancing, gymnastics and sprinting), the medial (tibial) sesamoid is most frequently injured due to its positioning directly beneath the head of the first metatarsal^[1,14,23,41,42]. Radiographs are the first line imaging, though changes can be absent in up to 95% of cases^[25]. In such cases, with persisting symptoms, MRI is the second line imaging investigation^[24]. CT scan can be useful in assessing the progression of union of these fractures^[24].

Current management protocols advocate conservative management as the first line treatment for all such injuries. This comprises activity cessation, with a period of 4 to 8 wk limited-weightbearing in below knee cast, or moonboot^[1,14,23,41,42]. Following this, weightbearing should be progressed, using a forefoot offloading shoe or modified orthotic, as required for comfort^[1,14,23,41,42]. Return rates to sport following successful conservative management include 100%, with return times ranging 3 wk to 1 year^[43,44]. There is however a high rate of delayed union, nonunion, and recurrence with this treatment, so if the patient remains symptomatic after 3 to 6 mo of conservative treatment, surgical intervention should be considered^[1,14,23,41,42]. Conversion from conservative management to surgical management ranges from 33% to 100% in the published studies^[43-45]. There is a variety of surgical techniques available, which include closed reduction and percutaneous fixation, drilling with bone grafting, partial-sesamoidectomy and sesamoidectomy with soft tissue reconstruction^[1,14,23,41,42]. Where possible retention of sesamoids should be performed to preserve joint biomechanics and avoid the development of hallux deformities^[1,14,23,41,42]. If sesamoidectomy is required, soft tissue reconstruction should be performed in conjunction to try restore such biomechanics^[1,14,23,41,42]. The preferred choice of surgical management is guided by the fracture plane (transverse or longitudinal) and fracture displacement^[44]. Transverse undisplaced fractures should be managed by either by screw fixation or drilling and grafting^[44]. Transverse displaced fractures should be managed by screw fixation when possible, however partial or complete sesamoidectomy can often be required^[44]. Longitudinal fractures are best managed by either drilling and grafting or sesamoidectomy^[44]. Reported return rates following surgery range from 90% to 100% with return times ranging 2.5 to 6 mo^[43-51].

For conservative management, recommended re-

habilitation techniques advise activity cessation and limited weightbearing in a below knee cast or moonboot for 6 wk followed by progressive weightbearing in modified footwear as pain allows^[1,14,23,41,46,51]. For operative management, recommended rehabilitation techniques now advocate a more accelerated recovery with crutch-assisted weight-bearing for 1 wk post-operatively, followed by full unassisted weightbearing as pain allows^[1,14,23,41,46,49-51]. Under guidance of the physiotherapists, running activities can normally be commenced around 6 wk post-operatively, followed by a return to full level sport as symptoms and physical fitness allow^[1,14,23,41,46,49-51]. There are no validated prevention interventions for this fracture type at present^[21,22].

LOW RISK SPORT-RELATED LOWER LIMB STRESS FRACTURES

Low risk stress fractures are those with a low risk of fracture propagation, delayed union, or non-union, with reliable healing patterns and resolution of symptoms when managed accordingly^[15]. This is because they are often located on the compression side of the involved bone, and they develop in an area with robust vascularity. The most common low risk stress fractures are those of the Postero-Medial Tibial Diaphysis, the Metatarsal Shafts, the Distal Fibula, the Medial Femoral Neck, the Femoral Shaft and the Calcaneus^[1,9-12,15].

Postero-medial tibial diaphysis

Common in running athletes, these injuries appear as a sclerotic line on the postero-medial border of the proximal to mid tibial diaphysis^[1,2,15]. However, radiographic changes can be absent in up to 85% of cases^[25]; with persisting symptoms and negative radiographs, the second line imaging of choice is now MRI Scan^[24]. If however, the history and examination findings are high suggestive of the diagnosis, the injury can be managed expectantly, with repeated radiographs alone, due to the benign nature of the condition^[15].

The severity of the fracture can be graded by presence of changes on each of the MRI sequences, using either the Fredericson^[16] or the Arendt^[17] Scale (Table 1). The Fredericson Scale was developed from a cohort of postero-medial stress fractures, within which the severity of grading was shown to be associated with return to running times: Grade 1 injuries took 2 to 3 wk to return to running; Grade 2 injuries 4 to 6 wk; Grade 3 injuries 6 to 9 wk; and Grade 4 injuries 12 wk, with initial cast treatment for 6 wk^[16]. To note, there is growing evidence that "shin splints" or "tibial periostitis" form a continuum with tibial stress fractures injuries, with MR Studies demonstrating periosteal and bone oedema in cohorts of athletes with "shin splints"^[20]. When present, it is advised to treat "tibial periostitis" as Grade 1 injuries, in order to prevent progression and prolongation of the injury^[1,5,15].

Current management protocols advocate conservative management for these stress fractures^[1,2,15].

The standard treatment is cessation of activities, with restricted weightbearing, until symptoms resolve^[1,2,15]. Adjuncts such as ultrasound and pneumatic bracing can improve return to sport times^[1,2,15]. A recent systematic by Robertson *et al.*^[2] found that return rates following posterior TDSFs are universally good with all studies reporting return rates of 100%. Return to sport times averaged around 2 mo: Use of pneumatic bracing reduced return times to 1 mo post-injury; use of pulsed ultrasound enabled return to sport immediately post-treatment. Surgical management is reserved for non-unions, with delayed unions treated expectantly; these however are extremely rare due to the well vascularised nature of the postero-medial tibial diaphysis^[1,2,15].

Recommended rehabilitation techniques advise cessation of activities which provoke symptoms, with weightbearing as per pain allows^[1,2,15]. Some studies advocate immediate return to full weightbearing and sporting activities using an aircast brace, if the patient is completely painfree with the orthotic^[2,52]. This is followed by a graduated return to exercise programmes under the care of the physiotherapists^[1,2,15]. Return to full level sport should only be performed with clear evidence of clinical and radiological union^[1,2,15].

Validated prevention interventions include the use of shock absorbing insoles, as well as physiological optimisation of the athlete prior to the commencement of vigorous exercise, performing progressive training regimes and limiting training volumes within recommended targets^[21,22,26].

Metatarsal shaft

Commonly seen in distance runners and ballet dancers, these most often develop in the second metatarsal, followed by the third and fourth metatarsals^[1,15,23,53]. The first line imaging of these injuries is plain radiographs; however radiographic changes can be absent in up to 69% of cases^[25]. With persisting symptoms, the second line imaging investigation is MRI Scan^[24]; however this injury can initially be imaged with serial radiographs, if the history and clinical exam are conclusive with the diagnosis^[15]. Current management protocols advocate conservative management for these injuries^[5,15,23,53].

This is in the form of activity restriction for 6 to 8 wk, either in a moonboot, short leg cast or fore-foot offloading shoe, with a progressive return to exercise as pain allows^[5,15,23,53]. Further adjuncts, such as a firm-based insoles or midfoot taping, can progress mobility and relieve symptoms during the rehabilitation period^[5,15,23,53]. Occasionally, with delayed union or in the presence of severe pain, protracted application of cast may be necessary, for around 12 wk post injury^[5,15,23,53]. However, most of these stress fractures heal after 4 wk of compliant conservative management^[5,15,23,53]. While, delayed unions can be treated expectantly with prolonged casting, non-unions require surgical intervention in the form of plating and bone graft; this however happens very rarely with compliant treatment^[5,15,23,53]. Reported return to sport

times range from 4 to 12 wk, with second (10 wk) and third (12 wk) metatarsal fractures taking longer to return than 4th metatarsal fractures (4 wk)^[53].

Recommended rehabilitation techniques advise 6 to 8 wk limited weightbearing in a short leg cast, moonboot or forefoot offloading shoe followed by commencement of a graduated activity program once the symptoms have resolved^[5,15,23,53]. Following this, a graduated return to sport programme should be undertaken under the care of the physiotherapist^[5,15,23,53]. Full level sport should only be commenced once there is clear evidence of clinical and radiological union^[5,15,23,53]. Validated prevention interventions include use of viscoelastic insoles, as well as appropriate limitation of training volumes, as athletes who run over 20 m/wk are at increased risk of developing these injuries^[14,21-23].

Distal fibula

These injuries are most commonly seen in running and jumping athletes; the distal third region is the most common site for stress fracture in the fibula^[1,15,23,53]. Standard radiographic changes consist of a sclerotic or radiolucent line at the level of lateral malleolus^[15,23]; however radiographs can be negative in up to 40% of cases^[25]. In such situations, the second line imaging investigation is currently MRI Scan^[24]; however, if the history and clinical exam are conclusive with the diagnosis, the injury can be managed with serial radiographs initially^[15].

Current management protocols advocate conservative management for this injury, with cessation of sports, activity modification and immobilisation in a moonboot, air cast or below knee cast for 6 wk, followed by a graduated return to activities as symptoms allow^[1,15,23,53]. Immobilisation is preferable with a moonboot or air cast, as this allows ongoing physiotherapy exercises to be performed during treatment^[1,15,23,53]. Reported return times to sport are around 13 wk^[53]. Some studies advocate immediate return to sporting activities using an aircast brace, if the patient is completely painfree with the orthotic^[52]. However, the authors advise caution with this as an over-accelerated return to full level sport, particularly in the high level athlete, can prevent adequate healing and provoke development of a delayed or non-union^[1,15,23,53]. Any athlete treated as such should be followed up closely to avoid this occurring^[1,15,23,53]. While delayed unions can normally be treated with prolonged casting, non-unions will most often require surgical intervention, in the form of plating and bone graft^[1,15,23,53].

Recommended rehabilitation techniques advise limited weightbearing with crutches for 6 to 8 wk, in a moonboot, air cast or below knee cast, followed by a graduated return to activities, as symptoms allow, under the care of the physiotherapists. If an accelerated return to sport is attempted using an aircast, clinicians must remain vigilant for development of a delayed or non-union^[1,15,23,53]. In order to avoid this, return to full level sport should only be performed when there is clear evidence of clinical and radiological union^[1,15,23,53]. There

are no validated prevention interventions for this injury type at present^[21,22].

Medial (compression side) femoral neck

Most often recorded in marathon and long distance runners, these injuries are visualised on plain radiographs as an area of sclerosis or radiolucency at the medial aspect (compression side) of the femoral neck, perpendicular to the osseous trabeculae^[1,5,8,15,54,55]. However, radiographic changes can be absent in up to 80% of cases^[25]; when radiographs are negative, and the history and examination findings are suggestive of this condition, the second line imaging investigation is now MRI Scan^[24]. This can allow grading of severity of the stress fracture using the Arendt Scale, which has been found to predict return times to sport post-treatment (Table 1)^[17,24,56].

Current management protocols guide management based on the extent and displacement of the fracture, as per the Naval Medical Centre San Diego Classification^[1,5,8,15,54,55]. Compression FNSFs which span less than 50% of the femoral neck width can be treated conservatively, with limited weightbearing followed by a graduated return to exercise programme^[1,5,8,15,54,55]. However, if the fracture line spans more than 50% of the femoral neck width, or if there is displacement, surgery is indicated to stabilise the fracture^[1,5,8,15,54,55]. The compression fracture is oblique in nature, and biomechanically more stable than the tension fracture; so MCS can be used as the preferred fixation method^[32-34]. Other surgical techniques include DHS plus or minus de-rotation screw. With the largest series of sport-related compression FNSFs to date ($n = 27$), Ramey *et al.*^[56] reported a return to sport rate of 100% for conservative management, with a mean return to sport time of 14.1 wk. Return times were noted to increase with worsening severity of fracture on the Arendt Scale (Grade 1: 7.4 wk, Grade 2: 13.8 wk, Grade 3: 14.7 wk, Grade 4: 17.5 wk)^[56]. Reports of surgically managed compression FNSFs in the athlete are limited, and none provide formative sporting outcome data^[57].

For both conservative and surgical management, recommended rehabilitation techniques advise 6 wk toe-touch weightbearing with crutches, followed by 6 wk partial to full weightbearing with crutches^[1,5,8,15,54-56]. Hydrotherapy and upper limb exercises can be commenced 2 wk post-immobilisation^[36]. After this, weightbearing is permitted as tolerated, and return to sport is performed in a graduated manner under the care of the physiotherapy team^[1,5,8,15,54-56]. Full level sport should only be commenced once there is clear evidence of clinical and radiological union. Clinical and radiographic follow-up should be maintained for a minimum of 2 years to ensure delayed post-treatment AVN does not ensue^[1,5,8,15,54-56].

Validated prevention interventions include education programmes to promote physiological optimisation prior to engaging in rigorous activity, as well performing progressive training regimes (limit training volume

increases to 10%) and limiting training volumes within recommended targets (around 160 km over a 12 wk when starting)^[8,37-39].

Femoral shaft

Most commonly seen in running athletes and lacrosse players, these fractures mainly develop on the medial compression side of the femoral shaft, within the proximal and middle thirds of the bone^[1,5,15,24]. Plain radiographs form the first line of imaging; however, radiographic changes can be absent in up to 80% of cases^[25]. With persisting symptoms and negative radiographs, the second line imaging of choice is now MRI Scan^[24].

Current management protocols direct management based on the extent, nature and location of the fracture^[1,5,15,24]. The majority of femoral shaft stress fractures are incomplete, non-displaced and compression-sided, and these can be successfully treated by a period of activity cessation, restricted weightbearing with crutches, for 4 wk, followed by a graduated return to activity^[1,5,15,24]. Return times to sport following such regimes are normally around 12 wk^[1,5,15,24,58]. Surgical intervention should be considered for displaced fractures, tension-sided (lateral cortex) fractures, delayed union, and non-unions^[1,5,15,24]. Surgical techniques available include femoral IM Nailing and lateral sided compression plating. The preferred surgical technique is currently the femoral IM Nail as this provides the strongest biomechanical construct to stabilise the fracture site and allow healing^[1,5,15,24].

For conservative management, recommended rehabilitation programmes advise 4 wk toe-touch weightbearing, with progression to full weightbearing as pain permits^[1,5,15,24,58]. With this injury, it is normally possible to return to light athletic training within 6 wk and to commence full level sport within 3 mo^[1,5,15,24,58]. Regular follow-up, with interval radiographs, is required to ensure the fracture progresses to union; return to full level sport should only be performed with clear evidence of clinical and radiological union^[1,5,15,24,58]. For surgical management, recommended rehabilitation programmes advise commencement of a progressive weight-bearing programme within 1 wk post-operatively, with return to full-impact loading activities between 6 to 8 wk post-operatively^[1,5,15,24]. This is then followed by a progressive return to activity programme, under the guidance of the physiotherapists, with return to sport often achieved between 12 to 16 wk post-operatively^[1,5,15,24]. Full level sport should only be commenced once there is clear evidence of clinical and radiological union^[1,5,15,24].

Validated prevention interventions include education programmes to promote physiological optimisation prior to engaging in rigorous activity, as well as performing progressive training regimes and appropriate limitation of training volumes^[8,37-39].

Calcaneus

Reported in long distance runners and basketball

players, these fractures most commonly develop on the posterosuperior aspect of the calcaneus, but can also develop on the anterior process or the medial tuberosity of the calcaneus^[15,23,41]. Plain radiographs form the initial imaging investigation, and are often positive when the condition is present, with as many as 87% of cases showing positive X-ray findings^[25]. This is most often seen as an area of sclerosis, which traverses perpendicular to the trabeculae of the postero-superior calcaneus^[15,23,24,41]. When radiographs are negative, and symptoms persist, MRI scan is the preferred second line imaging investigation, allowing exclusion of associated differential diagnoses such as plantar fasciitis, Achilles tendinosis and retrocalcaneal bursitis^[24].

Current management protocols advocate conservative management for these injuries, in the form of cessation of activity and immobilisation in a moon boot or below knee cast, non-weightbearing for 4 wk, then partial weight-bearing for a further 4 wk^[15,23,41,59]. For conservative management, return rates post injury is 100%, with return times ranging between 11 to 12 wk^[23,59]. Surgical management is reserved for fracture which fail to unite despite prolonged compliant conservative management; the current recommended treatment is drilling of the fracture site, with or without bone graft^[60]. Occasionally the fracture is associated with a Calcaneo-Navicular Coalition; in such cases, if the fracture fails to heal with conservative management, excision of the coalition with fixation of the fracture should be considered^[61,62].

Recommended rehabilitation techniques following conservative management advise 4 wk of non-weight-bearing with crutches in a moonboot, followed by 4 wk partial weightbearing, and then a progressive return to exercise programme under the care of the physiotherapy team^[15,23,41,59].

There are no validated primary prevention interventions for the fracture type at present^[21,22]. However, padded heel orthotics and stretching exercises of the calf muscles and plantar fascia have been shown to be valuable secondary prevention measures^[15,23,41].

Case 1: An anterior tibial diaphyseal stress fracture

A 25-year-old professional ballet dancer presented to the Sports Medicine Clinic with a 6 mo history of atraumatic left anterior shin pain. She was otherwise in good health. Radiographs revealed an anterior stress fracture of the tibial diaphysis (Figure 1A). The limb was distally neuro-vascularly intact and the overlying skin was healthy. Her blood tests (bone profile and biochemistry) were normal and her body mass index (BMI) was 20 kg/m². With the distinct radiographic changes, demonstrating a clear fracture line, MRI scan was not felt to be necessary.

Following an informed discussion in clinic, she was advised that the first line treatment for this injury was conservative management, with activity cessation, cast immobilisation for 6 wk and limited weightbearing for at least 3 mo, followed by progression of weightbearing,

as pain allowed. She was in agreement with this.

After 3 mo of conservative treatment, she was still very painful at the fracture site, with limited evidence of healing on radiographs. She was advised that, given the limited clinical and radiological progress, surgical intervention was now recommended to aid fracture union. Following an informed discussion regarding the risks and benefits of surgery, she decided to proceed with surgical management, and, later that week, underwent a tibial intra-medullary nail uneventfully (Figure 1B).

Post-operatively, she engaged upon a progressive weight-bearing programme over the following 3 mo, under the care of physiotherapy. She returned to light dancing activities 4 mo post-surgery, and returned to full-level dancing 6 mo post-surgery.

At 2 years follow-up, she reports occasional anterior knee pain, but has no pain at the fracture site and radiographs show complete healing of the stress fracture.

Key message: Primary management of anterior tibial diaphyseal stress fractures comprise conservative management with rest, limited weight-bearing and activity modification, with a graduated return to activities as able. However, if, the patient remains symptomatic after 4 to 6 mo of conservative management, with limited evidence of healing on radiographs, surgical management should be considered, with either an intra-medullary nail or a compression plate.

Case 2: A postero-medial tibial diaphyseal stress fracture

A 24-year-old middle distance runner presented to the Sports Medicine Clinic with a 4 mo history of atraumatic posterior right lower limb pain. He was otherwise in good health. Radiographs revealed a posterior stress fracture of the tibial diaphysis (Figure 2). The limb was distally neuro-vascularly intact and the overlying skin was healthy. His blood tests (bone profile and biochemistry) were normal and his BMI was 23 kg/m². An MRI scan showed a Fredericson Grade 3 Postero-Medial Tibial Diaphyseal Stress Fracture.

Following an informed discussion in clinic, he was advised the recommended treatment for this injury was conservative management, with activity restriction and limited weightbearing in a well-padded moonboot, with progression of weightbearing as pain permits. He was in agreement with this.

Following 3 mo of conservative treatment, he was painfree over the fracture site, with clear evidence of healing on radiographs. He had returned to running training at 4 mo post-treatment, and competed successfully in a running race 6 mo post-treatment.

At 2 years follow-up, he reports no symptoms and continues to participate at high level middle distance running.

Key message: Primary management of posterior tibial diaphyseal stress fractures is conservative management with activity modification and limited weightbearing

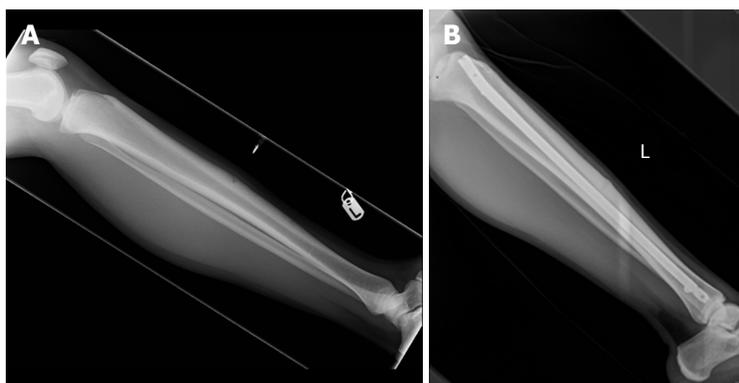


Figure 1 The management of an anterior tibial diaphyseal stress fracture. A: Pre-operative lateral radiograph; B: Post-operative lateral radiograph.



Figure 2 The management of a postero-medial tibial diaphyseal stress fracture. Diagnostic lateral radiograph.

with a graduated return to activities as able. This can be supplemented by pneumatic bracing and ultrasound therapy, both of which has been shown to improve return to sport times.

Case 3: A tension-sided femoral neck stress fracture

A 24-year-old marathon runner presented to the Emergency Department with severe right groin pain after completing a marathon the previous day. She had been training incrementally for this over the last 3 mo and has noted worsening right groin pain for the last month. This was only present during exercise and her coach diagnosed it as ilio-psoas tendinitis. There was no preceding trauma. She was otherwise in good health. Radiographs revealed a minimally displaced tension-sided fracture of the lateral femoral neck (Figure 3A). The limb was distally neuro-vascularly intact and the overlying skin was healthy. She reported pain with full flexion of the hip and with axial compression of the hip. Otherwise her pain was minimal at rest. Her blood tests (bone profile and biochemistry) were normal and her BMI was 19 kg/m². With the distinct radiographic changes, demonstrating a clear fracture line, MRI Scan was not felt to be necessary.

She was admitted as an in-patient and kept on strict bed rest. Following discussion with the on-call consultant in the morning ward round, she underwent Dynamic Hip Screw fixation that day (Figure 3B).

Post-operatively she was kept toe-touch weight-

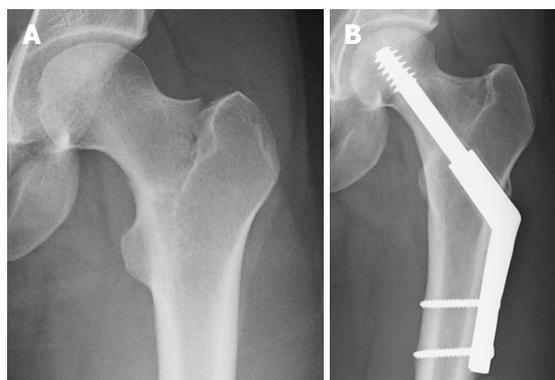


Figure 3 The management of a minimally-displaced tension sided femoral neck stress fracture. A: Pre-operative antero-posterior radiograph; B: Post-operative antero-posterior radiograph.

bearing with crutches for 6 wk, followed by partial weight-bearing with crutches for a further 6 wk. After this, she was allowed to weight-bear as pain permitted, and progressed in a graduated exercise programme under the care of the physiotherapists. Lower limb athletic activity was commenced 18 wk post-surgery, with clear evidence of fracture union radiologically and no pain clinically. With further input from physiotherapy, she returned to running at 6 mo post-surgery, and competed in a marathon again 10 mo post-surgery.

She had dedicated follow-up over 2 years with sequential radiographs to assess that the fracture united and that the fixation did not lose reduction or displace.

At 2 years follow-up, she reports occasional pain at the fracture site with prolonged exercise, particularly in the cold, though her radiographs show complete healing of the stress fracture.

Key message: Primary management of a minimally displaced lateral femoral neck stress fracture comprises of surgical fixation, with a Dynamic Hip Screw, ideally within 24 h of presentation.

Case 4: A compression-sided femoral neck stress fracture

A 20-year-old middle distance runner presented to the Sports Medicine Clinic with a 3 mo history of worsening atraumatic exercise-related left groin pain. He had

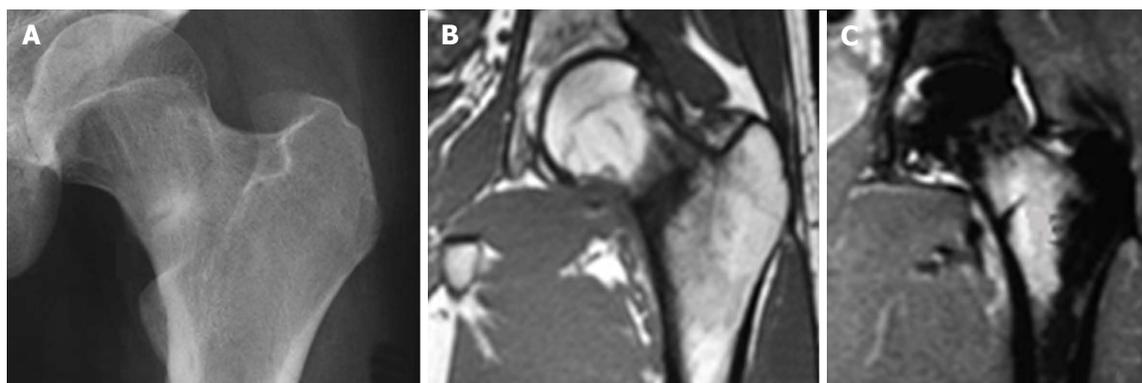


Figure 4 The management of an undisplaced compression sided femoral neck stress fracture. A: Diagnostic antero-posterior radiograph; B: Diagnostic T1 sequence coronal-plane magnetic resonance imaging (MRI) view; C: Diagnostic short tau inversion recovery sequence coronal-plane MRI view.

been training incrementally over the last 4 mo and had noted worsening left groin pain for the last month. This was initially felt to be a groin sprain and treated with analgesia and exercise modification. He was otherwise in good health. Radiographs revealed a compression sided fracture of the medial femoral neck (Figure 4A). The limb was distally neuro-vascularly intact and the overlying skin was healthy. He had mild pain at full flexion of the hip as well on axial compression, but otherwise the hip was painfree. His blood tests (bone profile and biochemistry) were normal and his BMI was 22 kg/m².

He was placed on crutches, non-weightbearing, and underwent a MRI scan which showed a compression fracture which extended 25% across the width of the femoral neck (Figure 4B and C).

Following discussion in clinic, he was advised that the recommended treatment for this was conservative management, with limited weightbearing on crutches, followed by a progressive weight-bearing regime, as pain allows, under the supervision of the physiotherapists.

He was kept partial weight-bearing, with crutches for 6 wk, and then underwent progressive weightbearing as pain allowed. Lower limb athletic activity was commenced in a graduated manner 10 wk post-diagnosis, with input from physiotherapy, as there was clear evidence of fracture union radiologically, and clinically there was no pain. With further guidance from physiotherapy, he returned to running at 6 mo post-diagnosis, and returned to racing 9 mo post diagnosis.

He had dedicated follow-up over 2 years with sequential radiographs to assess that the fracture united and did not displace.

At 2 years follow-up, he reports no symptoms and his radiographs show complete healing of the stress fracture.

Key message: The first line management of undisplaced medial-sided compression femoral neck stress fractures, which extend less than 50% of the femoral neck width, is conservative management, with limited weight bearing using crutches, followed by a

progressive weight-bearing programme and then a return to exercise programme, under the supervision of the physiotherapy team.

Case 5: A medial malleolar stress fracture

A 21-year-old high performance middle distance runner presented to the Sports Medicine Clinic with a 4 mo history of atraumatic medial ankle pain. He was otherwise in good health. Radiographs revealed an undisplaced completed medial malleolar stress fracture (Figure 5A). The limb was distally neuro-vascularly intact and the overlying skin was healthy. His blood tests (bone profile and biochemistry) were normal and his BMI was 23 kg/m². With the distinct radiographic changes, demonstrating a clear fracture line, MRI Scan was not felt to be necessary.

During an informed discussion in clinic, he was advised that both surgical and conservative management were options, with surgical management most likely offering a quicker return time to sport but with the risk of developing surgical complications. Due to a desire to return to sport as quickly as possible, he chose to undergo surgical management of his fracture. The following day, he underwent fixation of his fracture with two 4.0-mm AO cannulated cancellous screws (Figure 5B).

Post-operatively, he was non-weight-bearing for 3 wk, and then he progressed to full weight-bearing in an Aircast cast boot. He returned to light running training 2 mo post-surgery, and to full-level sports 3 mo post-surgery.

At 2 years follow-up, he continues to participate at the same level of running he was at pre-injury. He reports occasional pain at the fracture site, particularly on prolonged running in the cold, but otherwise is asymptomatic and radiographs show complete healing of the stress fracture.

Key message: Primary surgical management of undisplaced completed medial malleolar stress fractures can result in improved return to sport times compared to conservative management, though this exposes the patient to the risk of surgical complications.

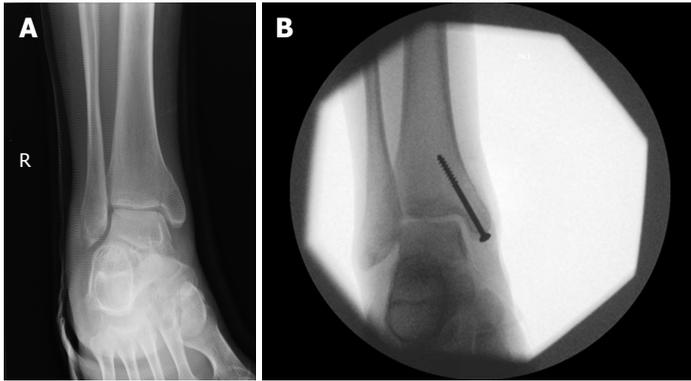


Figure 5 The management of an undisplaced completed medial malleolar stress fracture. A: Pre-operative antero-posterior radiograph; B: Intra-operative antero-posterior radiograph.

DISCUSSION

Within this editorial, we have outlined the currently recommended management strategies for the most common sport-related lower limb stress fractures, determining the treatments which offer the best proven results for the athlete, as well as the proven rehabilitation methods to allow the earliest return to sport possible. This is based on the most recent high quality literature in the field, derived from either systematic reviews or high impact clinical studies on each fracture type. With this, we have also reviewed the current evidence-based preventative interventions for each of the fracture types. Integration of the case studies then provides clinicians with a realistic perspective of how to manage such injuries in clinical practice. From this, we hope to provide clinicians with both a management framework for these injuries, along with, the most up-to-date evidence-based information on their treatment; this should allow provision of a systematic and evidence-based approach to assessing and treating lower limb sport-related stress fractures in their practice.

Areas found to be of particular value in the management of these injuries, were the site specific classifications, which were effective in guiding treatment and prognosis of these injuries^[1,16-19,54]. As such, we recommend the development of further evidence-based classifications for lower limb sport-related stress fractures.

Areas requiring further clarification in the management of these injuries include the role for surgical management of certain high risk injuries, the optimal surgical modality in such cases, and the optimal rehabilitation methods for each fracture type, particularly the role for various adjuncts such as air casts^[1-6,14,15,44]. Further work is required in these areas to better define the optimal treatment methods of these injuries.

The provision of optimal care when managing sport-related stress fractures is vital to maximise return rates to sport, to minimise return times and to limit persisting symptoms and recurrence of injury^[1,14,15,23]. The treatment of these injuries is specific to the location and the nature of the fracture, and a specialist knowledge of the topic

is required to provide optimal management^[1-4,6,8,14,15,23]. It is vital for clinicians to be appropriately informed of the common mode of presentation of these injuries, their optimal imaging modality and the most effective treatment strategies, in order to maximise the care of the athlete^[1,14,15,23,24]. The use of preventative measures against such injuries is an evolving concept, and can be a valuable aid to athletes and sports teams accordingly^[21,22]. Management of the high profile athlete remains a pressurised a situation, as time away from sport can have significant financial and social consequences, so specialist input from experienced personnel should be co-ordinated to ensure optimal care^[1].

In order to maximise the management and outcome of these injuries, it is essential that clinicians continue to participate and support in research in this area^[1,14,15,23]. All treating clinicians should keep documentation of their management and outcome of such injuries, allowing regular publication of relevant case series^[1,14,15,23]. Furthermore, well established specialists centres should co-ordinate more extensive cohort studies and epidemiological studies, to further establish the effects of variations in practice on outcomes^[1,14,15,23]. Where possible, randomised controlled trials in this field should be funded and supported, as these will provide "gold standard" evidence to determine the optimal treatment modalities of sport-related stress fractures^[1,14,15,23].

When managing such injuries, clinicians should remember to provide a holistic approach, performing a detailed assessment of each patient to establish predisposing risk factors, such as abnormal gait biomechanics or nutritional deficiencies, which should be addressed appropriately, to avoid recurrence of the condition. Similarly, when managing the female athlete, clinicians should always consider the female athlete triad as an underlying cause of the condition, assessing and managing this accordingly^[1,14,15,23]. Lastly, it should be noted that all athletes and clinicians should adhere to the established treatment principles that have been developed for these conditions^[1,14,15,23]. Such treatment protocols have been developed from well-organised research within military and sporting populations, both of

which provide robust patient cohorts. Thus any attempt to over-accelerate rehabilitation in the athlete, is likely to result in inadequate treatment and recurrence of the condition^[1,14,15,23]. With appropriate compliance to the recommended treatment, athletes should be reassured that outcomes from these injuries are largely positive, with high return rates to previous level sport and favourable return times^[1,14,15,23]. Given the importance of providing well-informed, individually directed care for such injuries in the high level athlete, it remains important that specialised sport physicians and sports surgeons provide care for these individuals, in order to optimise their management and outcome^[1,14,15,23].

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Basic Study

Spinal alignment evolution with age: A prospective gait analysis study

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Abstract

AIM

To describe, using gait analysis, the development of spinal motion in the growing child.

METHODS

Thirty-six healthy children aged from 3 to 16 years old were included in this study for a gait analysis (9 m-walk). Various kinematic parameters were recorded and analyzed such as thoracic angle (TA), lumbar angle (LA) and sagittal vertical axis (SVA). The kinetic parameters were the net reaction moments (N.m/kg) at the thoracolumbar and lumbosacral junctions.

RESULTS

TA and LA curves were not statistically correlated to the age (respectively, $P = 0.32$ and $P = 0.41$). SVA increased significantly with age ($P < 0.001$). Moments in sagittal plane at the lumbosacral junction were statistically correlated to the age ($P = 0.003$), underlining the fact that sagittal mechanical constraints at the lumbosacral

junction increase with age. Moments in transversal plane at the thoracolumbar and lumbosacral junctions were statistically correlated to the age ($P = 0.0002$ and $P = 0.0006$), revealing that transversal mechanical constraints decrease with age.

CONCLUSION

The kinetic analysis showed that during growth, a decrease of torsional constraint occurs while an increase of sagittal constraint is observed. These changes in spine biomechanics are related to the crucial role of the trunk for bipedalism acquisition, allowing stabilization despite lower limbs immaturity. With the acquisition of mature gait, the spine will mainly undergo constraints in the sagittal plane.

Key words: Sagittal balance; Spine biomechanics; Gait analysis; Thoracic kyphosis; Spine growth

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Core tip: Many postural changes occur during childhood, including the adaptation of the spine to maintain an erect posture. The aim was to describe, using gait analysis, the development of spinal motion during growth. Various kinematic parameters were recorded in 36 healthy children. Thoracic kyphosis and lumbar lordosis were not found to increase during childhood whereas sagittal vertical axis increased with age. The kinetic analysis showed a decrease of torsional constraint while sagittal constraint increased. These changes in spine biomechanics are related to the crucial role of the trunk for bipedalism acquisition, allowing stabilization despite lower limbs immaturity.

Pesenti S, Blondel B, Peltier E, Viehweger E, Pomero V, Authier G, Fuentes S, Jouve JL. Spinal alignment evolution with age: A prospective gait analysis study. *World J Orthop* 2017; 8(3): 256-263 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i3/256.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i3.256>

INTRODUCTION

With the acquisition of bipedalism, many anatomical and postural changes occurred in humans^[1-3]. Among these changes, an adaptation of the spine has been necessary to maintain an erect position, in combination with an adaptation of the pelvis and the lower limbs^[4-6]. Although gait acquisition is apparently complete by the age of 3, adaptation to erect posture continues until the end of growth. According to Peterson *et al*^[7], mature gait patterns are visible in children only from the age of 12.

With the development of modern tools for gait analysis, it is possible to obtain a precise evaluation of the kinematic and kinetic for different segments of the human body. While many of these tools have been developed for lower limbs analysis, various authors have demonstrated

their accuracy for trunk dynamic analysis^[8-10]. Many studies have described the evolution of spinal curvatures with radiological or other methods^[11,12]. Using these tools, it has been shown that thoracic kyphosis and lumbar lordosis increase with age.

To our knowledge, there is no evidence in literature about this development using gait analysis tools. Moreover, gait analysis provides dynamic data such as constraints applied to spinal joints, these parameters having never been discussed in literature before. The hypothesis of this work was that spinal motion changes all along growth. The aim of this study was to describe, using gait analysis, the development of spinal motion in the growing child.

MATERIALS AND METHODS

Study design

To obtain a homogenous pediatric cohort, only healthy volunteers were included in this prospective study after informed consent. Inclusion criteria were children aged from 3 to 16 years old, without known disease and volunteers to participate to the study. Exclusion criteria were every history of orthopedic or neurologic disorders, major orthopedic trauma or allergy to the components used for gait analysis.

Anthropometric data

For each participant, the following anthropometric data were collected for gait analysis: Age, weight, height, lower limb length and knee and ankle diameters.

Gait analysis

All measurements were obtained using an optoelectronic system (Vicon, Oxford, United Kingdom) with six high-resolution cameras with infrared light and a sampling frequency of 100 Hz which recorded the position of passive retroreflective markers and two force platforms (AMTI, United States). This protocol included all the markers necessary to obtain parameters of a standing posture and to calculate the force of external efforts in the different intersegmental centers, as described by Blondel *et al*^[13], according to the International Society of Biomechanics^[14,15].

Subjects were equipped with a set of 28 retroreflective markers as described in Table 1 and Figure 1. These markers allowed an analysis of different body segments such as head and neck, the scapular girdle, the thorax and thoracic spine, the abdomen and lumbar spine, the pelvis and the lower limbs.

Before the beginning of gait analysis, a short trial was performed to check the good positioning of the markers according to the analysis of knee valgus/varus^[16].

For gait analysis, subjects were asked to walk at a self-selected speed, barefoot, on a flat and straight 9 m-walkway. A minimum of seven trials was recorded to collect kinematic and kinetic data.

The data collected by the 6 high-resolution cameras were converted into a 3D model using NEXUS software

Table 1 Optoelectronic markers placement following anatomical landmarks according to Blondel *et al*^[13] gait analysis protocol

Parameters	
Head	Vertex: 1 Nasion: 1 Tragus: 2
Trunk - thorax	Acromion: 2 Manubrium: 1 Xiphoid: 1 C7: 1 T6: 1 T9: 1
Trunk - abdomen	T12: 1 L3: 1 S1: 1
Pelvis	ASIS: 2
Lower limbs - thighs	Femoral shaft: 2 Lateral femoral condyle: 2
Lower limbs - legs	Tibial shaft: 2 Lateral malleolus: 2
Lower limb - feet	Calcaneus: 2 2 nd metatarsal head: 2



Figure 1 Gait analysis model used for trunk motion assessment. Retroflective markers were placed according to anatomical landmarks, such as described by Blondel *et al*^[13] (Table 1). Six markers were used for spine motion.

Table 2 Kinematic parameters measured during gait analysis

	Frontal	Sagittal	Transversal
Overall balance		SVA Ad	
Shoulders			APA
Thoracic spine		TA	
Lumbar spine		LA	
Pelvis		Pelvic version	
Lower limbs	Knee Varus/valgus	Hip flex/ext Knee flex/ext	

SVA: Sagittal vertical axis; APA: Angle pelvis-acromion; TA: Thoracic angle; LA: Lumbar angle.

Table 3 Kinetic parameters measured during gait analysis

	Frontal moments	Sagittal moments	Transversal moments
Thoracolumbar junction	Lateral bending	Flexion-extension	Torsion
Lumbosacral junction	Lateral bending	Flexion-extension	Torsion

(Vicon Motion Systems, Oxford, United Kingdom) for the lower limbs and data were integrated to MATLAB software for trunk analysis.

The characteristic moments of the beginning and the end of the double stance phase were used to compare subjects.

For kinetic analysis, calculations were made from anthropometric reference tables^[17].

Gait parameters

Kinematic parameters during gait are described hereafter and summarized in Table 2 and Figure 2: (1) Sagittal Vertical Axis Adimensioned (SVA Ad): distance between

the marker "S1" and the vertical line passing by the marker "C7". This value was weighted by the height of the subject to be comparable between subjects, regardless to age and height (SVA Ad=SVA/Height). This parameter reflects trunk position during gait: A great value of SVA indicates that the trunk is leaning forward; (2) angle pelvis-acromion (APA): Angle defined in the transverse plane between the line joining the 2 "Acromion" markers and the line joining the 2 "anterosuperior iliac spine" markers. The APA-rom (range of motion) was calculated as the difference between the maximum and the minimum values of the APA during a gait cycle^[18]; (3) thoracic angle (TA): Angle between the "C7"- "T7" line and the "T9"- "T12" line; and (4) lumbar Angle (LA): Angle between the "T12"- "L3" line and the "L3"- "S1" line.

Kinetic parameters are detailed in Table 3. In frontal plane, moments applied to the spine are relative to lateral bending movements, in sagittal plane they are flexion-extension movements and in transversal plane, they were consecutive to torsional movements. These data were dimensioned (*i.e.*, divided by the weight) to be comparable between individuals, independently from their body mass.

Statistical analysis

Gait data were analyzed to compare subjects in a continuous analysis according to age. A Pearson Product Moment Correlation Coefficient (*r*) was used to determine differences between subjects according to age. Level of significance was set at 5% for every statistical analysis.

RESULTS

Demographic data

From October 2012 to October 2013, 36 subjects were included in this study. Mean age of the population was

Table 4 Details of demographic and anthropometric data

Subject No.	Sex	Age (yr)	Height (cm)	Weight (kg)	Lower limb length (cm)		Knee diameter (cm)		Ankle diameter (cm)	
					Right	Left	Right	Left	Right	Left
1	F	3.3	880	11	420	420	55	55	45	45
2	F	3.4	1060	17	510	510	80	80	60	60
3	M	3.9	935	14	500	500	70	70	44	44
4	F	3.9	1050	19	520	520	80	80	60	60
5	M	4.1	1080	18	550	550	70	70	50	50
6	F	4.6	1090	16	650	650	50	50	45	45
7	F	5.8	1135	19	570	570	70	70	50	50
8	M	6.1	1150	19	575	575	80	80	60	60
9	F	7.0	1345	27	670	670	90	90	65	65
10	F	7.2	1200	21	570	570	70	70	50	50
11	F	7.4	1160	21	585	585	80	80	60	60
12	M	7.7	1370	34	730	730	110	110	70	70
13	F	7.7	1300	31	680	680	95	95	70	70
14	F	7.8	1280	26	650	650	90	90	70	70
15	M	8.0	1340	27	680	680	90	90	70	70
16	M	8.1	1330	28	685	685	95	95	65	65
17	M	8.5	1360	33	710	710	90	90	55	55
18	M	8.8	1400	40	720	720	110	110	70	70
19	F	8.9	1380	37	720	720	100	100	65	65
20	M	9.1	1320	24	680	680	80	80	60	60
21	M	9.2	1420	26	750	760	55	55	50	50
22	F	9.3	1524	38	820	820	100	100	65	65
23	M	9.5	1395	36	750	750	110	105	65	65
24	F	10.0	1360	29	710	710	70	70	55	55
25	F	10.6	1370	39	740	740	95	95	60	60
26	F	10.8	1425	32	750	750	90	90	65	65
27	F	11.0	1530	41	810	810	105	105	70	70
28	M	11.1	1520	51	850	850	100	100	70	70
29	F	11.1	1463	47	740	740	105	105	70	70
30	F	11.3	1610	46	840	840	105	105	70	80
31	M	11.9	1390	34	700	700	85	85	60	60
32	F	12.5	1470	35	740	740	100	100	70	70
33	F	12.7	1570	54	900	900	115	110	75	70
34	F	13.9	1690	47	925	925	100	100	70	70
35	M	15.5	1650	48	830	830	85	85	65	65
36	M	15.6	1770	87	930	930	100	100	70	70

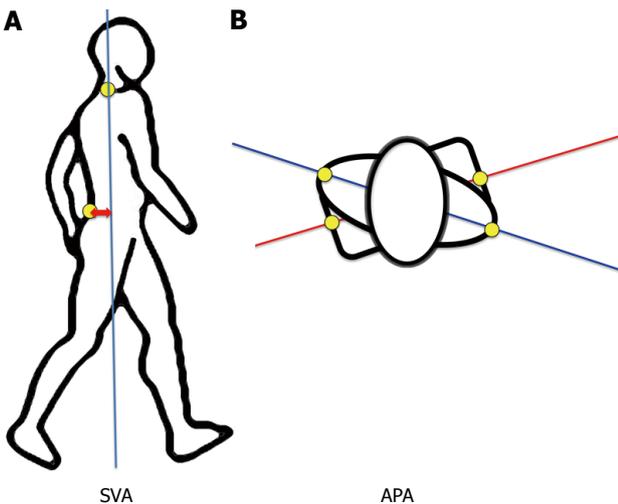


Figure 2 Sagittal vertical axis and angle pelvis-acromion. A: SVA was defined as the distance between the marker "S1" and the vertical line passing by the marker "C7". This parameter reflects trunk position during gait: A great value of SVA indicates that the trunk is leaning forward; B: APA was defined as the angle between the line joining the 2 "Acromion" markers and the line joining the 2 "anterosuperior iliac spine" markers. SVA: Sagittal vertical axis; APA: Angle pelvis-acromion.

8.8 years old (3.3 to 15.6 years old). Demographic and anthropometric data are shown in Table 4.

Gait analysis: Kinematics

Sagittal plane: TA and LA curves were not statistically different (respectively, $r = 0.06$ and $r = 0.023$, $P = 0.32$ and $P = 0.41$, Figure 3).

SVA Ad was significantly correlated to the age ($r = 0.488$, $P < 0.001$), revealing a progressive anterior increase of the projection of the C7 marker with regards to the S1 marker (Figure 4).

Transversal plane: There was a non-significant negative correlation between APA-rom and age ($r = -0.063$, $P = 0.71$).

Gait analysis: Kinetics

Sagittal plane: Results showed that flexion-extension moments at the lumbosacral junction were statistically correlated to age ($r = 0.356$, $P = 0.003$). In other words, mechanical sagittal constraints at the lumbosacral junction increase during growth. At the thoracolumbar

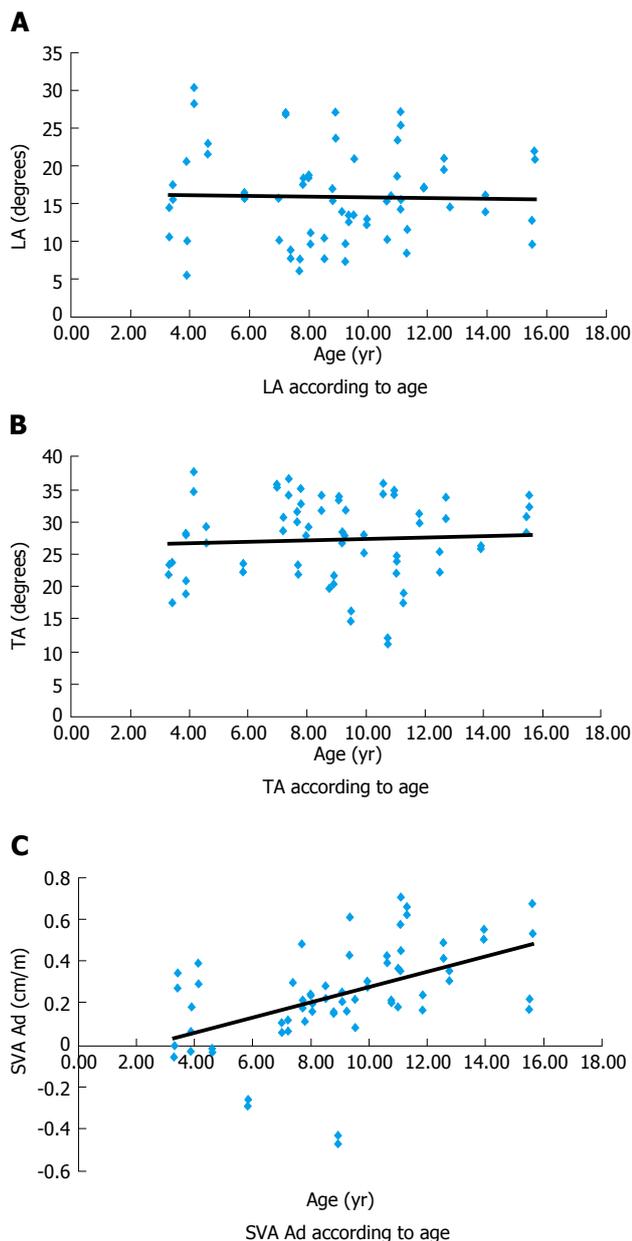


Figure 3 Continuous analysis of kinematic parameters according to the age. A: TA; B: LA; C: SVA. TA: Thoracic angle; LA: Lumbar angle; SVA: Sagittal vertical axis.

junction, sagittal constraints were not significantly correlated to age ($r = 0.189, P = 0.13$, Figure 5).

Transversal plane: Results demonstrated that torsion moments at thoracolumbar and lumbosacral junctions were statistically correlated to age ($r = -0.613$ and $r = -0.563, P = 0.0002$ and $P = 0.0006$). In other words, transversal mechanical constraints at thoracolumbar and lumbosacral junctions decrease with age (Figure 6).

DISCUSSION

This study is the first to analyze spinal motion in children *via* gait analysis tool. Changes occur in spine motion in children with the acquisition of a mature gait

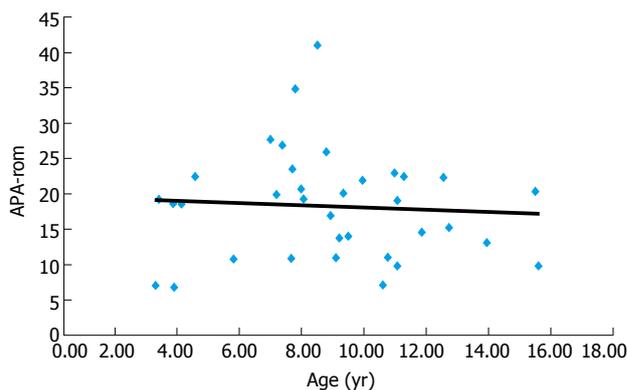


Figure 4 Continuous analysis of angle pelvis-acromion-rom according to the age. APA: Angle pelvis-acromion.

even if dynamic parameters of the spine during growth seem to be established before the age of 3.

So far, only few studies have studied dynamic development of the spine according to age *via* gait analysis^[19]. The studies from Wagner *et al*^[20] and Farfan^[21] showed that the presence of a lumbar spinal curvature concave toward the back is a necessary biomechanical condition for a stable erect posture, enabling an economic muscular functioning despite the posterior position of the spine. Lumbar lordosis thus appears as being a fundamental prerequisite to bipedalism, explaining its early appearance during childhood. Parameters determining bipedalism are acquired very early during growth^[21,22]. However, some skeletal parameters which are not involved in the acquisition of bipedalism are variable and change until the end of growth. Some of these parameters are even found to be genetically predetermined during fetal life. This is, for example, the case of the morphology of the femoral trochlea^[23] or the lumbar lordosis^[24], which are genetically predetermined in humans. Their early kinematic setting is an element explaining the ability to bipedalism.

The spine appears to be of fundamental importance in the adaptation of the skeleton to bipedalism and we can define a real "spinal motor of bipedalism"; the spine being the first skeletal element to adjust its posture and functioning to bipedalism as the main element of locomotion^[25]. The lower limbs adapt secondarily, around the age of 7, with a progressive pelvic anteversion, a progressive extension of the hips and the knees, lately mature.

Some radiographic and morphologic studies have evaluated the development of spinal curvatures during growth^[11,12]. These studies revealed that from the age of 3 years until skeletal maturity, there is a linear enhancement of the thoracic kyphosis and lumbar lordosis. According to us, these changes do not reflect the adaptation of the skeleton to bipedalism, but an adaptation to the major constraints applied to the trunk during growth. In other words, formation of overlying sagittal curvatures to the lumbar lordosis with the appearance of thoracic kyphosis and cervical lordosis is related to biomechanical adaptation to an increase of load on the

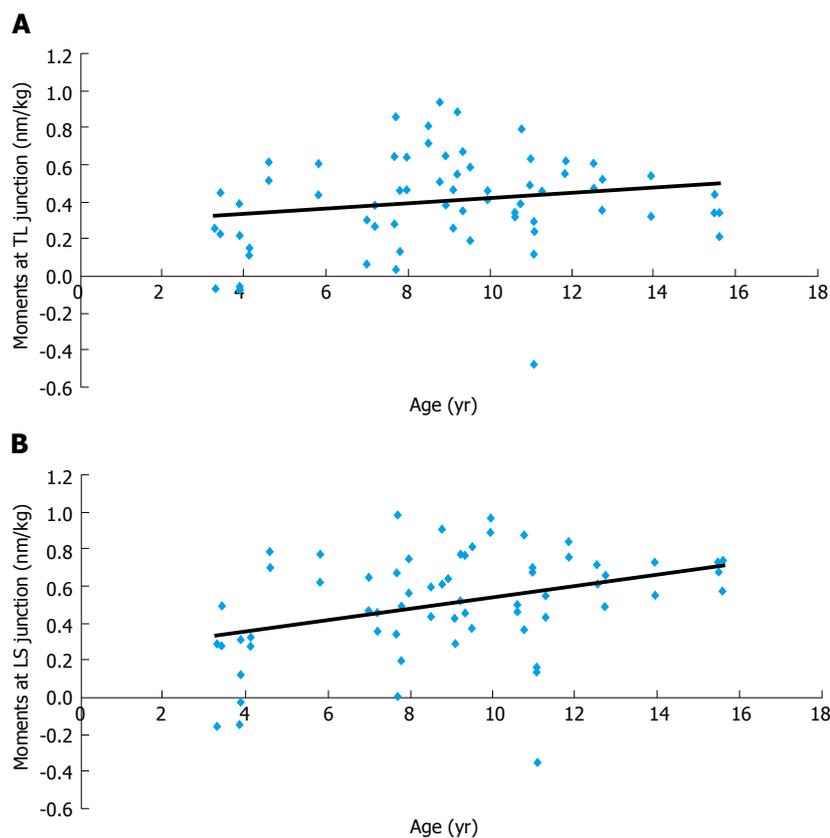


Figure 5 Sagittal kinetic parameters of the trunk according to the age. A: TL; B: LS. Frontal plane constraints are relative to flexion-extension movements. TL: Thoracolumbar; LS: Lumbosacral.

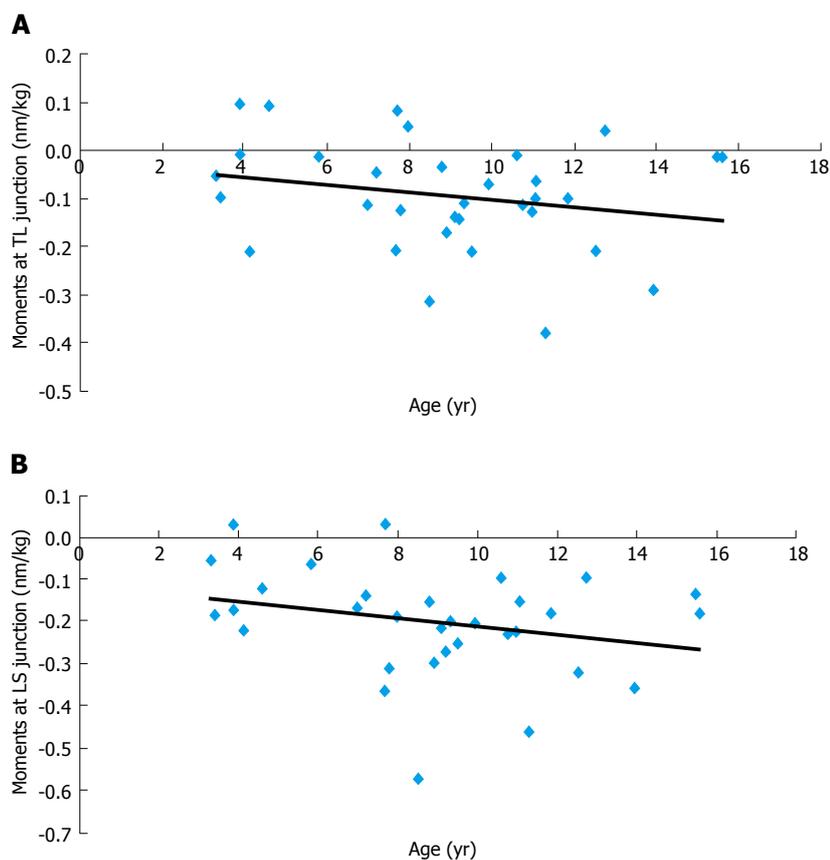


Figure 6 Transversal kinetic parameters of the trunk according to the age (continuous analysis). Transversal plane constraints are relative to torsional movements of the trunk. TL: Thoracolumbar; LS: Lumbosacral.

spine.

Most of the parameters used in this study for kinematic analysis, such as SVA, were chosen according to previous works^[18]. These parameters seemed to be good descriptors because they are the dynamic equivalent of radiographic parameters. Thoracic angle and lumbar angle were meant to be the equivalent of thoracic kyphosis and lumbar lordosis, which are 2 radiographic parameters used in clinical practice.

Results from this study suggest that the sagittal efforts applied on the spine increase significantly with age leading to increased flexion-extension constraints at the lumbosacral junction. This phenomenon can be explained by the accentuation of spinal curvatures with age as a response to the increased load on the spine, deporting the lumbar spine forward and thereby increasing the lever arm and the moment applied to the underlying lumbosacral junction.

With regards to the kinetic parameters in the transverse plane, our results showed a significant reduction in torsional constraints at the thoracolumbar and lumbosacral junctions during growth. Although lumbar lordosis is acquired from fetal life, the central maturation processes coordinating the acquisition of a mature gait for the lower limbs appear only around the age of 7. Before this turning point, the lower limbs do not have a mature kinematics allowing balance and stability for satisfactory and stable erect posture. These results are in line with the posturographic study from Peterson *et al.*^[7] who have shown that sensory systems ensuring a satisfactory balance for maintaining erect station were efficient only from the age of 12. Thus, the spine undergoes greater constraints to compensate this permanent balance research. Large constraints applied to the spine and their reduction with age are a sign of the compensation by the trunk of a lack of stability due to lower limbs and sensory system immaturity. Prior to the acquisition of a definitive and mature bipedalism, the trunk is fundamental for the possibility of early bipedalism.

Furthermore, the significant increase of SVA during growth could be related to the same conclusion. The low value of SVA in young children reflects the need to keep the shoulders over the pelvis to stabilize the erect posture. With maturation and the acquisition of a final biped balance, the subject is projected more forward, then changing the direction of the constraints on the spine from the transverse plane to the sagittal plane.

These findings allow a better comprehension of the importance of constraints in the lumbar spine and can be a source of explanation for specific degenerative disorders of this anatomical region.

The small number of subject in each age group may be at the origin of a lack of statistical power and may explain the lack of significant difference. However, in similar series, changes in lower limb parameters are clearly established, these parameters being definitively acquired after the age of 7^[26-31]. The protocol used for trunk assessment has been validated before in the study by Blondel *et al.*^[13]. This protocol is designed for clinical use and a low number of markers is a clear advantage

in that case. The authors have demonstrated that 6 markers were sufficient to assess trunk kinematics and kinetics precisely. Moreover, there was a wide amount of variability. Including a greater number of subjects may increase statistical power and allow to highlight differences in sagittal kinematic parameters.

The biomechanical model developed by Blondel *et al.*^[13] in adults has enabled us to achieve the first dynamic study of spine development with age. The comparison of age groups and continuous analysis did not highlight major kinematic evolution of spinal curvatures during skeletal maturation. The acquisition of the lumbar lordosis and thoracic kyphosis is a morphological characteristic that probably appears very early in children, before the age of 3.

The kinetic analysis revealed a progressive decrease in torsional constraints applied on the spine while the constraints in flexion-extension increase with age. These changes allow stabilization of erect posture despite the immaturity of the lower limbs. With the acquisition of mature gait, the spine will mainly undergo constraints in the sagittal plane. These changes point out the major role of the trunk during the acquisition of bipedalism.

COMMENTS

Background

Although gait acquisition is apparently complete by the age of 3, adaptation to erect posture continues until the end of growth. Many studies have described the evolution of spinal curvatures with radiological methods. Using gait analysis tools, it is possible to obtain a precise analysis of the evolution of spinal alignment with age.

Research frontiers

Even if the sample size is quite limited, this study provides interesting information about evolution of spinal dynamics with growth. This study may help to understand changes in gait in spinal disorders.

Innovations and breakthroughs

Results from this study confirm the technical feasibility of the protocol in young children. Using this methodology, it was possible to evaluate net moments applied to spinal junctions. To the authors' knowledge, this the first study to provide dynamic data of the spine of healthy children.

Applications

By providing normative data, this study may help to understand the changes that occur in children with spinal disorders. It could also help to evaluate the behavior of the spine in children after spinal surgery.

Peer-review

Although the sample size is relatively small, this is an interesting study.

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Retrospective Cohort Study

Results of single stage exchange arthroplasty with retention of well fixed cement-less femoral component in management of infected total hip arthroplasty

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Institutional review board statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved with institutional review board of sunny brook health science hospital University of Toronto. Toronto, Ontario, Canada.

Informed consent statement: Informed consent was obtained from all individual participants included in the study.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at dr.waelrahman@gmail.com. Participants gave informed consent for data sharing.

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Abstract**AIM**

To investigate success of one stage exchange with retention of fixed acetabular cup.

METHODS

Fifteen patients treated by single stage acetabular component exchange with retention of well-fixed femoral component in infected total hip arthroplasty (THA) were retrospectively reviewed. Inclusion criteria were patients with painful chronic infected total hip. The patient had radiologically well fixed femoral components, absence of major soft tissue or bone defect compromising, and infecting organism was not poly or virulent micro-organism. The organisms were identified preoperatively in 14 patients (93.3%), coagulase negative Staphylococcus was the infecting organism in 8 patients (53.3%).

RESULTS

Mean age of the patients at surgery was 58.93 (\pm 10.67) years. Mean follow-up was 102.8 mo (36-217 mo, SD 56.4). Fourteen patients had no recurrence of the infection; one hip (6.7%) was revised for management of infection. Statistical analysis using Kaplan Meier curve showed 93.3% survival rate. One failure in our series; the infection recurred after 14 mo, the patient was treated successfully with surgical intervention by irrigation, and debridement and liner exchange. Two complications: The first patient had recurrent hip dislocation 12 years following the definitive procedure, which was managed by revision THA with abductor reconstruction and constrained acetabular liner; the second complication was aseptic loosening of the acetabular component 2 years following the definitive procedure.

CONCLUSION

Successful in management of infected THA when following criteria are met; well-fixed stem, no draining sinuses, non-immune compromised patients, and infection with sensitive organisms.

Key words: Total hip arthroplasty; Infection; One stage exchange; Complication

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Core tip: Peri-prosthetic hip infection is a devastating complication: We hypothesized that a well-fixed circumferentially ingrown cement-less stem can act as a shield and prevent the spread of pathogens and formation of biofilm around the body of the femoral stem. Therefore, single stage exchange of the acetabular component with retention of the well-fixed femoral component can be a successful option in management of infected total hip arthroplasty, when the following criteria are met; well-fixed femoral component, no draining sinuses, non immune compromised patients, and infection with sensitive organisms.

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INTRODUCTION

Peri-prosthetic hip infection is a devastating complication, up to 2% of primary total hip arthroplasty (THA) and 4%-6% after revision THA are complicated by infection^[1,2]. The goal of treatment is eradication of infection and durable functional reconstruction^[3,4]. There are variable surgical options for management of infected THA. Two-stage exchange arthroplasty has been considered the

gold standard treatment^[5-7]. However, it is expensive and associated with high rates of surgical morbidity^[8-11]. One-stage exchange arthroplasty remains an attractive alternative option since it requires only one operation, and is associated with shorter hospital stay and faster rehabilitation^[12-15]. Previous studies have shown good results of single stage exchange arthroplasty with preservation of a well-fixed cement mantle^[16].

Hypothesis

We hypothesized that a well-fixed circumferentially ingrown cement-less stem can act as a shield and prevent the spread of pathogens and formation of biofilm around the body of the femoral stem. Therefore, single stage exchange of the acetabular component with retention of the well-fixed femoral component can be a successful option in management of infected total hip arthroplasty, when the following criteria are met; well-fixed femoral component, no draining sinuses, non immune compromised patients, and infection with sensitive organisms. Failure of treatment was defined by recurrence of infection that required either further surgical intervention or the use of long-term suppressive antibiotics.

MATERIALS AND METHODS

Research Ethics Board approved this retrospective study at our institution. The Electronic Patient Record was searched for the patients who had single stage acetabular component exchange with retention of a well-fixed femoral component in management of infected THA.

From January 1997 to January 2012, 15 hips in 15 patients (9 females and 6 males) were managed with single stage acetabular component exchange with preservation of well-fixed femoral component. Inclusion criteria were patients with painful chronic infected total hip diagnosed with elevated erythrocyte sedimentation rate (ESR, \geq 30 mm/h) and /or C-reactive protein (CRP, \geq 20 mg/L) and/or elevated white blood cell count $>$ 11000. The patient had the following criteria; radiologically well fixed femoral components, absence of major soft tissue defect compromising wound closure and/or bone defect affecting implant stability, and infection was not associated with culture of polymicrobial or antibiotic resistant micro-organism in the preoperative hip aspiration culture.

Our exclusion criteria were patients presented with a sinus tract communicating with the prosthesis, culture of MRSA or poly-microbial infection, immunocompromised patients, patients treated previously for management of infected THA with either one or two stage exchange arthroplasty, radiological signs of loosening of the femoral component, and if the femoral component was discovered to be loose during the surgical procedure.

All the patients included in the study were consented for single stage acetabular component exchange or two-

Table 1 Patients demographic characteristics and comorbidities

Patient	Sex	Age	Pre ESR	Pre CRP	Re culture	Complication	Revision details	Culture in revision	Failure
1	F	38	NA	NA	Gram negative cocci	Recurrent dislocation	Constrained liner	None	No
2	F	44	37	27	Coagulase negative staph			None	No
3	F	47	33	44	Beta hemolytic strept			None	No
4	F	53	50	46	Beta hemolytic strept	Aseptic loosening acetabular component	Revision cup	None	No
5	F	55	50	80	No growth				No
6	F	65	44	57	Beta hemolytic strept				No
7	F	68	30	26	Coagulase negative staph				No
8	F	70	55	82	Beta hemolytic strept				No
9	M	77	60	130	Coagulase negative staph				No
10	M	58	50	30	Coagulase negative staph	Infection	Debridement and liner exchange	Coagulase negative staph	Yes
11	M	60	65	102	Coagulase negative staph				No
12	M	65	49	86	Coagulase negative staph				No
13	M	65	63	30	Coagulase negative staph				No
14	M	52	25	45	Gram negative cocci				No
15	M	68	24	40	Coagulase negative staph				No

F: Female; M: Male; NA: Not available.

Table 2 Patient details, laboratory results, microorganism, and success of the procedure

Characteristics	n of patients
Hip joints	15
Gender	
Male	6
Female	9
Age at index surgery: Mean, (SD), range	58.93 yr, SD 10.6 (range; 38-76 yr)
BMI kg/m ² , SD, range	30, SD 8.8 (range; 18-51)
ASA INDEX	
I	3
II	5
III	6
IV	1
Smoking	
Non smoker	11
Smoker	4
Comorbidities	
Diabetes mellitus	2
Hypertension	6
Rheumatoid arthritis	1
Hyperlipidemia	2
Patients with previous cardiac history (myocardial infarction)	1

BMI: Body mass index.

stage exchange arthroplasty if the were intra-operative finding of loose femoral component, or highly contaminated hip joint with purulent material and extensive damage of the soft tissue.

Mean age of the patients at operation was 58.93 years (range; 38-76 years, SD 10.6). Patient body mass index averaged 30 kg/m² (range; 18-51 kg/m², SD 8.8). ASA level was I (n = 3), II (n = 5), III (n = 6), and IV (n = 1). Eleven patients were non-smokers, while 4 patients were smokers. The patients had the following comorbidities; diabetes mellitus (n = 2), hypertension (n = 6), myocardial infarction (n = 1), hyper lipidemia (n = 2) and rheumatoid arthritis (n = 1) (Table 1).

Surgical procedures before infection were primary total hip arthroplasty in (n = 11), and revision total hip arthroplasty in (n = 4); cup revision for aseptic loosening of the acetabular component (n = 1), linear exchange for management of poly wear (n = 1) and irrigation and debridement for management of acute infection in (n = 2). The mean interval between the previous primary total hip arthroplasty and single stage acetabular component exchange was 78.6 mo, SD 75.86 (range; 12-242 mo).

The organisms were identified from the aspirated fluid before single stage acetabular component exchange in 14 patients (93.3%), no organism was identified in 1 hips (6.7%), coagulase negative staphylococcus was the infecting organism in 8 patients (53.3%). Details of the infecting organism are summarized in (Table 2). All the patients included in the study an un-cemented acetabular and femoral components.

During the operative procedure, aggressive debridement of the joint was performed; 5 tissue samples were sent for microbiological analysis. All the patients received intra-operative prophylactic antibiotics after obtaining the soft tissue cultures. All the femoral components were assessed intra-operatively and were well-fixed. Mechanical cleansing with diluted povidine- iodine was used to clean the exposed metal parts of the femoral component. The acetabular components were loose in 6 hips, fibrous ingrown in 6 hips, and well fixed in 3 hips which required use of the Explant system (Zimmer, Warsaw, IN, United States). The acetabular component, liner and femoral head were removed carefully with minimal damage of the bone stock (Figure 1).

A through irrigation was done again using 3 L of saline using pulsatile lavage and one liter of diluted povidine-iodine. The instruments were changed and the patients were re-draped before re-implantation. Cement less acetabular component, high cross-linked polyethylene liner, and cobalt chrome femoral head were used in all the patients included in the study. The acetabular components used in the definitive procedure

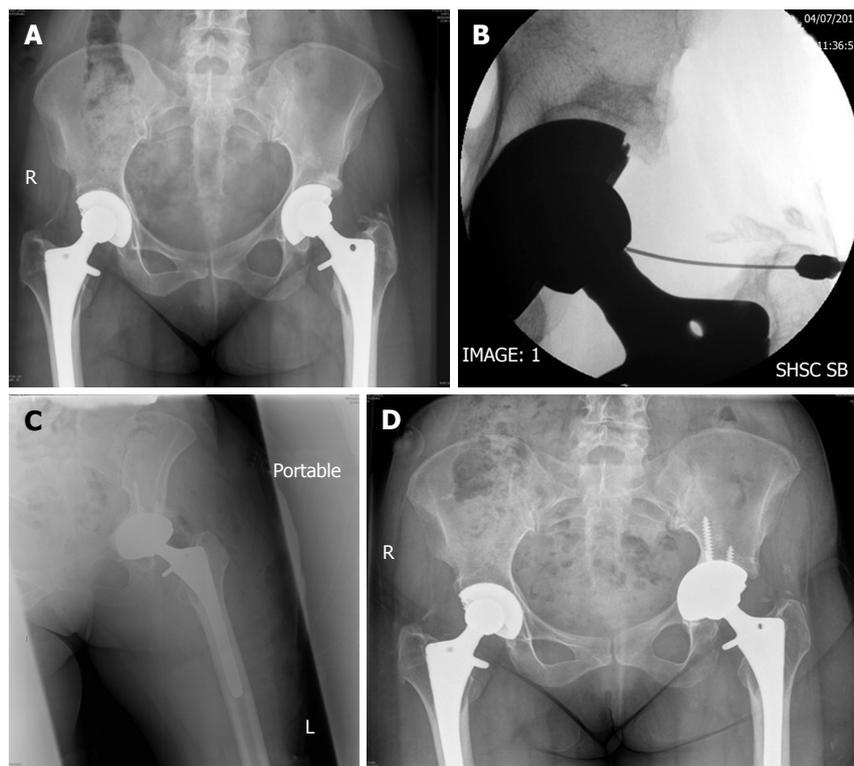


Figure 1 Case demonstration. A: Preoperative X-ray; B: Hip aspiration; C: Post operative X-ray; D: Five-year follow-up.

were as follows; Trilogy ($n = 13$), HGP II ($n = 1$) and Trabecular metal modular cup ($n = 1$) (Zimmer Inc., Warsaw, IN). No drain was used and closure of the hip abductors, Iliotibial band, and subcutaneous tissue were performed with non-absorbable suture (coated VICRYL; Ethicon, Johnson and Johnson, Cornelia, GA), followed by sub-cuticular suture for skin closure. AQUA CELL AG surgical dressing (ConvaTec INC, Greensboro, NC) was used for wound dressing.

All patients were evaluated and managed by the infectious diseases team in our hospital. Postoperatively, the patients were treated with broad-spectrum antibiotics until the results of the culture were available. Organism-specific IV antibiotics were administered for 6 wk. Antibiotics used were doxycycline ($n = 8$), Vancomycin ($n = 3$), Clindamycin ($n = 2$), cephazolin ($n = 1$) and ceftriaxone ($n = 1$). After discontinuation of the intravenous antibiotics, all the patients continued on oral antibiotics for additional 6 wk, doxycycline ($n = 12$), and ciprofloxacin ($n = 3$).

At follow-up, the patients were seen at 6 wk, 3, 6, 9, 12 mo and annually thereafter. Clinical, radiological and laboratory evaluation (using serial white cell count, ESR, and CRP) was performed at each follow up.

RESULTS

Mean follow-up was 102.8 mo (36-217 mo, SD 56.4). No patients were lost to follow-up. Fourteen patients had no recurrence of the infection; one hip (6.7%) was revised for management of infection. Statistical analysis

using Kaplan Meier curve showed 93.3% survival rate.

The only failure in our series occurred in a 58-year-old male patient; this patient had acetabular fracture, which was treated by open reduction and internal fixation at the age of 40 then primary THA for management post-traumatic arthritis of the hip joint at age 48. Subsequently the patient underwent revision THA for management of polyethylene wear (liner exchange) at age of 61 years. The patient was diagnosed with chronic infected THA 2 years following revision THA. Eventually, the patient had good result after single stage acetabular component exchange with preservation of the femoral component, but unfortunately the infection recurred after 14 mo. The patient was treated successfully with surgical intervention by removal of the acetabular fixation, irrigation, and debridement and liner exchange. Coagulase negative staphylococcus aureus was the infective organism at all the stages of management.

Two complications occurred in 2 patients. The first patient was 38-year female; the patient suffered from recurrent hip dislocation 12 years following the definitive procedure, this complication was managed by revision THA with abductor reconstruction and constrained acetabular liner, no clinical signs of infection were found during the revision procedure and no organism was grown from the intra-operative cultures. The second complication occurred in a 53-year-old female patient, the acetabular component was revised due to aseptic loosening 2 years following the definitive procedure. No evidence of infection was seen at the revision procedure (Table 2).

DISCUSSION

Infection after THA is a devastating complication; there is no randomized prospective study to evaluate the outcome of different management options. Two-stage exchange arthroplasty is generally felt to be the gold standard method of management. However, this strategy has some drawbacks; long duration of treatment, patient morbidity and high economic cost. The reported failure rates after two-stage hip revision range from 5% to 18%^[6,17,18]. One stage revision is an attractive option for the management of infected hip arthroplasty, with a comparable reinfection rates to two stage exchange and higher functional outcome scores, reduce morbidity, and cost of the management^[7,19-21].

The concept of single stage acetabular exchange arthroplasty with retention of well fixed femoral component in management of chronic infected total hip arthroplasty was brought into attention because removal of well fixed cement less femoral component is a complex procedure, which necessitates extensive soft tissue dissection and femoral osteotomies that can de-vascularize the proximal femur and may result in degradation of the bone stock, and significant post operative morbidity.

Bacterial adherence and subsequent biofilm formation on implant are involved in the origin and chronicity of implant-related infection. Different biomaterials are claimed to differently suffer from microorganism adherence and biofilm formation, justifying partial component exchange in some acute prosthetic joint infection. Experimental studies showed more adherences of microorganisms and formation of biofilm to rough surfaced Ti alloys than polished surfaces^[22].

In a recent study, Gómez-Barrena *et al.*^[23] proved that sonification of retrieved implants after prosthetic joint infection showed almost no bacterial adherence to the polished femoral head components in total hip replacement, while knee infections basically seeded on the tibial trays with minimal seeding on the polished femoral component. Theoretically, a well fixed circumferentially ingrown cementless femoral stem can isolate the femoral canal from the infected joint fluid and prevent the formation of biofilm layer on the femoral stem. Therefore, there is high possibility to control infection without the need to remove the well fixed femoral component which seal the femoral canal from the infecting microorganisms.

Two recent reports demonstrate high success rate of two-stage partial exchange with retention of the well-fixed cement less femoral component. In the first report by Lee *et al.*^[24], 17 infected THA were managed by two stage exchange arthroplasty; in the first stage irrigation and debridement was done followed by removal of the acetabular components, the femoral component was retained and the exposed metal parts of the femoral stem and femoral head was covered by antibiotic loaded bone cement. The acetabulum was reconstructed in the second stage. At mean follow-up of 4 years, 15 of the 17

(88%) demonstrated no recurrence of infection^[24]. The second report by Ekpo *et al.*^[25], reported 19 infected hips treated with two stage partial exchange with retention of the well-fixed cement less femoral component. At mean follow-up of 4 years, 17 of the 19 (89%) demonstrated no recurrence of infection^[25].

The Exeter group reported their outcome of management of infected cemented (THA) by two-stage exchange with preservation of the original femoral cement mantle. The hypothesis was that Osteointegrated cement-bone interface is not part of the effective joint space and is inaccessible to infecting organisms. Fifteen patients were treated with two-stage exchange with retention of the well-fixed cement mantle; infection was controlled in 14 patients at mean follow-up of 82 mo^[16].

The main purpose of this study was to evaluate the success of single stage acetabular component exchange with retention of well-fixed femoral component. To our knowledge, this is the first report evaluating the results of this procedure.

From January 1997 to January 2012, the senior author performed 600-revision Total hip arthroplasty for various reasons, 92 of them were two-stage exchange for infected Total Hip arthroplasty. Single stage exchange with retention of well-fixed acetabular component was performed in 15 cases which represent (14%) of the cases treated for management of infected Total hip arthroplasty.

We defined failure by recurrence of infection that requires either surgical intervention or chronic suppressive antibiotics. Our infection recurrence rate was 6.7% at mean follow-up of 102.8 mo. The results compare favourably with previously published data of two-stage exchange^[6,7,11,17,20-25]. We are comparing the success of the procedure to two-stage exchange arthroplasty as it is considered the gold standard management option of such problem.

Our study has several limitations. First, this study was a retrospective, which can introduce the possibility of selection bias. Second, because of the small number of the patients we could not further analyze data stratifying for virulence of the organism, type of infection, and duration of infection. However, 15 patients treated with this technique for management of infected total hip arthroplasty reflect that strict selection protocol was applied to use this method of treatment and reflect that we are considering this technique when specific criteria are met. Different treatment modalities were utilized when these specific selection criteria for single stage, single component revision were not met. The infecting organism was not identified in one patient prior to the surgery, which raises the possibility that these patients might be infected with virulent microorganisms but in the meantime these patients met all other inclusion criteria. Finally, functional outcomes were not recorded in this study because of the retrospective nature of the study, but we believe that success of eradication of infection is a strong predictor of functional improvement.

In conclusion, our results of management of infected THA with single stage acetabular component exchange with retention of a well-fixed femoral component is encouraging and showed low risk of future recurrence. Retention of the femoral component preserves the femoral bone stock, decreases patients' morbidity, and lessens reconstructive complexity at the time of the revision. Based on our results, success can be achieved with this technique when the following criteria are met: (1) well-fixed femoral component; (2) good patient general health; (3) no draining sinuses; and (4) sensitive microorganisms isolated.

We are not proposing this method of treatment as alternative tool to two stage exchange for management of infected Total hip arthroplasty but it should be considered as one of the management options for treatment of this problem provided strict selection criteria are met. Further randomized controlled trial and trials with large volume of patients is needed to validate the best treatment option.

COMMENTS

Background

Peri-prosthetic hip infection is a devastating complication: The authors hypothesized that a well-fixed circumferentially ingrown cement-less stem can act as a shield and prevent the spread of pathogens and formation of biofilm around the body of the femoral stem. Therefore, single stage exchange of the acetabular component with retention of the well-fixed femoral component can be a successful option in management of infected total hip arthroplasty, when the following criteria are met; well-fixed femoral component, no draining sinuses, non immune compromised patients, and infection with sensitive organisms.

Research frontiers

Preservation of well fixed cementless femoral component in infected total hip arthroplasty cases will decrease the morbidity of management infected total hip arthroplasty patients. This is the only report in their literature up to the authors' knowledge presenting this technique. This study presents long term results of this procedure.

Innovations and breakthroughs

Most of the papers in the literature present results about either one stage or two stage exchange in management of infected total hip arthroplasty. The authors present a very good success rate of our procedure in management of selected patients with infected total hip arthroplasty. The authors' protocol of management can be added to the treatment option of infected total hip arthroplasty.

Applications

This article will encourage other surgeons either to use this technique or present their work if using similar technique in management of infected hip arthroplasty, this can lead to increase the credibility of using single stage exchange with preservation of well fixed femoral stem in management of infected total hip arthroplasty if selected criteria were met.

Terminology

THA: Total hip arthroplasty; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cell count; BMI: Body mass index; ASA: American Society of Anesthesiologist.

Peer-review

This paper gives readers one of the management options for treatment of infected total hip arthroplasty provided strict selection criteria are met. The manuscript is suitable for the readers.

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Retrospective Study

Role of dynamic computed tomography scans in patients with congenital craniovertebral junction malformations

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Abstract

AIM

To evaluate the role of dynamic computed tomography (CT) scan imaging in diagnosing craniovertebral junction (CVJ) instability in patients with congenital CVJ malformations.

METHODS

Patients with symptomatic congenital CVJ malformations who underwent posterior fossa decompression and had a preoperative dynamic CT scan in flexion and extended position were included in this study. Measurements of the following craniometrical parameters were taken in flexed and extended neck position: Atlanto-dental interval (ADI), distance of the odontoid tip to the Chamberlain's line, and the clivus-canal angle (CCA). Assessment of the facet joints congruence was also performed in both positions. Comparison of the values obtained in flexion and extension were compared using a paired Student's *t*-test.

RESULTS

A total of ten patients with a mean age of 37.9 years were included. In flexion imaging, the mean ADI was 1.76 mm, the mean CCA was 125.4° and the mean distance of the odontoid tip to the Chamberlain's line was + 9.62 mm. In extension, the mean ADI was 1.46 mm ($P = 0.29$), the mean CCA was 142.2° ($P < 0.01$) and the mean distance of the odontoid tip to the Chamberlain's line was + 7.11 mm ($P < 0.05$). Four patients (40%) had facetary subluxation demonstrated

in dynamic imaging, two of them with mobile subluxation (both underwent CVJ fixation). The other two patients with a fixed subluxation were not initially fixed. One patient with atlantoaxial assimilation and C23 fusion without initial facet subluxation developed a latter CVJ instability diagnosed with a dynamic CT scan. Patients with basilar invagination had a lower CCA variation compared to the whole group.

CONCLUSION

Craniometrical parameters, as well as the visualization of the facets location, may change significantly according to the neck position. Dynamic imaging can provide additional useful information to the diagnosis of CVJ instability. Future studies addressing the relationship between craniometrical changes and neck position are necessary.

Key words: Craniovertebral junction; Dynamic imaging; Basilar invagination; Chiari malformation; Treatment

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Core tip: This study shows the importance of the dynamic image in patients with congenital craniovertebral junction anomalies. A total of ten patients with a mean age of 37.9 years were included. We could demonstrate that 40% of the patients had facetary subluxation demonstrated in dynamic imaging and two of them required surgery for craniovertebral junction due to instability. This study reported the importance of routine dynamic imaging evaluation in patients with craniovertebral junction anomalies even without evidence of instability in static computed tomography scan or magnetic resonance imaging.

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INTRODUCTION

Basilar invagination (BI) is a congenital craniovertebral junction (CVJ) malformation characterized by the ascension of the upper cervical spine into the skull base and can be associated with other bone anomalies, such as atlas assimilation, Klippel-Feil syndrome, condyle hypoplasia and atlanto-axial instability^[1-4]. BI is generally diagnosed when the tip of the odontoid process is at least 5 mm above the Chamberlain's line (a line traced from the posterior edge of the hard palate to the posterior margin of the foramen magnum)^[5].

Surgical treatment of BI is well accepted in the setting of clinical symptoms^[6,7]. Symptoms are usually caused

by tonsillar herniation, brainstem/upper cervical spine compression and/or CVJ instability, which should be recognized by the surgeon before planning the surgical strategy^[3,7,8].

Increased atlanto-dens interval, atlanto-axial dislocation (AAD), and the tip of the odontoid above the McRae's line (a line drawn from the basion to the opisthion), are clear signs of CVJ instability^[8], therefore, in such cases, stabilization concomitant to neural structures decompression is generally recommended^[8,9].

However, some patients may present symptoms of BI with a relative normal or near normal CVJ alignment^[4]. For those patients, dynamic craniovertebral junction computed tomography (CT) scans with sagittal reconstructions can provide detailed information about the facet joints and CVJ alignment, as well as showing abnormal motion of the CVJ suggestive of instability.

Dynamic imaging (such as CT or magnetic resonance imaging in flexion and extension) is commonly used in traumatic spinal diseases, although the literature is relative scarce about its use in CVJ malformations^[10]. Considering the potential benefits of dynamic CT scans in patients with CVJ without clear and evident instability, we proposed to evaluate our experience with this exam in our practice.

MATERIALS AND METHODS

We performed a retrospective study of our database of patients with CVJ who underwent surgical treatment from 2010 to 2016 by the same surgeon (AFJ).

Inclusion criteria

Symptomatic congenital CVJ malformation: Chiari Malformation (CM), characterized by tonsillar herniation through the foramen magnum or BI with or without CM who underwent posterior fossa decompression; age > 15 years old (younger patients have incomplete ossification of the region and were excluded)^[11]; a complete sagittal CT scan of the CVJ in flexion and in extension (a head holder was used to flex the neck and a pad roll was placed below the shoulders for the extended position); non evident AAD or facet subluxation on static radiological exams.

Patients were followed by the same surgeon (AFJ). Neurologic status (pre and post-surgery as well as during the follow-up) was assessed using the Nürick scale (Table 1)^[12,13]. Complications were described in details. Statistical analysis was performed using a paired Student's *t*-test - considering statistical significance a *P* value < 0.05. Analysis was made using the software Stata/MP version 13.0 for Windows (StataCorp/LP[®]). This study was approved by our Institutional Review Board (CAAE: 49070915.9.0000.5404).

Radiologic measurement

The radiological data were assessed by two authors together (OTS and AFJ). The acquisition of images

Table 1 Nurick score

0	Root involvement. No spinal cord disease
1	Signs spinal cord disease without restriction in walking
2	Difficulty in walking without impact on employment
3	Difficulty in walking with impact on employment
4	Walk only with aid or walker
5	Bedridden or chair bound

was performed in 64-row multidetector CT (Anquilion 64, Toshiba Medical Systems®). The images were reconstructed in 0.5 mm thick slices and analyzed in bone window settings, length 300 Hounsfield and width 2500 Hounsfield.

The measurements were performed in an imaging workstation and all images were downloaded in DICOM format and the measurements were performed using the PACS Aurora 2 (Pixon Medical System, version: 1.9.2)®. The measurements were assessed in both positions (flexion and extension), in sagittal view, following the criteria adopted by the study of Batista *et al.*^[14], as it follows: Atlanto-dental interval (ADI): Measured from the posterior margin of the anterior arch of C1 to the anterior portion of odontoid; clivus-canal angle (CCA): The angle formed by a line drawn from the posterior line of the clivus and a line marked from the posterior margin of the body of C2; distance of the tip of the Odontoid to the Chamberlain line: The distance from the tip of the odontoid to the Chamberlain's line. Presence or absence of facet joints subluxation of the occipital-lateral masses of the atlas and the atlanto-axial joints; diagnosis of clivus hypoplasia: Adopted when the clivus had less than 36.6 mm (less than 2σ of the mean of the normal population)^[11].

RESULTS

Thirty patients with congenital CVJ malformations were operated from 2010 to 2016 by the senior author (AFJ) at our institution. A total of ten patients had complete dynamic exams and were included according our inclusion criteria. The mean age of our population was 37.9 years (ranging from 15- to 56-year-old). Five patients (50%) were male and five were female (50%). Table 2 summarizes the clinical data of the patients.

All patients had some degree of tonsillar herniation (mean of 10.04 mm below the McRae line, ranging from 5 to 15.19 mm). Seven patients (70%) had also the diagnosis of BI (with the tip of the odontoid above at least 5 mm the Chamberlain's line).

The mean pre-operative Nurick grade was 2.8 (ranging from 1 to 5). The mean post-operative Nurick grade was 1.9 (ranging from 1 to 3), after a mean follow-up of 18.1 mo (ranging from 1 to 38 mo).

Treatment consisted in posterior fossa decompression with removal of the posterior arch of C1 in all cases. In all cases, duroplasty was performed, but only two cases had also tonsillar resection due to the severity of the tonsillar herniation. Two patients underwent concomitant

occipito-cervical fixation because they presented a mobile atlantoaxial subluxation on dynamic images, as explained below.

Bone anomalies

The main bone anomaly associated with BI was clivus hypoplasia. Five patients had clivus hypoplasia, four patients had atlas assimilation and two patients had a C2-C3 fusion (Table 3).

Dynamic CT scans measurements

Flexion CT scan: The mean CCA was 125.4° (ranging from 92° to 146°), with a ADI of 1.76 mm (ranging from 0.36 to 5.67 mm) and a mean distance of the odontoid tip to the Chamberlain's line of 9.62 mm above it (ranging from 0 to +22.86 mm). In the group with seven patients that also had the diagnosis of BI, the mean distance of the tip of the odontoid to the Chamberlain's line was +13.32 mm (ranging from +6.6 to +22.86 mm) and the mean CCA was 118.4° (ranging from 92° to 134°). One patient surgically treated at a different institution had a previous posterior fossa decompression and the Chamberlain's line was not accessed.

Extended CT scan: The mean CCA was 142.2° (ranging from 108° to 176°), with the mean ADI of 1.46 mm (ranging from 0.36 to 3.12 mm) and a mean distance from the tip of the odontoid to the Chamberlain's line was 7.11 mm above it (ranging from less than -5 mm to up to 19.34 mm). In the six patients with BI, the mean distance from the odontoid tip to the Chamberlain's line was 11.72 mm above it (ranging from 4 to 19.34 mm above it) and the mean CCA was 135.28° (ranging from 108° to 161°).

Facet dislocation

Four patients had some facet joints subluxation at the atlanto-axial region. Two of these patients underwent a cranio-cervical fixation due to their mobile subluxation: One patient had an increased facet subluxation in extension, from 4 to 7 mm, without changing the ADI distance and the other had an increased ADI in flexion, from 2.94 to 5.67 mm (Figure 1). The other two cases were treated initially without occipito-cervical fixation because their facet joints did not change on flexion and extension CT scan (Figure 2).

During the study follow-up, another patient who had BI and a congenital C2-C3 fusion developed latter cervical pain and dizziness when flexing the neck. A new dynamic CT scan was performed two years after posterior fossa decompression who had demonstrated a new atlanto-axial subluxation with dynamic change of 3.7 mm in the atlanto-axial right facet joint from flexion to extension. Additionally, this same patient also had an increased ADI varying from 1.51 mm in extension to 3.86 mm in flexion. We considered that she developed a postoperative instability and surgical fixation was proposed, but she refused it because she had a severe depression and familiar problems (Figure 3).

Table 2 Patients main characteristics according to clinical status, follow-up and radiological parameters analyzed

No.	Gender	Nurick pre	Nurick post	Follow-up (mo)	Pathology	Clivus hypoplasia	Atlas assimilation	Treatment	Tonsillar herniation
1	38	4	2	38	BI + Chiari	Present	Absent	PFD + Duropls	14.95
2	35	3	2	30	BI + Chiari	Present	Absent	PFD + Duropls	15.19
3	15	2	1	21	BI + Chiari	Absent	Absent	PFD + Duropls + Tonsilec	9.4
4	29	2	1	30	Chiari I	Absent	Absent	PFD + Duropls	11.45
5	20	2	2	6	BI + Chiari	Present	Present	PFD + Duropls	11
6	40	2	1	14	BI + Chiari	Present	Present	PFD + Duropls	5
7	48	4	3	28	BI + Chiari	Absent	Present	PFD + Duropls + OCFix	7
8	56	5	3	8	BI + Chiari	Present	Present	PFD + Duropls + OCFix	N/A
9	52	1	1	5	Chiari I	Absent	Absent	PFD + Duropls	9
10	46	3	3	1	Chiari I	Absent	Absent	PFD + Duropls	7.44
M	37.9	2.8	1.9	1654					10.04

M: Mean; BI: Basilar invagination; PFD: Posterior fossa decompression; Duropls: Duroplasty; Tonsilec: Tonsillectomy; OCFix: Occipito-cervical fixation; N/A: Not available.

Table 3 Description of the main radiological characteristics obtained in flexion and in extension sagittal computed tomography scan

N	Flexion position				Extension position			
	ADI	CCA	Facet dislocation	Chamberlain	ADI	CCA	Facet dislocation	Chamberlain
1	1.5	92°	Absent	+22.86	1.25	131°	Absent	+19.43
2	1.72	134°	Absent	+6.6	1.72	155°	Absent	+4.76
3	1.18	115°	Right side - 4 mm	+9.95	1.18	127°	Right side - 4 mm	+10.86
4	1.75	141°	Absent	0	1.75	155°	Absent	-3.7
5	0.5	120°	Absent	+20	0.6	125°	Absent	+19.3
6	3.27	130°	Absent	+12.28	3.12	140°	Absent	+12.11
7	5.67	130°	Left side - 2 mm	+8.26	2.94	161°	Right side - 3 mm	+4
8	1	108°	Right side - 4 mm	N/A	1	108°	Right side - 7 mm	N/A
9	0.36	146°	Absent	+3.97	0.36	176°	Absent	-5
10	0.7	138°	Left site 3.7 mm	+2.67	0.7	144°	Left side 3.7 mm	+2.32
M	1.76	125.4°		+9.62	1.46	142.2°		+7.11

M: Mean; ADI: Atlanto-dental interval; CCA: Clivus-canal angle; N/A: Not available.

Analysis of flexion vs extension

Comparing the differences of the measurements of the clivus canal angle and the distance of the tip of the odontoid to the Chamberlain’s line in flexion and extended position were statistically significant ($P < 0.01$ and 0.03 , respectively), but for the ADI the difference was not observed ($P = 0.29$).

DISCUSSION

Panjabi *et al*^[15] defined stability as the ability of the spine to maintain, under physiologic loads, the relationships between the vertebrae without resulting in pain, deformity or neurological compression. When specifically dealing with the mobile and complex CVJ, the criteria for instability are still debated^[4]. According to the most recent studies, in patients with clear AAD, stabilization is mandatory. However, the indications for craniocervical fixation in patients with tonsillar herniation without AAD are controversial^[2,6,8,16].

In congenital CVJ anomalies, instability may be secondary to bone hypoplasia, ligament and musculature laxity, and also by abnormal facet joints configuration that allows abnormal motion^[16,17]. The instability may be not visualized in static radiological exams. In our series of ten patients, four had dynamic changes in the facet joints

and one had late instability also well documented in flexion-extension CT scans, emphasizing the importance of adding this radiological modality in current investigation of congenital CVJ anomalies. Potential advantages of CT scans over plain radiographs include a better visualization of the facet joints and 3D reconstruction that allows better surgical planning and provides detailed anatomical visualization^[18].

Additionally, in this study, we also analyzed the basic craniometry using dynamic CT. The mean CCA was 125.4° in flexion and 142.2° in extended position, with a mean difference of 16.8° ($P < 0.01$). This emphasizes the importance of proper positioning during occipito-cervical fusions. In the plain radiographs era, Smoker *et al*^[19] had demonstrated that this angle changed about 30° from flexion to extension neck position, also reporting that normal range varied from 150° to 180°. Our limited variation from flexion to extension compared to the reported by Chandra *et al*^[11] may be explained by the fact that some of our patients had clivus hypoplasia and atlas assimilation which may decrease CVJ motion when compared with normal subjects. Platybasia may lead to a lower CCA and CVJ kyphosis, with brainstem symptoms as well as compensatory subaxial hyperlordosis.

We also reported that the distance of the tip of the odontoid from the Chamberlain’s line varies from flexion

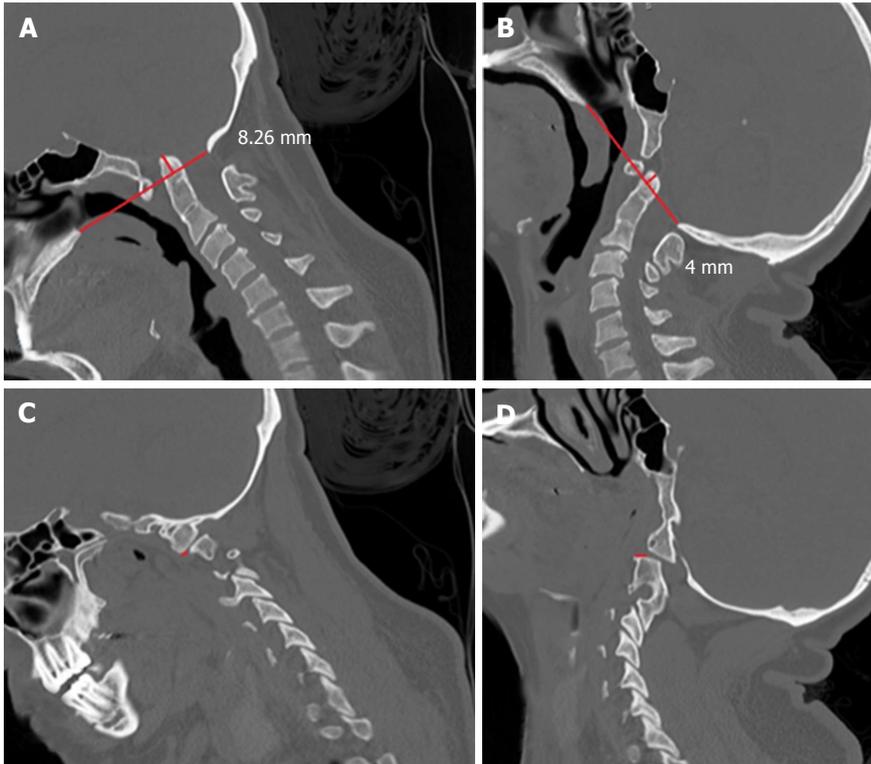


Figure 1 A 18-year-old woman with basilar invagination and tonsillar herniation of 7 mm. She also had atlas assimilation. A: Sagittal computed tomography (CT) scan in flexion shows the tip of the odontoid 8.26 mm above the Chamberlain's line; B: Sagittal CT scan in extended position shows the tip of the odontoid 4 mm above the Chamberlain's line; C: Sagittal CT scan showing anterior dislocation of the facet joint of C1 over C2 facetary of 2 mm; D: Sagittal CT scan showing posterior dislocation of the C1 facet joint over the facet of C2 of 3 mm, ranging 5 mm in dynamic exam. This patient underwent a craniocervical fusion concomitant to the posterior fossa decompression.

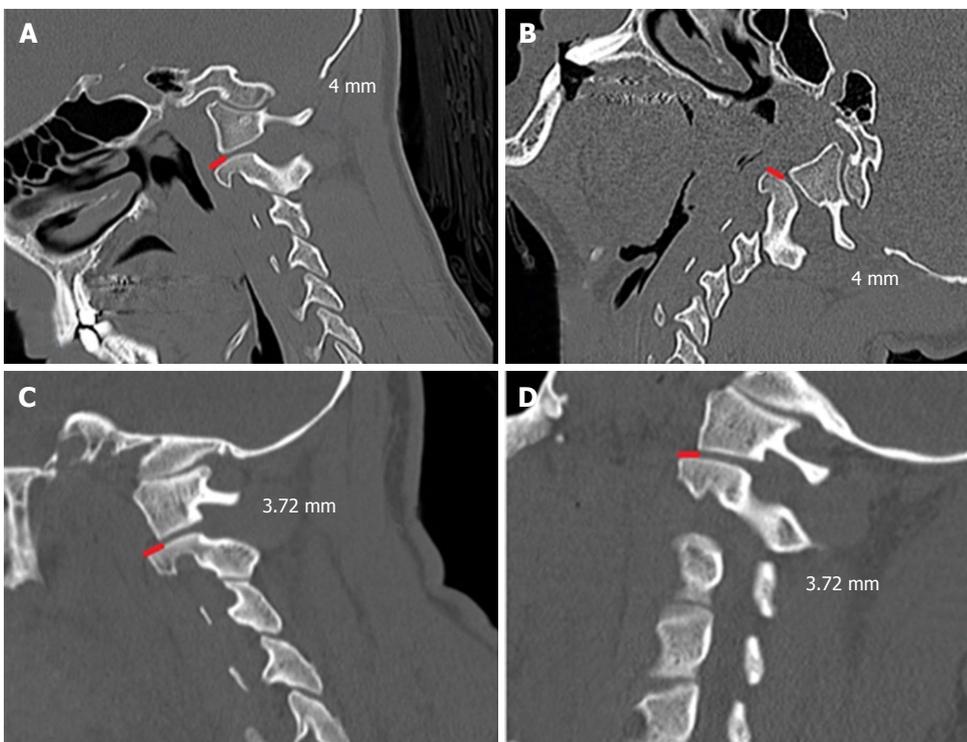


Figure 2 Dynamic sagittal computed tomography scan of 15-year-old boy, which had the diagnosis of a tonsillar herniation of 9.4 mm and basilar invagination. In both A and B positions, the facet dislocation of the C1 lateral mass posteriorly to the superior C2 joints was maintained (4 mm). We opted to perform only posterior fossa decompression without craniocervical junction instrumentation, obtaining a good clinical improvement; C and D: Dynamic sagittal computed tomography scan imaging - a forty-six-year-old man, with tonsillar herniation of 7.44 mm. In both positions the facet dislocation of the C1 lateral mass over the C2 superior facet joint was 3.72 mm. We also performed only a posterior fossa decompression without fusion in this patient, with a good clinical outcome.

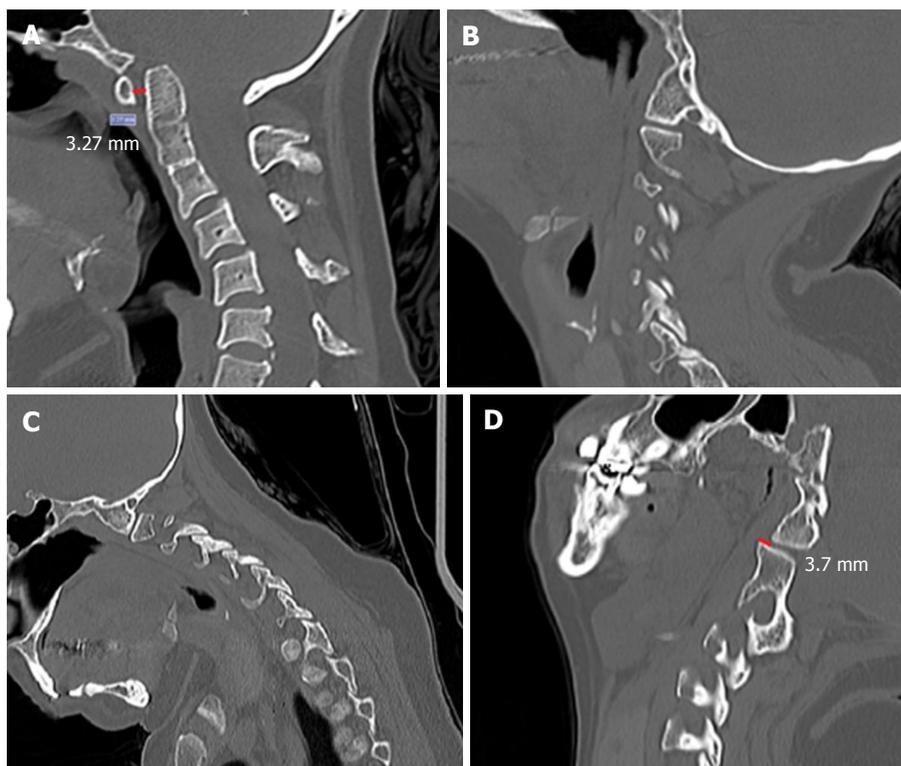


Figure 3 Forty-year-old woman with a tonsillar herniation of 5 mm and basilar invagination. Noted that she also had atlas assimilation and a congenital C23 fusion A, B and C: Pre-operative dynamic imaging, showing a atlanto-dental interval of 3.27 mm, but no signs of facet dislocation in flexion or in extension (B and C); D: Sagittal computed tomography scan obtained after some months after posterior fossa decompression showing an evident facet joints dislocation (the assimilated lateral mass of C1 was dislocated posteriorly over the superior facet joint of C2). She had some symptoms of dizziness and cervical pain when flexing the neck and an occipito-cervical fixation was proposed but the patient declined surgical treatment because she was not doing well with depression and mood disorders.

(mean of +9.62 cm above the tip of the dens) to extension (mean of +7.11 above the tip of the dens) ($P = 0.03$), which may influence the incidence of the diagnosis of BI in patients with Chiari Malformation according to patients neck position when underwent a CT scan.

In the past, Goel *et al.*^[3,8] proposed that patients with BI without AAD required only foramen magnum decompression. In this study, we observed that some patients with tonsillar herniation but without AAD may have instability in about 20% of the cases. Additionally, these patients may develop CVJ instability after surgery (10% of the patients in the present study). Menezes *et al.*^[20] reported that patients with Chiari Malformation, atlas assimilation and concomitant congenital C2C3 fusion may develop atlanto-axial instability after posterior fossa decompression.

Another fact is that not only facet subluxation can be visualized with dynamic exams, but also changes in the ADI, similarly to upper cervical spine trauma or rheumatoid arthritis patients. In two of our patients, we observed an increasing ADI when changing the neck position, suggesting an occult insufficient transverse ligament that may potentially result in atlanto-axial instability, cervical pain and neurological deficits. In these patients, the mean ADI was 3.03 mm in extension to 4.47 mm in flexion, with an increase of about 47.5% after changing the position. However, the differences of the

ADI in our series comparing flexion and extension were not significant ($P = 0.29$), probably because we excluded patients with evident AAD in static exams. The normal ADI obtained using CT scan in neutral position in a series of 100 patients without known CVJ anomalies varied from 0.5 to 1.7, using the exactly same methodology used in our study^[14].

We also noted that some patients (patients 3 and 10) may have mild facet joints subluxation without dynamic changes. These patients were treated with foramen magnum decompression without fixation with an acceptable clinical outcome (both had improvement of their clinical symptoms).

Our study is limited by a small case series and limited follow-up. Additionally, we excluded many patients treated in our institution for congenital CVJ malformations because they did not have a complete preoperative dynamic exam. However, to our knowledge, we could clearly demonstrate the importance of dynamic CT scan evaluation in routine treatment of patients with symptomatic tonsillar herniation. Additionally, we reported that patients with mild subluxation without dynamics change may be considered for foramen magnum decompression alone. Dynamic CT was also useful for evaluating late postoperative instability.

In conclusion, we reported the utility of dynamic CT scans in the evaluation of the best treatment modality for patients with congenital CVJ anomalies. Significant

changes were observed in the CCA and in the position of the odontoid in the cranial base. Prospective studies are necessary to evaluate the role of the radiological findings of dynamic CT scans on patients' outcome.

COMMENTS

Background

Craniovertebral junction (CVJ) congenital malformations are challenging diseases. This study aims to identify which patient has signs of CVJ instability through a dynamic computed tomography scan.

Research frontiers

Diagnostic of CVJ instability in congenital disorders is still debated.

Innovations and breakthroughs

This article reported the importance of dynamic imaging evaluation of the CVJ in congenital malformation.

Applications

Decision making for surgical treatment of those patients that had CVJ congenital malformations, such as Chiari I.

Terminology

Atlanto-dental interval: Measured from the posterior margin of the anterior arch of C1 to the anterior portion of odontoid; clivus-canal angle: The angle formed by a line drawn from the posterior line of the clivus and a line marked from the posterior margin of the body of C2. Distance of the tip of the Odontoid to the Chamberlain line: The distance from the tip of the odontoid to the Chamberlain's line. Presence or absence of facet joints subluxation of the occipital-lateral masses of the atlas and the atlanto-axial joints; diagnosis of clivus hypoplasia: Adopted when the clivus had less than 36.6 mm (less than 2σ of the mean of the normal population).

Peer-review

Very well designed and honest paper, worth publishing in the present form.

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Observational Study

Relationship between biological factors and catastrophizing and clinical outcomes for female patients with knee osteoarthritis

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Abstract**AIM**

To investigate the correlations between clinical outcomes and biopsychological variables in female patients with knee osteoarthritis (OA).

METHODS

Seventy-seven patients with symptomatic knee OA were enrolled in this study. We investigated the age, body mass index (BMI), pain catastrophizing scale (PCS) and radiographic severity of bilateral knees using a Kellgren-Lawrence (K-L) grading system of the subjects. Subsequently, a multiple linear regression was conducted

to determine which variables best correlated with main outcomes of knee OA, which were pain severity, moving capacity by measuring timed-up-and-go test and Japanese Knee Osteoarthritis Measure (JKOM).

RESULTS

We found that the significant contributor to pain severity was PCS ($\beta = 0.555$) and BMI ($\beta = 0.239$), to moving capacity was K-L grade ($\beta = 0.520$) and to PCS ($\beta = 0.313$), and to a JKOM score was PCS ($\beta = 0.485$) and K-L grade ($\beta = 0.421$), respectively.

CONCLUSION

The results suggest that pain catastrophizing as well as biological factors were associated with clinical outcomes in female patients with knee OA, irrespective of radiographic severity.

Key words: Osteoarthritis; Pain catastrophizing; Knee pain; Physical function; Japanese Knee Osteoarthritis Measure

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Core tip: Plenty of previous studies have focused on biological factors such as aging, gender, body mass index, ethnicity and history of knee injury for knee pain in cases where there was a discordant relationship between radiographic severity and symptoms in knee osteoarthritis (OA). However, in the present study, we found that pain catastrophizing thought was highly associated with knee-related clinical outcomes, irrespective of radiographic severity, for female patients with knee OA, especially pain severity and quality of life.

Ikemoto T, Miyagawa H, Shiro Y, Arai YCP, Akao M, Murotani K, Ushida T, Deie M. Relationship between biological factors and catastrophizing and clinical outcomes for female patients with knee osteoarthritis. *World J Orthop* 2017; 8(3): 278-285 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i3/278.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i3.278>

INTRODUCTION

Knee osteoarthritis (OA) is a common problem causing knee pain and functional decline and disabilities in the elderly^[1-3]. Although there is a widespread belief of inconsistency between clinical symptoms and radiographic disease severity^[4], recent studies have revealed that knee symptoms were associated with not only disease severity but also female gender, aging, overweight and psychological factors^[5-11], in spite of the fact that these independent variables are sometimes associated with each other.

To establish comprehensive outcome measures relevant to the disabilities, the OMERACT conference first convened in 1992 (OMERACT was originally an

acronym for Outcome Measures in RA Clinical Trials, now it represents the more inclusive scope of "Outcome Measures in Rheumatology"). Several years later, a key objective of the OMERACT III conference was to establish a core set of outcome measures for OA^[12]. A consensus was reached by at least 90% of expert participants that the following 4 domains should be evaluated for knee, hip, and hand OA: Pain, physical function, patient global assessment, and joint imaging.

On the other hand, although a number of previous studies have revealed that radiographic disease severity, female gender, aging, being overweight and psychological factors such as catastrophizing thought were related to knee OA symptoms, it still remains unclear which variables best correlated with clinical disability.

It has been established that women are more sensitive to pain than men^[13], and more likely to complain of chronic musculoskeletal burden compared to men^[14]. Moreover, it has been suggested that women reported greater levels of catastrophizing with more painful symptoms than men^[15]. Recently, pain catastrophizing has been studied in patients suffering from knee OA^[11,16], and Somers *et al*^[16] have reported that pain catastrophizing rather than radiographic severity appears to be an important variable in understanding pain, disability, and physical function in overweight/obese patients with knee OA. Therefore, it would be important to understand the lack of relationships between the outcomes of knee OA and related variables for female patients with knee OA. Hence, the aim of the present study was to address the correlations between each of the clinical outcomes or between each outcome and relevant variables in knee OA patients with chronic pain or stiffness, limited to female participants using bivariate correlation and multivariate regression analysis. We speculated that pain catastrophizing rather than radiographic severity was a more influential factor for predicting the severity of knee pain, functional capacity, and quality of life for female patients with knee OA.

MATERIALS AND METHODS

Subjects

A previous study found relationships ($pr^2 = 0.10$) between pain catastrophizing and pain severity of knee OA patients^[16]. Based on this finding, the sample size for a power of 0.80 with two-tailed alpha at a 0.05 significance level to run a multivariate regression for seven predictors required a minimum of 74 subjects. After obtaining approval from the ethics committee, we announced research related to knee symptoms in female elderly patients 50 years of age or older from February to August 2015 and recruited participants who were interested in this study through physical-fitness center or orthopedic clinic located within Aichi Medical University. Before investigating their status, each subject was fully informed by the investigator 1: that content of this study and 2: that the personal information of the subject would be kept confidential.

Ninety-five people with chronic knee symptoms were interested in the study and they received a knee X-ray to confirm if they were eligible for the study. The eligibility criteria for this study were as follows: (1) female with knee symptoms persisting for at least three months or more; (2) 50 years old or older; (3) radiographic knee OA with a face of more than grade-2 according to the Kellgren-Lawrence (K-L) grading system on at least a unilateral knee, because most previous studies used grade-2 as a main defining feature for radiographic knee OA; and excluded (4) presence or history of major neurological disorders such as stroke and Parkinson's disease, and history of total knee arthroplasty (TKA).

In the end, we enrolled 77 female patients with knee pain in this study.

Data collection

Demographical background: First, we investigated the age, and body mass index (BMI) of the subjects. The BMI was calculated from weight and height measurements using the formula $BMI = \text{weight (in kg)} / \text{height (in m}^2\text{)}$.

The K-L grading system

After investigation of the subjects' demographic background (age, BMI), they underwent a radiographic examination of both knees by posterior-anterior view in the fixed standing position by a radiological technician. To avoid assessment error, all radiographs were assessed by two orthopedic physicians together (Tatsunori Ikemoto and Machiko Akao) according to the K-L grading system that uses the following grades: 0, normal; 1, possible osteophytes only; 2, definite osteophytes and possible joint space narrowing; 3, moderate osteophytes and/or definite joint space narrowing; and 4, large osteophytes, severe joint space narrowing, and/or bony sclerosis^[17].

Previous studies related to knee OA have assessed either side, although OA often affects bilateral knees^[18] and this bilaterality may amplify the magnitude of symptoms^[19]. Firstly, we assigned the subjects into either a unilateral group or a bilateral group according to whether radiographic knee OA was observed in one side or both sides. Subsequently, we used the total score of both sides (*e.g.*, if the right side was grade-2 and the left side was grade-1 then the total was 3) as radiographic severity because of the possibility that they have a substantial influence on the outcome measures despite asymptomatic knees^[20].

Japanese Knee Osteoarthritis Measure

The Japanese Knee Osteoarthritis Measure (JKOM) was developed to reflect the specifics of the Japanese cultural lifestyle, which is characterized by bending to the floor or standing up^[21]. The validity and reliability of JKOM has been examined by comparing it with the widely accepted QOL measure, the Western Ontario and McMaster University osteoarthritis index (WOMAC) and the 36-item short-form health survey (SF-36). The JKOM consists

of a pain rating based on a visual analogue scale (VAS) which was a 100-mm line with "no pain" at one end and "worst pain possible" at the other end and scores for a subscale of four symptoms based on a disease-specific questionnaire addressing four dimensions: "Pain and stiffness in knee", "condition in daily life", "general activities" and "health conditions", with 8, 10, 5 and 2 items, respectively. Each item is rated on an ordinal scale from 0-4, with higher scores indicating a symptom or medical condition of higher severity. The four symptom subscales can be scored separately or combined to represent the aggregated total symptoms. Lower JKOM scores indicate better QOL. We assessed the pain severity of participants in accordance with the VAS score.

Pain catastrophizing

Catastrophizing was assessed using the Pain Catastrophizing Scale (PCS). The PCS consists of 13 items that describe an individual's specific beliefs about their pain and evaluates catastrophic thinking about pain^[22].

Participants responded to each item using a Likert-type scale from 0 ("not at all") to 4 ("all the time"). The scale provides a total score and scores on 3 subscales: Rumination (4 items), magnification (3 items), and helplessness (6 items)^[23]. This scale is well known for its reliability and validity in the Japanese version^[24]. Although catastrophizing is known to be a cognitive distortion closely linked to anxiety and depression^[22], we confirmed that no subjects took anti-anxiety drugs or anti-depressants in the present study.

The timed up and go test

Timed up and go test (TUG) measures the time it takes a subject to stand up from a chair (46 cm seat height from the ground), walk a distance of 3 m, turn and walk back to the chair, and sit down^[25]. All subjects performed two trials and the superior time was used. TUG was originally established as an objective measure of physical function in the elderly population. It is also used to assess the risk of falls in older adults^[26].

Statistical analysis

Data were presented as mean and standard deviation and median because each variable resulted in not only parametric but also non-parametric distributions.

We assumed that there were three outcomes, which were pain rating, TUG, and the JKOM score as essential measures for knee OA based on the OMERACT III description. Firstly, we compared the differences in the scores of each outcome between the unilateral group and bilateral group by using the Mann-Whitney *U* test.

Subsequently, we also determined the four independent variables: Age, BMI, K-L grade, and PCS score, which were assumed to influence each clinical outcome. The relationship between each of the variables was analyzed using Spearman's correlation for bivariate regression analysis. Further analysis using a stepwise multiple linear regression was conducted to determine

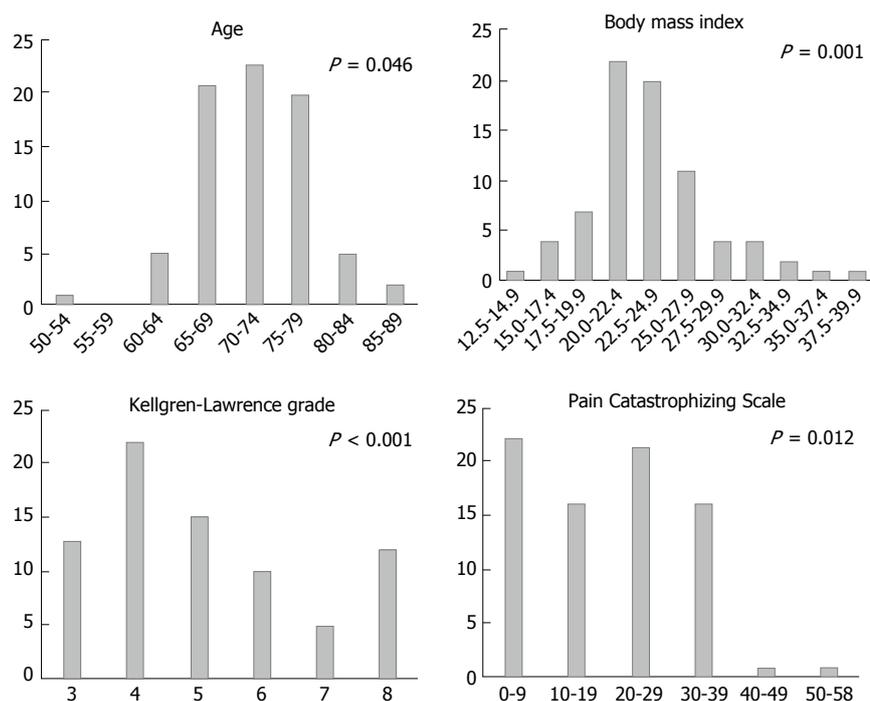


Figure 1 Distributions of the scores of each independent variable. Normality of each distribution was assessed by a Shapiro-Wilk test. The *P*-value within each variable indicates non-parametric distribution ($P < 0.05$).

Table 1 Characteristics of study subjects

Variables	<i>n</i> = 77
Age (yr)	72 (50-86)
BMI (kg/m ²)	23.7 (14.5-41.7)
K-L grade (Rt + Lt)	5 (3-8)
PCS	20 (0-50)
Pain rating (VAS)	26 (0-99)
TUG (s)	6.0 (4.1-16.5)
JKOM	18 (1-81)

Data are shown as the median (range). BMI: Body mass index; K-L grade: Kellgren-Lawrence grading system; VAS: Visual analogue scale; TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure; PCS: Pain Catastrophizing Scale.

which independent variables best correlated with the severity of each outcome measure.

For a priori power analysis, we used G*power3 software^[27] to determine sample size for study destination. Bivariate correlation analysis and multivariate regression analysis were performed with SPSS software (version 20.0J; SPSS Inc., Chicago, IL, United States). Differences were always considered significant at a level of $P < 0.05$.

RESULTS

The subject characteristics are presented in Table 1 and Figure 1 shows the distributions of the scores of each independent variable.

The subjects were assigned as follow: 17 subjects (22%) in the unilateral group; and 60 subjects (78%) in the bilateral group. Comparisons of the dichotomous groups revealed that there were no significant differences

Table 2 Comparison of each outcome between unilateral and bilateral knee osteoarthritis

Variables	Unilateral (<i>n</i> = 17)	Bilateral (<i>n</i> = 60)	<i>P</i> -value
Pain rating (VAS)	24 (0-95)	26 (0-99)	0.51
TUG (s)	5.5 (4.4-7.2)	6.3 (4.1-16.5)	0.02
JKOM	13 (2-35)	18 (1-81)	0.23

Data are shown as the median (range). The Mann-Whitney *U* test was used to compare differences between two groups. VAS: Visual analogue scale; TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure.

in severity of knee pain and JKOM scores between the unilateral group and bilateral group, while TUG was significantly faster in the unilateral group than in the bilateral group (Table 2).

The correlation coefficients (ρ) between each of the clinical outcomes or between each outcome and relevant variables using a bivariate regression analysis are shown in Table 3. Each outcome measure was significantly associated with each other. The pain rating showed significant positive correlations with K-L grade and PCS. TUG showed significant positive correlations with BMI, K-L grade, and PCS. The JKOM score showed a significant positive correlation with K-L grade and PCS.

In addition, the results of a stepwise multiple linear regression analysis for each outcome measure are shown in Table 4. We found that the significant contributor to a pain rating was PCS ($\beta = 0.555$) and BMI ($\beta = 0.239$), to TUG was K-L grade ($\beta = 0.520$) and PCS ($\beta = 0.313$), and to a JKOM score was PCS ($\beta = 0.485$) and K-L grade ($\beta = 0.421$), respectively.

Table 3 Spearman's correlation coefficients between each variable

	Age	BMI	K-L grade	PCS	Pain rating	TUG	JKOM
Age	1.000	-0.144	0.100	-0.023	-0.079	0.170	-0.017
BMI		1.000	0.322 ^b	0.084	0.212	0.257 ^c	0.046
K-L grade			1.000	0.182 ^d	0.281 ^a	0.587 ^d	0.467 ^d
PCS				1.000	0.574 ^d	0.404 ^d	0.594 ^d
Pain rating					1.000	0.487 ^d	0.721 ^d
TUG						1.000	0.588 ^d
JKOM							1.000

Value (p): Correlation coefficient. Small letters show the statistical significance: ^a $P < 0.05$, ^b $P < 0.01$, ^d $P < 0.001$. BMI: Body mass index; K-L grade: Kellgren-Lawrence grading system; PCS: Pain Catastrophizing Scale; TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure.

DISCUSSION

In the present study, although there is some disagreement regarding our speculation, pain catastrophizing has been highly associated with knee-related clinical outcomes for female patients with knee OA, especially pain severity and QOL score. To our knowledge, this is the first report that comprehensively investigates the relationships between knee OA related outcomes and related factors limited to female samples.

Knee pain with OA is known as a cause of disabilities among older adults as well as low back pain^[28,29]. Knee pain is also an important outcome for patients with knee OA. However, previous studies have focused on biological factors such as aging, gender, BMI, ethnicity and history of knee injury for knee pain in cases where there was a discordant relationship between radiographic severity and symptoms^[4,30]. On the other hand, recent studies have suggested that there were apparent relationships between pain catastrophizing and physical disabilities as well as pain severity in both pediatric and adult patients with musculoskeletal disorders^[11,31,32]. Moreover, Forsythe *et al*^[33] have reported that preoperative PCS scores predicted the presence of postoperative pain in patients who received TKA for primary knee OA.

In the present study, we found no interrelationships between pain catastrophizing and age, BMI and radiographic severity, while pain catastrophizing was a significant predictor which correlated with pain severity, and disease-specific QOL scores in female patients with knee OA, irrespective of disease severity. This finding is not only consistent with a previous report^[16], but also suggests that pain catastrophizing is an important factor rather than aging, and body weight associated with physical disabilities in female patients with knee OA, if radiographic severity is progressive.

The term catastrophizing was originally introduced by Ellis^[34] and subsequently adapted by Beck *et al*^[35] to describe a mal-adaptive cognitive style employed by patients with anxiety and depressive disorders. Keefe *et al*^[36] found a high test-retest correlation between catastrophizing thought during a 6-mo period in patients

with rheumatoid arthritis, and suggested it was invariable. Three prospective studies of TKA have included measures of catastrophizing in their test batteries^[31,37,38]. In these studies, catastrophizing scores did not significantly decline over time despite reduced pain in study participants and therefore it could be a personality trait such as neuroticism. By contrast, Wada *et al*^[39] recently reported that a change in pain intensity was associated with a change in catastrophizing for patients with TKA during a 6-mo follow-up. Furthermore, a number of studies have examined whether pain catastrophizing is an active cognitive process variable in multidisciplinary pain treatment settings, and have shown that pre- to post-treatment reductions in pain catastrophizing are associated with reductions in pain severity^[40-42]. Indeed, Marra *et al*^[43] have reported that multidisciplinary intervention for knee OA was superior to usual care with an educational pamphlet in terms of overall improvements, pain and function scores according to the Western Ontario and McMaster Universities' Osteoarthritis Index.

Besides, in the present study, TUG as an index of moving capacity was associated with not only disease severity but also pain catastrophizing after adjusting for BMI. We found that a correlation coefficient between TUG and K-L grade was higher than that between TUG and pain rating. This indicates that an assessment of bilateral knees may predict the moving capacity in female patients with knee OA, irrespective of pain severity. While a significant relationship between moving capacity and catastrophizing was consistent with a report by Somers *et al*^[16], the underlying mechanism, which can explain the correlation between them, is still unknown. Perhaps, pain-related fear may be related to physical performance with effort (*i.e.*, walking fast) in chronic pain^[16,44].

Taken together, this study suggests that clinicians should make sure to include an assessment of radiographic severity bilaterally and pain catastrophizing to explain the outcome measures in female patients with knee OA. This is because they may be able to improve both functional capacity and symptoms even at a progressive stage without knee arthroplasty by psychological intervention, which ameliorates mal-adaptive cognition in patients with high catastrophizing thought.

Several limitations should be taken into account when interpreting our data. Firstly, this was a cross-sectional study, therefore causal relationships between each outcome score and related variables could not be identified. Further longitudinal investigation is necessary to identify the interactions between the chronology of outcome measures and changes in variables. Secondly, the severity of radiographic OA was only assessed by posterior-anterior view in this study, although knee joints consisted of three components. Lanyon *et al*^[45] have reported that 24% of patients with radiographic knee OA was missed by not visualizing the patella-femoral joint. Thirdly, although we assess biological and psychological factors as influential variables on the outcome in knee OA, we didn't evaluate the strength of the quadriceps, which has been consistently associated with knee pain

Table 4 Multiple linear regression analysis of factors associated with each outcome

Outcome	Independent variables	R ²	Unstandardized coefficients: B	95%CI for B	β	P-value
Pain rating	BMI	0.397	0.162	0.039-0.284	0.239	0.010
	PCS		0.139	0.093-0.184	0.555	< 0.001
TUG	K-L grade	0.431	0.638	0.419-0.856	0.52	< 0.001
	PCS		0.053	0.023-0.082	0.313	0.001
JKOM	K-L grade	0.492	4.556	2.737-6.374	0.421	< 0.001
	PCS		0.719	0.470-0.968	0.485	< 0.001

TUG: Timed up and go test; JKOM: Japanese Knee Osteoarthritis Measure; BMI: Body mass index; K-L grade: Kellgren-Lawrence grading system; PCS: Pain Catastrophizing Scale.

and disabilities^[46]. Furthermore, we didn't evaluate the patient's background such as underlying disease, educational level and previous treatment which might be associated with clinical outcome. Finally, we have emphasized catastrophizing for the outcome and mentioned the possibility of improving catastrophizing thought in patients with chronic pain by a multifaceted intervention. However, there is little consensus on the effectiveness of a cognitive-behavioral intervention for knee OA pain^[47]. Hence, we must attempt to ameliorate these limitations and conduct a further investigation into whether an intervention to catastrophizing in relation to knee pain can improve the clinical outcomes for the female patient with knee OA.

This study showed that pain catastrophizing was a significant predictor which correlated with pain severity, physical function, and disease-specific QOL scores in female patients with knee OA, irrespective of disease severity. This finding suggests that pain catastrophizing is an important factor to explain knee symptoms and disabilities in female patients with knee OA.

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COMMENTS

Background

There is a widespread belief of inconsistency between clinical symptoms and radiographic disease severity in knee osteoarthritis (OA). Recent studies revealed that knee symptoms were associated with not only disease severity but also female gender, aging, overweight and psychological factors. However, there is little evidence reporting comprehensive relationships between biological and psychological factors and severity of symptoms in female patients with knee OA.

Research frontiers

Although a recent study has suggested that pain catastrophizing thought, as a psychological factor for pain symptoms, was associated with functional capacity as well as severity of knee pain in patients with knee OA, to what extent this psychological factor contributes to the severity of symptoms in female patients with knee OA, is still poorly understood. The research hotspot is to introduce

the contributing degrees of both biological and psychological factors to the severity of symptoms in female patients with knee OA.

Innovations and breakthroughs

Knee pain is an important outcome for patients with knee OA. However, previous studies have focused on biological factors such as aging, gender, body mass index (BMI), ethnicity and history of knee injury for knee pain in cases where there was a discordant relationship between radiographic severity and symptoms. On the other hand, the study revealed that pain catastrophizing has been highly associated with knee-related clinical outcomes for female patients with knee OA, irrespective of disease severity, especially pain severity and QOL score. To our knowledge, this is the first report that comprehensively investigates the relationships between knee OA related outcomes and related factors limited to female samples.

Applications

This study suggests that clinicians should make sure to include an assessment of pain catastrophizing as well as radiographic severity to explain the outcome measures in female patients with knee OA, because they may be able to improve both functional capacity and symptoms even in a progressive stage without knee arthroplasty by psychological interventions which ameliorate maladaptive cognition in patients with high catastrophizing thought.

Terminology

The term "catastrophizing" was originally introduced by Albert Ellis and subsequently adapted by Aaron Beck to describe a mal-adaptive cognitive style employed by patients with anxiety and depressive disorders. In the present study, catastrophizing was assessed using the Pain Catastrophizing Scale (PCS) invented by Sullivan *et al* (1995). The PCS consists of 13 items that describe an individual's specific beliefs about their pain and evaluates catastrophic thinking about pain.

Peer-review

The authors investigated the factors associated with clinical outcomes in female patients with knee OA. They concluded that pain catastrophizing scores well correlated with ADL scores and gait ability. The manuscript was concise and well written.

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Hip resurfacing arthroplasty complicated by mismatched implant components

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Informed consent statement: The patient involved in this study gave his written informed consent authorizing use and disclosure of his protected health information.

Conflict-of-interest statement: Campbell P is a consultant for DePuy Synthes, Wright Medical Technology and her lab receives funding for retrieval analysis of metal-on-metal implants from DePuy Synthes; all the other authors have no conflicts of interests to declare.

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Abstract

Metal-on-metal hip resurfacing has gained popularity as a feasible treatment option for young and active patients with hip osteoarthritis and high functional expectations. This procedure should only be performed by surgeons who have trained specifically in this technique. Preoperative planning is essential for hip resurfacing in order to execute a successful operation and preview any technical problems. The authors present a case of a man who underwent a resurfacing arthroplasty for osteoarthritis of the left hip that was complicated by mismatched implant components that were revised three days afterwards for severe pain and leg length discrepancy. Such mistakes, although rare, can be prevented by educating operating room staff in the size and colour code tables provided by the companies on their prostheses or implant boxes.

Key words: Hip resurfacing; Mismatch; Revision

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Core tip: The authors present a case of a man who underwent a resurfacing arthroplasty for osteoarthritis of the left hip that was complicated by mismatched implant components that were revised three days afterwards for severe pain and leg length discrepancy. Such mistakes,

although rare, can be prevented by educating operating room staff in the size and colour code tables provided by the companies on their prostheses or implant boxes.

Calistri A, Campbell P, Van Der Straeten C, De Smet KA. Hip resurfacing arthroplasty complicated by mismatched implant components. *World J Orthop* 2017; 8(3): 286-289 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i3/286.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i3.286>

INTRODUCTION

Metal-on-metal hip resurfacing has gained popularity as a feasible treatment option for young and active patients with hip osteoarthritis and high functional expectations. This procedure is more technically challenging than routine total hip replacement, mainly for surgeons new to the procedure and it should only be performed by surgeons who have trained specifically in this technique. The learning curve is known to be longer than in other hip arthroplasty procedures and is expected to be more than 50-70 surgeries^[1,2]. During the learning curve the surgeon should follow the technique thoroughly. Preoperative planning is essential for hip resurfacing^[3]. This step is important to help the surgeon perform a successful procedure and preview any technical problems.

The correct placement of both acetabular and femoral components is critical for the optimal functioning of the bearings. A smooth surface and perfect clearance are the key factors for the bearing, but equally important is the need for optimal placement to ensure good clinical results. High abduction angles and impingement will lead to early wear of the metal-on-metal articulation^[4]. The problem of malpositioned components is becoming increasingly recognized as the cause of premature failure. An unusual cause for failure is the accidental implantation of mismatched components^[5]. One such case is described below.

CASE REPORT

In July 2007, a 51 years old man was admitted at the ANCA Medical Centre in Gent with a mismatch of implants. Three days prior, at another hospital, the patient underwent a resurfacing arthroplasty for osteoarthritis of the left hip, with a posterior approach assisted with computer navigation (Brainlab®). A Birmingham Hip Resurfacing (Smith and Nephew, Memphis, Tennessee) was used. In the recovery room, the patient complained of severe pain and a rigid immobility of the hip that did not disappear the day after surgery. The patient at clinical examination presented a flexion contracture on the right side and pain in the groin. X-rays confirmed a mismatch between the femoral and the acetabular component diameters (Figure 1). A size 56-mm cemented femoral component was combined with a size 62-mm cementless

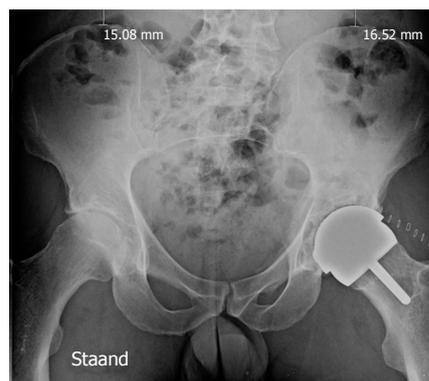


Figure 1 The post-operative X-ray, showed a mismatch between the femoral and the acetabular component diameters.

acetabular component thick shell that should have been applied with a 54-mm head instead of a 56-mm head.

The patient was treated with a revision to total hip arthroplasty two days later with the same posterolateral approach. The femoral component was revised with a Profemur L stem (Wright Medical Technology, Arlington, Tennessee, United States) and the socket was replaced by a Pinnacle™ Acetabular Cup System (DePuy Orthopaedics, Inc., Warsaw, United States) with Delta on Delta BioloX Ceramic couple 36 mm. Routine post-operative thrombo-prophylaxis was carried out. He experienced no pain and was allowed full weight bearing the day after revision surgery. The patient experienced an ordinary postoperative course and was habitually followed up in outpatient clinic.

The implants were analysed using a coordinate measuring machine to measure both components. This confirmed the size mismatch; the femoral component was 55.75 mm while the acetabular component was 54.054 mm. The coordinate measuring machines (CMM) map indicated damage to the femoral component (Figure 2). The effect of the mismatched sizing is demonstrated by comparing the removed components to a correctly sized set using a 54-mm femoral component obtained from the retrieval lab (Figure 3).

DISCUSSION

There is a decreasing demand and interest from orthopaedic surgeons for hip resurfacing arthroplasty. Consequently, from a peak of 14 implant manufacturers, currently only 8 different MOM hip resurfacing implants are available for use in clinical practice in Britain and Europe. For each design, there can be special sizes with different increments.

To help operating room staff to select the appropriately matched implants, some manufacturers provide a colour chart to show the size of the femoral head that the surgeon can match with the corresponding different acetabular sizes, with the same colour code.

In this present case report, despite various colour codes, the improper components were selected during

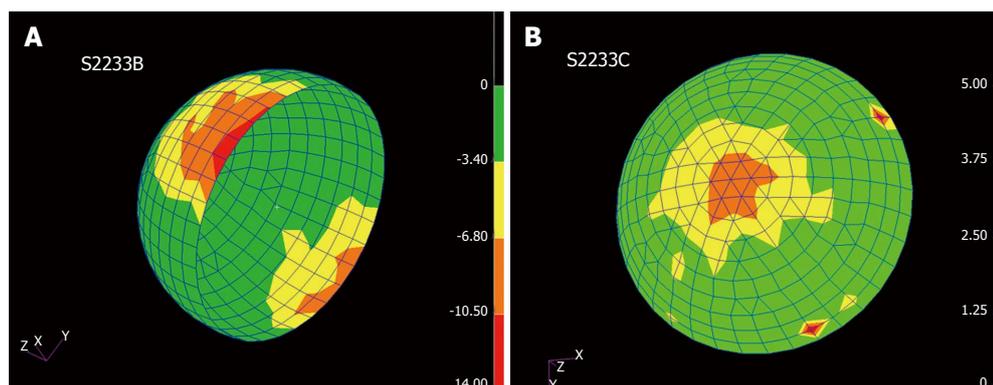


Figure 2 Coordinate measuring machines wear measurement of the mismatched couple showed that the femoral component had already been damaged.

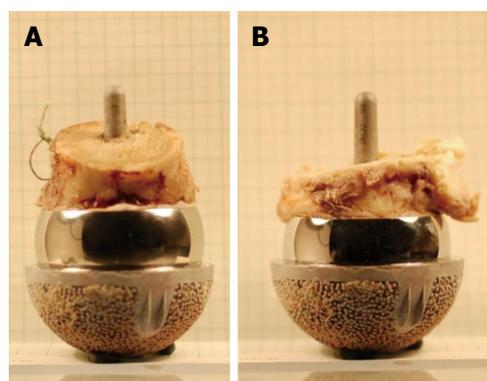


Figure 3 The 62-mm cup mismatched with and 56-mm head and but correctly matched with a 54-mm head. A: Mismatched couple with 62-mm cup and 56-mm head. Note how the femoral head was not fully seated in the socket by 3 to 4 mm. Compared to B; B: The same 62-mm thick shell cup correctly matched with a 54-mm head.

the case. The thin shell component, cup size 62-mm was requested but the 62-mm thick shell which can be used only with a 54-mm head was mistakenly provided instead. This thick shell is a special acetabular component that can be used for particular cases of head/neck mismatch or hip articulation deformity such as coxa profunda and protrusion acetabuli.

In the literature, Hanks *et al*^[6] reported this technical complication in total hip arthroplasty; in two cases the head size of the femoral component was larger than the corresponding inner diameter of the acetabular cup. The author suggests that the error can be prevented with a careful preoperative planning and appropriate selection of implants.

Morlock *et al*^[7] published on a mismatched zirconium/aluminium oxide couple with high wear in a total hip arthroplasty in a patient that had a squeaking noise but with good clinical function. No signs of loosening were detected on the radiograph. The revision was performed 42 mo after the first surgery. The analysis of the retrievals showed that the cup had large deviations from an ideal sphere but minor wear signs and the head revealed heavy local damage in the articulation zone resulting in high stress concentrations and increased wear of the zirconium head.

One of the advantages of hip resurfacing is an easier conversion to a secondary procedure if failure occurs^[8]. In this case an early revision was necessary for the pain and leg length difference the patient was experiencing. The retrieval analysis of this case revealed no clear damage to the acetabular component but there was damage to the femoral component. More importantly, lack of proper contact between the ball and the cup presented the risk of high wear with metallosis if the mismatched components had been allowed to be used. It has also been established that wear and degradation particles are released into the periprosthetic tissues and transported systemically throughout the body^[9]. Furthermore, there was also a risk that the increased torque between the mismatched bearings could have compromised fixation and stability.

Operating room staff needs to be reminded to pay careful attention to component size markings, particularly in the designs where more acetabular component sizes exist for one femoral component size. Implants also only can be matched if they are from the same manufacturer. The tight clearance specifications that make these implants work well can be dramatically mismatched if implants from different manufacturers are mixed. As seen in the present case, some implants labelled or marked as 55-mm head (nominal size), are in reality 55.5-mm. If these are matched with a real 55 mm internal diameter cup from another design we would have an equatorial mismatch with all of the attendant complications and high wear.

Care should be taken in the theatre to provide the surgeon with the correct implants. Mistakes only can be prevented by a well trained team of nurses and assistants, and they must be familiar with the size and colour code tables provided by the company on the prostheses or implant boxes. All companies should provide the surgeons with a chart that shows all different increments of the femoral head and cup sizes that can be matched together.

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COMMENTS

Case characteristics

A 51-year-old man was admitted at our institution with a mismatch of implants.

Clinical diagnosis

The patient at clinical examination presented a flexion contracture on the right side and pain in the groin.

Laboratory diagnosis

Coordinate measuring machines (CMM) wear measurement of the mismatched couple showed that the femoral component had already been damaged.

Imaging diagnosis

X-ray.

Treatment

The patient was treated with a revision to total hip arthroplasty two days later with the same posterolateral approach. The femoral component was revised with a Profemur L stem (Wright Medical Technology, Arlington, Tennessee, United States) and the socket was replaced by a Pinnacle™ Acetabular Cup System (DePuy Orthopaedics, Inc., Warsaw, United States) with Delta on Delta BioloX Ceramic couple 36 mm.

Term explanation

CMM is a technique that has been widely used for dimensional inspection of complex shaped objects both for evaluating their shape which can be used to estimate wear distribution over the surface.

Peer-review

The authors reported a case of a patient underwent a hip resurfacing arthroplasty for osteoarthritis of the left hip that was complicated by mismatched implant components. They also reported the results of the patient treated with a revision to

total hip arthroplasty two days later. As a typical case report, it could be accepted for publication.

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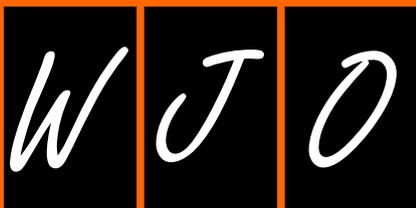
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Orthopaedic education in the era of surgical simulation: Still at the crawling stage

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Abstract

Surgical skills education is in the process of a crucial transformation from a master-apprenticeship model to simulation-based training. Orthopaedic surgery is one of the surgical specialties where simulation-based skills training needs to be integrated into the curriculum efficiently and urgently. The reason for this strong and pressing need is that orthopaedic surgery covers broad human anatomy and pathologies and requires learning enormously diverse surgical procedures including basic and advanced skills. Although the need for a simulation-based curriculum in orthopaedic surgery is clear, several obstacles need to be overcome for a smooth transformation. The main issues to be addressed can be summarized as defining the skills and procedures so that simulation-based training will be most effective; choosing the right time period during the course of orthopaedic training for exposure to simulators; the right amount of such exposure; using objective, valid and reliable metrics to measure the impact of simulation-based training on the development and progress of surgical skills; and standardization of the simulation-based curriculum nationwide and internationally. In the new era of surgical education, successful integration of simulation-based surgical skills training into the orthopaedic curriculum will depend on efficacious solutions to these obstacles in moving forward.

Key words: Surgical simulation; Orthopaedic surgery; Education; Skills training

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Core tip: Simulation-based surgical skills training outside the operating room has become essential for modern trainees due to restricted work-hours, cost pressures, emphasis on patient safety, and the increasing number of minimally invasive and technically challenging procedures. Orthopaedic surgery has fallen behind some other surgical specialties in integrating surgical simulation into its curriculum due to several obstacles. The authors aim to clarify these obstacles and suggest solutions for a smooth transformation to simulation-based curriculum in orthopaedic surgery.

Atesok K, MacDonald P, Leiter J, Dubberley J, Satava R, VanHeest A, Hurwitz S, Marsh JL. Orthopaedic education in the era of surgical simulation: Still at the crawling stage. *World J Orthop* 2017; 8(4): 290-294 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/290.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.290>

INTRODUCTION

The traditional method of teaching surgical skills in the operating rooms (OR) has been based on the master-apprenticeship (*i.e.*, learning on the patient) model for over one hundred years^[1]. Although this model has been successful throughout many generations, simulation-based surgical skills training outside the OR has become essential for modern trainees due to restricted work-hours, cost pressures, emphasis on patient safety, and the increasing number of minimally invasive and technically challenging procedures^[2]. In general surgery, once the need for surgical skills training outside the OR was recognized, surgical simulation was formally acknowledged as evidence-based and integrated into residency curriculum and board certification^[3,4].

Orthopaedic surgery arguably covers the broadest human anatomy and related pathologies among the surgical specialties. Hence, the learning of countless basic and advanced surgical procedures during orthopaedic surgery training is required. In addition, as a specialty with a focus on both bone tissue pathologies and soft tissue disorders, trainees are expected to be familiar with a diverse range of both surgical and non-surgical equipment throughout the course of their training, which indicates a strong need for simulation-based skills training. However, orthopaedic surgery has fallen behind some other surgical specialties in integrating surgical simulation into its curriculum.

Although efforts are underway to make this training a part of orthopaedic education, issues that must be addressed include the definition of skills fundamental to orthopaedic surgery that are amenable to simulation. The optimal time period and amount of exposure to the chosen simulations during orthopaedic training must be

determined. There must be objective, valid and reliable metrics to measure the effects of simulation training on both the development and progress of surgical skills. Finally, simulation-based curriculum for training in orthopaedic surgery needs to be standardized at national and international levels.

CURRENT OBSTACLES TO SIMULATION-BASED EDUCATION IN ORTHOPAEDICS

Defining areas in need of simulation-based skills training

Simulation-based training should aim to hasten the process of learning surgical skills in a safe environment that is away from the stress of the OR and also allows the opportunity to both make and learn from mistakes without causing harm to patients. Because orthopaedic surgery encompasses the broadest human anatomy, simulated orthopaedic procedures need to be defined carefully so that both basic and advanced orthopaedic surgical skills can be improved outside the OR effectively.

Currently, the majority of the educational programs in United States have already integrated simulated training of basic surgical skills in to their first postgraduate year (PGY1) either as a one-time intensive course (*i.e.*, boot camp) or as longitudinal training sessions throughout the year since this training is required by the American Board of Orthopaedic Surgery (ABOS) and Residency Review Committee (RRC) in orthopaedic surgery. However, the content of these courses is not well-defined. In addition, there is no consensus among orthopaedic training programs as to what type of advanced procedures need simulator training. Almost all advanced orthopaedic surgical skills' courses that are presently available are limited in terms of both procedure types and practiced surgical tools due to their commercial nature. As one of the first steps forward, priority will need to be given to the definition of both basic and advanced surgical skills to be trained on simulators in orthopaedic education.

Another important issue is the use of simulators for training and certification or recertification of orthopaedic surgeons already in practice. Simulation-based training might offer a valuable opportunity for practicing orthopaedic surgeons who have completed residency or fellowship training to learn new procedures and/or update their existing skills. Further, simulations may have a future role to assess surgical skills as benchmarks for certification or recertification of practicing orthopaedic surgeons. Likewise, simulators can be beneficial in selecting students for specialty training in orthopaedic surgery based on their aptitude in simulated performance of basic surgical skills. Nevertheless, all these potential areas in which simulators could have benefits need to be further identified and studied rigorously before simulators can be used in certification/recertification and trainee selection processes.

Arthroscopic surgery is an area where orthopaedic simulation is more advanced and that simulation-based

training can be very effective in improving skills of orthopaedic trainees^[5-7]. During the past few decades, there have been dramatic improvements in arthroscopic surgery of the knee, shoulder, hip, elbow, wrist and ankle joints. However, the amount of time that the trainees could spend for practicing arthroscopic surgery skills is limited because the duration of residency training is still the same as it was decades ago. Further, there are different arthroscopic procedure types for each joint, which makes it nearly impossible for trainees to become truly proficient in this field. Hence, simulated arthroscopic skills training could be an important learning opportunity for residents and fellows.

Current simulators are limited to mainly the knee and shoulder modules and do not include some of the commonly performed operations such as meniscectomy, rotator cuff repair, or even loose body removal. It is clear that simulation-based arthroscopic skills training needs to be integrated into the educational curriculum. However, the types of simulator devices and software, joints on which to focus, and procedures to be practiced using arthroscopy simulators are still waiting to be defined and standardized. Cost factors will be another limitation. As an example, the cost of a high-fidelity simulator can be as high as 100000 USD including the device, software, and maintenance.

After defining the skills for which training with simulators will be most effective, programs to educate and certify simulation lab instructors to supervise trainees during simulation-based skills training could be of value. Although such an initiative could only become relevant after a standard simulation based curriculum is established, this may also aid in achieving uniformity among educational programs nationwide.

Time, duration, and frequency of simulation-based skills training

Although surgical simulation in orthopaedic skills training has been recognized as a necessity, and the Accreditation Council on Graduate Medical Education recommends simulation training during residency education, specifics with regard to time, duration, and frequency of practicing with simulators are left to program directors to determine what they think is best for their residents^[2,8]. Since July 2013, orthopaedic residency programs in the United States have been required to incorporate laboratory-based surgical skills training into the curriculum during the first year of residency. Currently, some orthopaedic residency programs have included a one-month period of an intensive skills training course, or boot camp, into their curriculum before interns begin their training. There are existing concerns regarding the effectiveness of short-term intensive skills training, and the degree to which skills learned in these courses are retained and achieve the goal of improved integration into the actual OR is uncertain^[3]. Hence, some residency programs in the United States have decided to spread these skills training courses throughout the entire internship year *via* one

or two days of simulation-based training every week. Further research is required to prove the superiority of either method in surgical skills training during residency.

Due to the tremendous number of surgical skills and procedures that must be learned after the first year of residency, incorporation of simulation-based skills training into the latter years of residency should positively influence the development of trainees' skills. Choosing the time and duration of simulation-based training as well as determining the optimal time period for reinforcing the learned skills by repeating the simulated courses are of primary concern. Although more simulation-based surgical skills training may result in better learning for residents, this would also require more time spent in education and thus away from clinical service, which might be an obstacle to conducting lab-based training for extended periods during residency. The fellowship period might be a convenient time for practicing skills that are more advanced and specific to subspecialties and offer greater opportunities for dedicated time. However, fellowship programs may vary in terms of their goals and objectives for training, and standardized educational curriculum adjustments for simulation-based training during the fellowship period do not appear to be realistic at this stage. Also more advanced skills training is necessary at the fellowship level requiring higher fidelity simulations which may be cost prohibitive for many fellowship programs.

Proficiency-based-progression training

A notable simulation-based surgical skills training approach, which was recently proposed, is proficiency-based-progression (PBP). This approach can be defined as training based on a benchmark that has been established by expert performance. The benchmark that the novice must achieve is set by the mean performance scores of experts who undergo the same course (curriculum). Thus, the training is not completed in a given amount of time but rather continues until the benchmark scores are met for two consecutive trials. In addition, tasks are presented in a progressively increasing level of difficulty. The trainees are allowed to proceed to the next step only after the previous and easier task is accomplished proficiently. This notion also matches the Dreyfus and Dreyfus model of progression of skills performance from novice to master^[9]. In a prospective randomized blinded study, Angelo *et al.*^[5] demonstrated that the PBP protocol, when coupled with the use of a shoulder model simulator and validated metrics, produces superior arthroscopic Bankart repair skills when compared with traditional and simulator-enhanced training methods. It is evident that the integration of simulation-based surgical skills training into educational curriculum using such novel approaches will be more beneficial if certain factors, such as which skills require focus and at what point during the training they should be implemented, could be determined and organized beforehand.

MEASUREMENT OF SKILLS LEARNED IN SIMULATORS

In the process of simulation-based surgical skills training, measurement of trainees' progress in performing surgical procedures and assessment of their levels of proficiency is vital. As Rear Admiral Dr. Grace Hopper stated, "One accurate measurement is worth a thousand expert opinions"^[10]. Traditional assessment of surgical proficiency, which has been based on both the observations and personal opinions of experts regarding trainees' performances, will need to be replaced with valid, objective, and standardized techniques for the measurement of the skills learned using simulators.

Current measurement methods include questionnaires, objective structured assessment of technical skills (OSATS) and global rating scale of performance (GRS) scoring systems, structured assessments using video recording, motion tracking, and direct metric measurement of task performance. Although questionnaires can be practical and low-cost assessment tools, their inherent shortcomings are subjectivity and unfeasibility in terms of standardization. Further, comfort or knowledge questionnaires as proficiency measures in surgical procedures are not validated instruments^[11]. OSATS is performed by independent observers, who evaluate a trainee's performance objectively using a checklist of specific surgical maneuvers that have been deemed essential to the procedure (*e.g.*, measuring the screw length with depth gauge, verifying screw lengths, ensuring that screws securely engage the far cortex, *etc.*); GRS aims to measure characteristic surgical behaviors during the performance of any given procedure (*e.g.*, respect for soft tissues, fluidity of movements, familiarity with the instruments, *etc.*)^[2,12]. Hence, subjective criteria included in GRS result in limitations including ambiguity, poor inter-rater reliability, and frequent bias. Video-based feedback is a practical method that enables the assessment of surgical performance using the same measurement tools as OSATS or GRS at a later, convenient time for the rater^[13]. However, this means that the shortcomings associated with OSATS and GRS are also relevant to the video-based assessment of simulated surgical skills. Motion tracking and analysis systems can be mounted to surgical tools and attached to or worn on the hands as sensors^[14]. They can also be built within a simulator to track and analyze instrument tip trajectory data^[15]. Although motion analysis systems might be an objective and valid tool for assessing surgical skills in terms of precision and economy of movements during the performance of simulated surgical procedures, the impact of these metrics on a trainee's skill transfer to the OR has yet to be proven^[16,17]. Directly measuring a concrete aspect of a skill using universal metric measurements holds promise for improving reliability, validity, clinical relevance, and applicability in large-scale studies or high-stakes board exams, while decreasing time and expense. Examples

of such parameters include the mechanical strength of a knot or a fracture fixation construct; accuracy of reduction; or time to completion of a skill task^[18-20].

The abovementioned measurement methods can be used alone or in combination based on the preferences of each research group or institution. Therefore, heterogeneity exists in the literature in terms of available evidence to draw conclusions. Formation of standardized measurement protocols using reliable, valid, and objective metrics are essential before a simulation-based orthopaedic surgery education curriculum can become standard.

STANDARDIZATION OF SIMULATION-BASED CURRICULUM AMONG RESIDENCY AND FELLOWSHIP PROGRAMS

Although simulation-based surgical skills training in dedicated laboratories is already a requirement to learn basic surgical skills during residency in United States, there are no guidelines that each residency program is required to follow. Moreover, there is no requirement to implement simulation-based training in the fellowship period, during which more advanced procedural skills, such as arthroscopic treatment of intraarticular pathologies, are taught.

As an example for standardized curriculum change, the ABOS and the Orthopaedic RRC have taken initial steps by requiring simulation based training during the PGY 1 year. Organizations that focus on education such as American Orthopaedic Association/Council of Orthopaedic Residency Directors, American Academy of Orthopaedic Surgeons or subspecialty societies could develop a more robust simulation curriculum for later years in training. However further mandatory requirements will be necessary to widely incorporate simulation in to curriculum and to uniformly advance the field. It is likely that the accrediting and certifying bodies will want to see solutions to some of the other issues identified in this article before mandating further requirements. It is clear that proposing initiatives is easier said than done. However, improving surgical education and human health is worthy of the required intensive efforts.

CONCLUSION

Orthopaedic surgery requires the comprehensive integration of simulation-based surgical skills training into its educational curriculum. Although efforts are being made toward transitioning into simulation-based educational curriculum, orthopaedic surgery lagged behind other surgical disciplines in simulation. Current obstacles that require further work and research include definition of the areas that need simulation-based skills training in orthopaedic surgery, choosing the optimal time period in orthopaedic training for exposure to simulators; the

correct amount of such exposure; using objective, valid, and reliable metrics to measure the impact of the training on the development and progress of surgical skills; and standardization of the simulation-based curriculum both nationwide and internationally. A successful transition into simulation-based surgical skills training in the orthopaedic educational curriculum will depend on efficacious solutions to these obstacles.

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Growing spine deformities: Are magnetic rods the final answer?

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Abstract

Treatment paradigms for Early Onset Scoliosis have changed from fusion to fusionless methods as the harmful effects of early fusion on the growing spine

and thorax were realized. Magnetic rods are a recent addition to fusionless technology for controlling scoliosis in a growing spine. The clinical evidence base on magnet driven growth rods (MDGR) has accumulated over the last 4 years. It has implications for reduction in the number of repeat surgeries required with similar complications as the traditional growth rods (TGR) and at a higher initial cost. However in terms of patient psyche and avoidance of repeat surgeries which are necessary with the TGR, MDGR treatment works out less expensive in the long run with definitely better patient comfort. The authors look at the available literature coupled with their own experience to discuss the current status, limitations and future prospects for this type of technology.

Key words: Growing spine; Magnet driven growth rods; Magnetic growth rods; Growth rods; Early Onset Scoliosis

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Core tip: This editorial focuses on the current status of magnet driven growth rods in the management of Early Onset Scoliosis (EOS). The editorial gives a background of this technology vis a vis the traditional growth rods and looks at the advantages, limitations and complications associated with the magnetic growth rods. Also its effects on lung function and cost comparison with the traditional growth rods is made. The authors attempt to answer the question "Are magnetic growth rods the final answer for EOS?" in the light of the world literature and personal experience on the above subject.

Johari AN, Nemade AS. Growing spine deformities: Are magnetic rods the final answer? *World J Orthop* 2017; 8(4): 295-300 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/295.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.295>

Progressive Early-Onset Scoliosis (EOS) has remained a management challenge for decades with surgical management themes changing from early operative fusion to the more recent fusionless surgeries. With this there has been an increased interest to find an ideal tool to reach the goal with minimal complications. Desirable characteristics include ease of instrumentation without age restrictions, minimum number of surgeries for curve control or reduction with minimum hardware problems. The advantages and disadvantages of various growth friendly instruments are noted in Table 1.

EVOLUTION OF A NEW IMPLANT

The thought of achieving distraction without repeat surgical interventions started with Takaso *et al*^[1]. In 1998 they devised a growing rod that could be elongated with a remote controller. The rod contained a motor with remote control receiver (placed in the abdominal cavity). In their experimental study on induced scoliosis in beagle dogs they could achieve correction of curves by 3 weekly distractions using external remote controller non-invasively with the study animal awake. The limitations of the instrument were size of the outer cylinder of the rod (16 mm) and the site for placement of the remote control receiver.

BEGINNING OF MAGNETIC ERA (MAGNET CONTROLLED GROWING RODS, MCGR)

The very first report of a magnetic rod being used for scoliosis dates back to 2004 when Jean Dubousset and Arnaud developed and used the Phenix device. Arnaud Souberian a French aeronautical engineer adopted the idea from expandable rod for bone tumors^[2,3].

The Phenix device consisted of a magnetically controlled extensible rod that was distracted by placing a permanent magnet on the skin over the spine at home. It was first used in 8 paralytic patients. The clinical outcomes of this device were extremely limited. Miladi *et al*^[4] reported a limited human experience on them.

Akbarnia *et al*^[5] in 2009 presented the first technical note on Ellipse Technology Inc Device, wherein an implantable magnetic rod was distracted by external adjustment device. It was aimed at providing distraction to the spine by non-surgical means.

The next breakthrough came in 2012 when Akbarnia *et al*^[5] published their report on MAGEC rod in an experimental study on Yucatan pigs^[6]. In this well-designed study, the authors implanted the MAGEC rods designed by Ellipse technologies and compared the results with a sham group. The rod consisted of an actuator that had a magnet and could not be contoured. The proximal and distal parts could be contoured. Distraction was carried out at 7 mm/wk for 7 wk with the help of an external adjustment device. At the end of 10 wk of the study they found a significant difference in the vertebral unit

height in experimental (MAGEC rod) as compared to sham group. There were no rod related complications. Histological data of the para-aortic lymph nodes revealed inflammatory cells in 2/5 in experimental and 1/3 in sham group. No abnormalities were found in liver, spleen and kidney biopsies.

The post implant removal magnetic resonance imaging (MRI) showed healthy discs and the cord was found to be normal. They could achieve 80% of distraction given by the external adjustment device.

INDICATIONS

Magnetic rods have been designed for EOS of varied etiologies including neuromuscular, idiopathic, congenital, etc. The indications can be extended to a slightly elder age group up to 12 years in selected cases. Because of the limitations of size of the rod most studies have used the rods after 3 to 4 years of age with scoliosis involving the thoracic spine predominantly. It can be used for the more rigid congenital varieties, the results of distraction may not be favorable, but the fact that the rod can act as an internal brace in itself can be of help in maintaining curvature.

MAGNET CONTROLLED GROWING RODS IN THE RECENT ERA

Many studies have been published in last couple of years showing its efficacy in humans covering various aspects of EOS.

In the very first publication on the experience of MAGEC in humans, Cheung *et al*^[7] described the outcomes in 2 (one of Marfan's and other AIS) of the 5 patients who completed 2 years of follow-up. Length of instrumented segment increased by mean of 1.9 mm with each distraction (1.5-2 mm/mo). There were no implant related complications and no patient complained of pain. All the patients were satisfied with the procedure and had a good functional outcome as per the SRS-30 questionnaire. There was only one instance of loss of distraction that was rectified with the rod design.

Subsequent 3 years have seen a burst of papers on MAGEC exploring its efficacy. The first multicenter study of 33 patients by Akbarnia *et al*^[8] documented results in 14 cases of EOS (idiopathic, neuromuscular, congenital and neurofibromatosis) treated with MAGEC rod instrumentation. The mean age was 8 year and 10 mo. They compared the results of single vs dual rods. The mean improvement in Cobb angles was 46% and 48% respectively in single and dual rods respectively. There was no significant difference in both groups in the average T1-T12 growth but the difference was significant in T1-S1 growth. Partial loss of distraction was the most common complication after 11 of 68 distractions (2 in dual and 9 in single rods). The loss was regained and maintained in subsequent distractions. No other implant related complications were noted. In none of the cases

Table 1 Advantages and disadvantages of various growth friendly instruments

Modality	Advantages	Disadvantages
Traditional growth rods/VEPTR Shilla	Fusionless surgery Fusionless surgery, no repeat surgeries	Repeat surgical distractions, psychological issues Long term results awaited Growth potential dependent
Staple/tether	Less invasive, no repeat surgeries	Limited indications, lesser degree of severity

VEPTR: Vertical Expandable Prosthetic Titanium Rib.

proximal junctional kyphosis was seen^[8].

A second landmark paper came from Dannawi *et al*^[9] in 2013 with 34 children (mean age 8 years) of EOS with mean Cobb's angle of 69 degrees. At a mean follow-up of 15 mo (12 to 18 mo), both groups single and dual rods, had a statistically significant improvement in mean pre-operative, immediate post operative and final Cobb angles and also significant increase in the mean T1-S1 distance. No patient developed a post-operative fusion. The complications met were: Superficial infection and rod breakage in 2 (one in each group), loss of distraction in 2 patients with single rod (rectified subsequently) and hook pull out in one patient with dual rod. Trimming of rod was done in one with hardware prominence. Overall complications were fewer as compared to conventional growth rods.

Hickey in their comparative study of MCGR (magnet controlled growing rods) implantation in primary (mean age 4.5 year, mean Cobb 74 degrees) vs revision cases (mean age 10.9 years, Cobb 45 degrees) of EOS found encouraging results in term of maintenance of Cobb angle with comparable increase in the spinal growth (6 mm/year in primary, 12 mm/year in revision cases)^[10]. Of the two complications in primary procedure one was rod fracture and the other was proximal screw back out. In the revision group there was loss of distraction in one and failure of distraction in another.

La Rosa *et al*^[11], Ridderbusch *et al*^[12] and Yilmaz *et al*^[13] in their case series of EOS with MCGR found it efficacious in allowing non invasive distraction without repeat surgeries. It achieved spinal growth comparable to conventional growth rod techniques.

Teoh *et al*^[14] with the longest follow-up study till date could get a 43% correction of scoliosis in primary cases whereas it was only 2% in the conversion case, but the curves were maintained till the last follow-up.

IMPROVEMENT IN PULMONARY FUNCTION

Yoon *et al*^[15], in a study of the effects of MAGEC rod instrumentation on pulmonary function in cases with neuromuscular scoliosis, compared pre-operative FVC and FEV1 to the post-operative values. They found a significant improvement in the post-operative values; they felt that there may not be longitudinal improvement in the function because of the natural course of the neuromuscular etiology, but the benefits of avoidance of repeat anaesthesia and surgery remain.

Harshavardhana *et al*^[16] in a prospective study of 26 patients of EOS of various etiologies found the Magnet Driven Growth Rods (MdGR) to be effective in reducing the number of complications and distraction surgeries. They quoted a spectacular improvement of PFT in neuromuscular cases with reduced incidence of chest infections and emergency room admissions for pulmonary ailments.

DISTRACTION FREQUENCY

Three monthly vs small more frequent: Akbarnia *et al*^[17] studied the effect of frequency of distraction on the outcomes of MCGR. In the more frequent distraction group (weekly to 2 mo) there were more complications of failure of rod distraction and proximal junctional kyphosis as compared to rod breakage and proximal foundation failure which were seen in other group that underwent distraction every 3 to 6 mo.

CONVERSION FROM TRADITIONAL GROWTH RODS TO MAGEC

Keskinen *et al*^[18] compared the efficacy of using MdGR in primary vs conversion from previously operated traditional growth rods (TGR) and found that scoliosis can be equally controlled after conversion from TGR to MdGR, but the growth from baseline is less in conversion group.

The longest follow-up study (minimum longest follow-up of 44 mo) by Teoh *et al*^[14] quotes that the mid term results of MAGEC are not as promising as the short term results. Single rod construct should be avoided and they indicated a caution in using MAGEC in revision cases.

COMPLICATIONS

Choi *et al*^[19] in a retrospective multi-centric study of MCGR proposed a classification of complications related to the procedure. Of the 115 operated patients 54 had a minimum 1-year follow-up and were analyzed. They classified complications as wound/implant related and early (< 6 mo) or late > 6 mo. Implant related: (1) rod breakage; (2) failure of lengthening requiring revision surgery; and (3) anchor pull outs. Wound related complications: Surgical site infection (deep) requiring additional surgical intervention.

They summarized complications as: (1) 42% had at least 1 complication; (2) 15% revision surgery, at least one; (3) 11% rod breakage (33% early, 66% late); (4) 11% (6)

failure of lengthening, 4 distracted in subsequent visits, 2 rods were exchanged; (5) 13% anchor point problems; and (6) 3.7% (2) deep infection, one each early (drainage and antibiotic)/late (rod penetration, requiring removal of one of the dual rods).

In the longest follow-up study till date Teoh *et al*^[14] reported 75% (6/8) patients required revision surgeries, 4 of which were for rod problems and one for proximal junctional kyphosis. Rod failure occurred mainly after 3 years (average 39 mo). All single rod constructs required revision procedure for failure.

Harshavardhana *et al*^[16] encountered complications that include 3 single and 1 dual rod breakage, one superficial infection, four cases had proximal junctional kyphosis and distal anchor failure in two patients.

HURDLES

With MCGR emerging as the new hope for EOS as seen from the published articles and early results, it brings along with it its own sets of issues to be tackled. Some limitations are as follows: (1) radiation hazard due to frequent X-rays for monitoring the distraction; (2) MRI compatibility: Due to presence of internal magnet in the rod; and (3) cost.

ULTRASOUND FOR MEASURING DISTRACTION

In an effort to reduce radiation exposure due to repeated X-rays for measuring distractions, Stokes *et al*^[20] and Cheung *et al*^[21] found a good inter observer and intra observer variability in using ultrasound vs X-rays for measurement of distraction of the MCGR's, thus reducing the radiation hazard of frequent radiographs for monitoring distractions. This technique requires training, attention to details and rejection of sub-optimal images. Errors can occur during acquisition of images and selection of reference points. The limitations of this technique are the inability to assess the spinal alignment and integrity of construct. Therefore X-rays can be done at 6 monthly interval to assess these parameters.

MRI COMPATIBILITY

Sturm *et al*^[22] in a review article on the management of EOS mention the efficacy of MAGEC and also state that there is no evidence that the electromagnetic field causes any persistent or major side effect with repeated distractions. Although stiffness, spontaneous fusions and diminished returns will also be observed with this technique, avoidance of multiple surgeries is a colossal advantage over TGR.

Budd *et al*^[23] presenting their experimental study stated the safety of MRI with the MAGEC rods *in-situ*, *i.e.*, the lengthening mechanism was not triggered. They found no reduction or enhancement in the ability of the rods to lengthen but the rods did produce an artifact in

imaging the spine.

COST AS COMPARED TO TGR

Charroin *et al*^[24] compared the expenses in TGR vs MCGR over a period of 4 years based on a simulation model using assumptions obtained from literature search or their local experience. They found that MCGR procedure induces a strong expense at start, then costs evolve gradually because of the difference of TGR strategy. Despite its major unit cost, their results show that the use of MCGR could lead to lower direct costs with a time horizon of 4 years. Also improvement of quality of life could be indirectly evaluated considering that about 2 surgeries and hospital stays per patient-year could be avoided using MCGR. The limitations of the study included: (1) the basis of estimation of costs, *i.e.*, a simulation model; (2) not taking into account outpatient direct costs and indirect costs such as parent's time off work; and (3) assumptions of long term results of MCGR based on the short term, few published series. Jenks *et al*^[25] found equal efficacy of both but the added advantage of MAGEC being a robust cost saving at the end of 6 years. Thus NICE issued a positive recommendation for the use of MAGEC for EOS. Similar recommendations were made by Rolton *et al*^[26], Armoiry *et al*^[27], with a significant cost saving at the end of 5 years.

WHAT IS THE EVIDENCE?

Evidence based: TGR vs MAGEC

In the first case matched study between traditional growth rods (TGR) and MCGR in 2014 by Akbarnia *et al*^[28] they compared 12 MCGR patients to 12 case matched TGR patients. The average follow-up for TGR was 1.6 year more as compared to MCGR who had 2.5 year mean follow-up. Major curve correction, annual T1-T12 and T1-S1 growth was similar in both groups. Incidence of unplanned surgical revisions were similar in both groups but the MCGR patients had 57 fewer surgical procedures. Most of the complications were related to implant failure. In the MCGR group loss of distraction was commonest, 63%, and in the TGR it was anchor pull out and rod breakage.

Jenks *et al*^[25] in a meta-analysis of the published literature made provisional recommendations for NICE (National Institute for Health and Care Excellence). These were: (1) MAGEC would avoid repeat surgeries and reduce complications and have benefit for physical and psychological aspects of patient and family; (2) indicated for use in children between ages of 2 to 11; and (3) the system is cost saving as compared to conventional growth rods from about three years after the index procedure.

Figueiredo *et al*^[29] based on a systematic review of 6 papers found MCGR to be a safe and effective technique and an alternative to traditional growth rods. There were limitations due to the limitations of existing literature and

Table 2 Single centre series of 10 patients operated by the senior surgeon

Parameter	Mean
Age	10.6 yr
Pre operative Cobb angle	83.1°
Last follow-up	65°
No. distraction/patients	3.4
External remote controller distraction	12.15 mm
Actual distraction	8.9 mm (73.25%)
Follow-up	14.3 mo
Correction mean	18.3°
Percentage correction	21.62%

potential bias in literature due to this novel technique being in early phases.

The shortcomings of MAGEC

The results of MAGEC are promising but follow-up is short and the device technology does not guard against the risk of gradual stiffening of the spine between lengthening sessions and the limitation of the force of magnetic rod to overcome the scoliosis related stiffness in one or two years of use^[30].

With the newer long-term studies coming up, we are now coming across specific complications of growing rods *viz*: (1) failure of distraction; (2) fatigue failure of implant; (3) proximal junctional kyphosis; (4) loss of sagittal balance due to non-contourable long actuator; (5) less reliable results on conversion from traditional growth rods to MCGR; and (6) more reliability on dual rods.

In a study on sagittal profile following MCGR in EOS, Akbarnia *et al.*^[31] showed that the thoracic kyphosis was reduced in cases with pre-existing thoracic kyphosis more than 40 degrees and had no effect on other regional sagittal parameters.

Inaparthi *et al.*^[32] reported incidence of proximal junctional kyphosis (PJK) in 28% cases of EOS operated with MCGR. It was common in males, all the cases were syndromic in etiology and 50% of them were conversion from traditional growth rods. But the presence of PJK was not an indication for further surgery.

AUTHOR'S EXPERIENCE

We have been using the MAGEC (Ellipse Technologies) since November 2014. In our single centre series of 10 patients operated by the senior surgeon (Dr. Ashok N Johari), 9 cases were of congenital etiology and one neurogenic with associated syringomyelia without neurodeficit. All the patients were females. The data is as shown in Table 2. The mean age at surgery was 10.6 years range (8-13 years). The mean pre operative Cobb's angle was 83.1° and post-operative was 65°, with a mean correction of 21.62%. This correction was maintained till the last follow-up of a mean 14.3 mo (7-21 mo). There were 3.4 distractions per patient with 73.25% (8.9/12.15 mms) distraction achieved *in-situ*.

No patient had any intra-operative complications

or neurodeficit post-operatively but we had difficulties instrumenting the spine due to the complex anatomy of the congenital deformities and severe degrees of curvatures. The rods needed significant contouring and almost always we had to use hybrid constructs (hooks and pedicle screws). We had one rod breakage intra-operatively which was managed by using a rod to rod connector from the routine spine instrumentation inventory.

The patients were advised continuous bracing and distraction started 3 mo later at 3 mo interval. We had problems in distraction in one patient which was recovered in subsequent distraction under a setting of mild sedation in operation theatre as the patient was very apprehensive. Later on she had a smooth course of distraction. All the patients were satisfied with the procedure and none complained of pain during distraction.

SO, ARE MAGNETIC RODS THE FINAL ANSWER?

Problems similar to traditional growth rods like infection, anchors site failure/break outs persist with MCGR, except for elimination of repeat surgeries and its consequences. Although MCGR has reduced the number of planned surgeries for distraction, there are incidences of unplanned visits to operation theatre for its own reasons.

These issues need to be addressed before we give a final verdict on MAGEC. The technology still has scope for improvement. Due to its novel approach this technique kindles many a hopes and with traditional growth rods as the only competitor, MAGEC is here to stay till the next major breakthrough in instrumentation techniques.

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Syndesmotic *InternalBrace*TM for anatomic distal tibiofibular ligament augmentation

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Author contributions: Regauer M had the idea of syndesmotic *InternalBrace*TM, was the treating physician and was responsible for writing the paper and design of illustrations and figures; Mackay G had invented the general *InternalBrace*TM technique and revised the article critically for important intellectual content and correct English language as a native speaker; Lange M was responsible for acquisition of data and helped to design the illustrations and figures; Kammerlander C and Böcker W revised the article critically for important intellectual content and were responsible for the final approval of the version to be published.

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Abstract

Reconstruction of unstable syndesmotic injuries is not trivial, and there is no generally accepted treatment guidelines. Thus, there still remain considerable controversies regarding diagnosis, classification and treatment of syndesmotic injuries. Syndesmotic malreduction is the most common indication for early re-operation after ankle fracture surgery, and widening of the ankle mortise by only 1 mm decreases the contact area of the tibiotalar joint by 42%. Outcome of ankle fractures with syndesmosis injury is worse than without, even after surgical syndesmotic stabilization. This may be due to a high incidence of syndesmotic malreduction revealed by increasing postoperative computed tomography controls. Therefore, even open visualization of the syndesmosis during the reduction maneuver has been recommended. Thus, the most important clinical predictor of outcome is consistently reported as accuracy of anatomic reduction of the injured syndesmosis. In this context the TightRope[®] system is reported to have advantages compared to classical syndesmotic screws. However, rotational instability of the distal fibula cannot be safely limited by use of 1 or even 2 TightRopes[®]. Therefore, we developed a new syndesmotic *InternalBrace*TM technique for improved anatomic distal tibiofibular ligament augmentation to protect healing of the injured native ligaments. The *InternalBrace*TM technique was developed by Gordon Mackay from Scotland in 2012 using SwiveLocks[®] for knotless aperture fixation of a FiberTape[®] at the anatomic footprints of the augmented ligaments, and augmentation of the anterior talofibular ligament, the

deltoid ligament, the spring ligament and the medial collateral ligaments of the knee have been published so far. According to the individual injury pattern, patients can either be treated by the new syndesmotic *InternalBrace*™ technique alone as a single anterior stabilization, or in combination with one posteriorly directed TightRope® as a double stabilization, or in combination with one TightRope® and a posterolateral malleolar screw fixation as a triple stabilization. Moreover, the syndesmotic *InternalBrace*™ technique is suitable for anatomic re-fixation of displaced bony avulsion fragments too small for screw fixation and for indirect reduction of small posterolateral tibial avulsion fragments by anatomic reduction of the anterior syndesmosis with an *InternalBrace*™ after osteosynthesis of the distal fibula. In this paper, comprehensively illustrated clinical examples show that anatomic reconstruction with rotational stabilization of the syndesmosis can be realized by use of our new syndesmotic *InternalBrace*™ technique. A clinical trial for evaluation of the functional outcomes has been started at our hospital.

Key words: Syndesmosis injury; Rotational instability; Stabilization; Anatomic repair; *InternalBrace*™; Surgical technique

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Core tip: Reconstruction of unstable syndesmotic injuries is not trivial, and there are no generally accepted treatment guidelines. The TightRope® system is reported to have advantages compared to classical syndesmotic screws. However, rotational instability of the distal fibula is not safely eliminated by use of 1 or even 2 TightRopes®. Therefore, we developed a new syndesmotic *InternalBrace*™ technique using SwiveLocks® for knotless aperture fixation of a FiberTape® at the anatomic footprints of the injured ligaments for improved anatomic distal tibiofibular ligament augmentation to protect healing of the injured native ligaments.

Regauer M, Mackay G, Lange M, Kammerlander C, Böcker W. Syndesmotic *InternalBrace*™ for anatomic distal tibiofibular ligament augmentation. *World J Orthop* 2017; 8(4): 301-309 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/301.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.301>

INTRODUCTION

The ligaments stabilizing the syndesmosis prevent excess fibular motion in multiple directions: Anterior-posterior translation, lateral translation, cranio-caudal translation, and internal and external rotation^[1]. Appropriate fibular position and limited rotation are necessary for normal syndesmotic function and talar position within the ankle mortise^[2]. Reconstruction of unstable syndesmotic injuries is not trivial, and there is no generally accepted

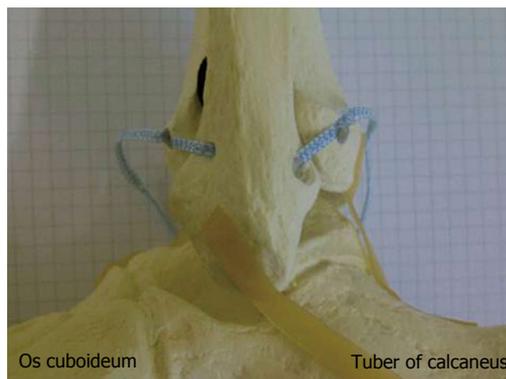


Figure 1 Lateral view on a skeletal model of a left ankle joint: Anatomic augmentation of the anterior and posterior tibiofibular ligament by use of an *InternalBrace*™ technique is simulated.

treatment guidelines^[1,3,4]. Thus, there still remains considerable controversies regarding diagnosis, classification and treatment of syndesmotic injuries^[1,5]. Syndesmotic malreduction is the most common indication for early re-operation after ankle fracture surgery, and widening of the ankle mortise by only 1 mm decreases the contact area of the tibiotalar joint by 42%^[6-9]. Syndesmotic instability is a strong predictor for less favorable clinical outcomes of ankle fractures, even after surgical syndesmotic stabilization. This may be due to a high incidence of syndesmotic malreduction revealed by increasing postoperative computed tomography (CT) controls^[10-14]. Therefore, even open visualization of the syndesmosis during the reduction maneuver has been recommended^[13]. Thus, the most important clinical predictor of outcome is consistently reported as accuracy of anatomic reduction of the injured syndesmosis^[12,14,15].

In this context the TightRope® system (Arthrex®, Naples, United States) is repeatedly reported to have advantages compared to classical syndesmotic screws^[12,16-18]. However, rotational instability of the distal fibula cannot be safely limited by standard use of 1 or even 2 TightRopes® as shown by Teramoto *et al.*^[18] who tried to imitate anatomy by use of different directions of the TightRopes®.

Therefore, we developed a new syndesmotic *InternalBrace*™ technique using SwiveLocks® (Arthrex®, Naples, United States) for knotless aperture fixation of a FiberTape® (Arthrex®, Naples, United States) directly at the anatomic footprints of the injured ligaments for an optimized imitation of the anatomy of the anterior and posterior syndesmosis to protect healing of the injured native ligaments. Figure 1 shows a simulation of an anatomic augmentation of the anterior and posterior tibiofibular ligament by use of a syndesmotic *InternalBrace*™ technique in a skeletal model of a left ankle joint.

SYNDESMOTIC INTERNALBRACE™ - THEORY AND PRINCIPLES

The *InternalBrace*™ technique was developed by Gordon

Mackay from Scotland in 2012 using SwiveLocks® for knotless aperture fixation of a FiberTape® at the anatomic footprints of the augmented ligaments, and augmentation of the anterior talofibular ligament^[19-22], the deltoid ligament^[3], the spring ligament^[23], and the medial collateral and cruciate ligaments of the knee have been published so far^[24-28].

The primary aim of an *InternalBrace*™ is repair of vital tissue rather than reconstruction or replacement with non-vital tendon transplants^[3]. Ligament healing should be standard rather than replacement, as the original footprints of ligaments tend to be much larger than tendon grafts could replace. So an important advantage of the the *InternalBrace*™ technique is preservation of proprioception instead of cutting out the ligament remnants. An *InternalBrace*™ acts as a check-rein or as a corner stone to stability just like a seat-belt, and thus the *InternalBrace*™ supports early mobilization of a repaired ligament and allows the natural tissues to progressively strengthen^[3,25]. In analogy to fracture repair, an *InternalBrace*™ applies AO principles to soft tissues.

The FiberTape® is a braided ultra-high-molecular-weight polyethylene/polyester suture tape which has an ultimate tensile strength of about 750 N^[3]. Until June 2014, when we started to use this new technique, about 732000 FiberTapes® have been sold, and a total of only 95 complications due to FiberTapes® have been reported so far (internal information by Arthrex). According to Peter Miller FiberTapes® have been recognized to be "incorporated" after 4 mo in revision shoulder surgery. Taken as a whole, FiberTapes® can be considered very safe implants. Alternative applications of FiberTapes®, SwiveLocks® or the *InternalBrace*™ technique, respectively, are augmentation of the anterolateral ligament of the knee, additional AC-joint stabilization in the horizontal plane, augmentation of the ulnar collateral ligaments for elbow stabilization, or minimally invasive repair of ruptured Achilles tendons^[3,29,30].

SYNDESMOTIC *INTERNALBRACE*™ - SURGICAL TECHNIQUE

Primary feasibility studies in human cadaver models showed that the syndesmotic *InternalBrace*™ technique can be performed easily in a minimally invasive fashion (Figures 2 and 3). A longitudinal incision about 15 mm long was performed at the level of the ankle joint line just a few millimeters anterior and posterior of the distal fibula. An aiming drill guide was used to insert a k-wire into the distal fibula from the anterior to the posterior footprint of the syndesmotic ligaments for creating a bone tunnel using a 2.7 mm cannulated drill (Figure 2A). A FiberTape® was inserted through the bone tunnel until the middle of the tape was inside the tunnel. The FiberTape® was then locked securely inside the bone tunnel of the distal fibula by use of an interference screw (SwiveLock® 3.5 mm) to avoid movements of

the tape inside the tunnel with potential sawing effects (Figure 2B). Using the existing approaches, 3.4 mm bone tunnels were drilled at the tibial footprints of the anterior and posterior syndesmotic ligaments identified by fluoroscopy, and after adequate tapping of the bone tunnels and correct positioning of the distal fibula, both free ends of the FiberTape® were fixed into the bone tunnels with a 4.75 mm SwiveLock® (Figure 2C-F). Control of the minimally invasively performed positioning of the implants was possible by extensive opening of the cadaver situs. The view from anterolateral (Figure 3A) and from posterolateral (Figure 3B) on the left ankle joint reveals correct placement of the four anchors for anatomic reduction and augmentation of the anterior and posterior tibiofibular ligaments. Based on these positive results of the feasibility studies we started to use this technique in patients.

According to the individual injury pattern, patients were either treated by the new syndesmotic *InternalBrace*™ technique alone as a single anterior stabilization (Figure 4), or in combination with one posteriorly directed TightRope® as a double stabilization (Figures 5 and 6), or in combination with one TightRope® and a posterolateral malleolar screw fixation as a triple stabilization (Figure 7).

SINGLE ANTERIOR STABILIZATION

Figure 4 shows the clinical example of a 32-year-old female soccer player with acute injury of the anterior syndesmosis after supination-inversion sprain of the right ankle (Figure 4A). We sutured the torn ligament (Figure 4B) and performed a single stabilization of the anterior syndesmosis with a 3.5 mm SwiveLock® at the fibular and a 4.75 mm SwiveLock® at the tibial footprint, respectively (Figure 4C). In case of open surgery, the fibular and tibial footprints can be identified by direct visualization just following the fibers of the injured ligament. Here it is important to avoid distal malpositioning of the SwiveLocks to prevent impinging of the FiberTape® on the anterolateral aspect of the talus. To avoid over-constraining of the anterior syndesmosis a hemostat clamp can be put under the FiberTape® during tensioning. After surgery we performed a CT scan to verify anatomic positioning of the ankle mortise and correct screw placement (Figure 4D).

DOUBLE STABILIZATION

Figure 5 shows a double stabilization with an anterior *InternalBrace*™ and one posteriorly directed TightRope® resulting in a perfect indirect reduction of the small posterolateral avulsion fragment. The 45-year-old male patient sustained a type B ankle fracture with posterolateral subluxation of the talus due to an avulsion of the posterolateral malleolus (Figures 6A, C, E and G). After standard plate osteosynthesis of the distal fibula the syndesmosis remained unstable, especially when performing external rotation or posterior translation of the distal fibula. Due to the multidirectional instability of



Figure 2 Minimally invasive anatomic augmentation of the anterior and posterior syndesmosis in a cadaver model (A-F). Note: The FiberTape® has to be locked securely inside the bone tunnel of the distal fibula by use of an interference screw to avoid movements of the Tape inside the tunnel with potential sawing effects.

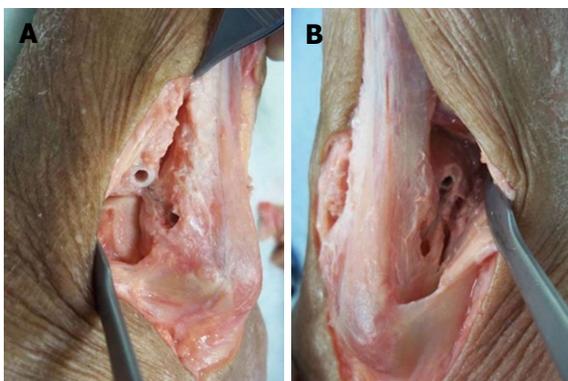


Figure 3 Control of the positioning of the implants by extensive opening of the cadaver situs. View from anterolateral (A) and from posterolateral (B) on a left ankle joint: correct placement of the four anchors for anatomic reduction and augmentation of the anterior and posterior tibiofibular ligament.

the syndesmosis a double stabilization was performed. Here the sequence of stabilization is important: First the anterior stabilization should be performed ensuring anatomic positioning of the distal fibula under direct visualization so that the posteriorly directed second stabilization using the TightRope® will not lead to malreduction. In contrast, not directing the TightRope® posteriorly could lead to malreduction in kind of anterior displacement or malrotation of the distal fibula. To protect the neurovascular bundle the surgeon has to check under fluoroscopy if the aiming k-wire enters the tibia on the lateral side and comes out of the tibia at the medial side, and before overdrilling the k-wire the surgeon has to ensure that the k-wire comes out of the tibia at the medial side anterior to the tendon of the posterior tibial muscle. Figure 6 shows the comparison of preoperative

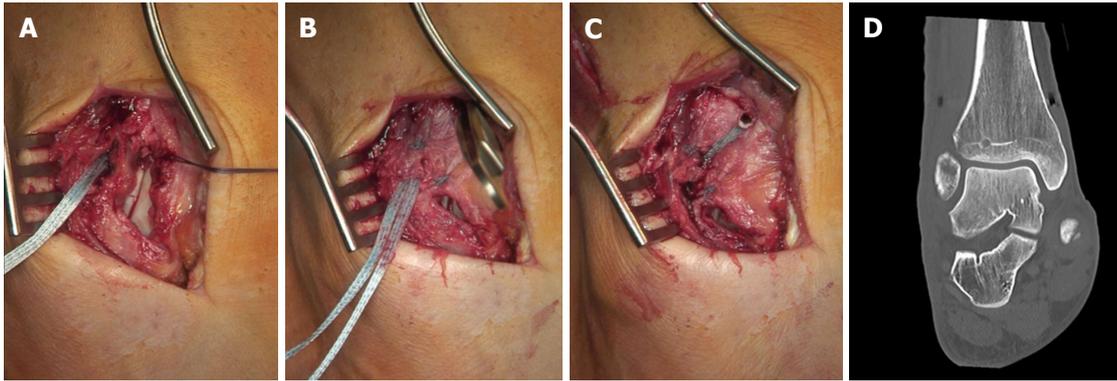


Figure 4 Syndesmotic *InternalBrace*™ for anterior single stabilization after suturing of the disrupted anterior syndesmotic ligament (A-D).

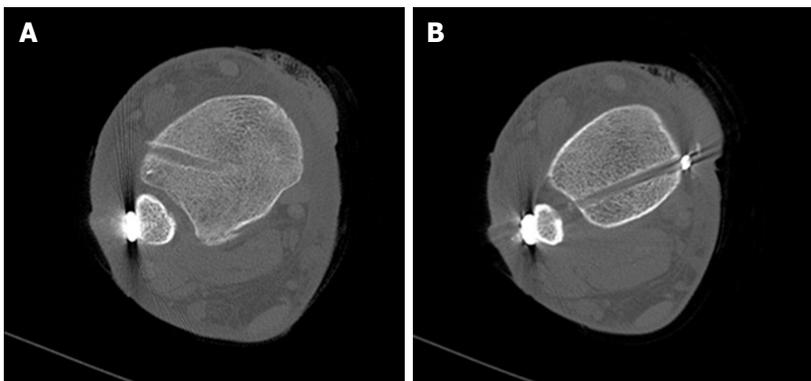


Figure 5 Syndesmotic *InternalBrace*™ for double stabilization by combination with a slightly posteriorly running *TightRope*® for indirect reduction (A) and stabilization (B) of the fracture of the posterior malleolus.



Figure 6 Syndesmotic *InternalBrace*™ for double stabilization. Comparison of preoperative (A, C, E, G, I) and postoperative (B, D, F, H, J) CT scans. Note: anatomic positioning (F, H) and rotation (J) of the distal fibula and indirect anatomic reduction of the fracture of the posterior malleolus (D, F, H).

(left) and postoperative (right) CT scans revealing anatomic positioning (Figure 6F, H) and rotation (Figure 6J) of the distal fibula and indirect anatomic reduction of the fracture of the posterior malleolus (Figure 6D, F and H).

TRIPLE STABILIZATION

Figure 7 shows a syndesmotic *InternalBrace*™ for triple

stabilization with an additional posterolateral screw. The 27-year-old male patient sustained a type C Maisonneuve ankle fracture during a mountain bike accident. The anterior syndesmosis was disrupted and the posterolateral malleolus was fractured. The high fibular fracture did not need osteosynthesis. In a first step, the posterior malleolus was directly refixed with a lag screw *via* a posterolateral approach (Figure 7A). Then

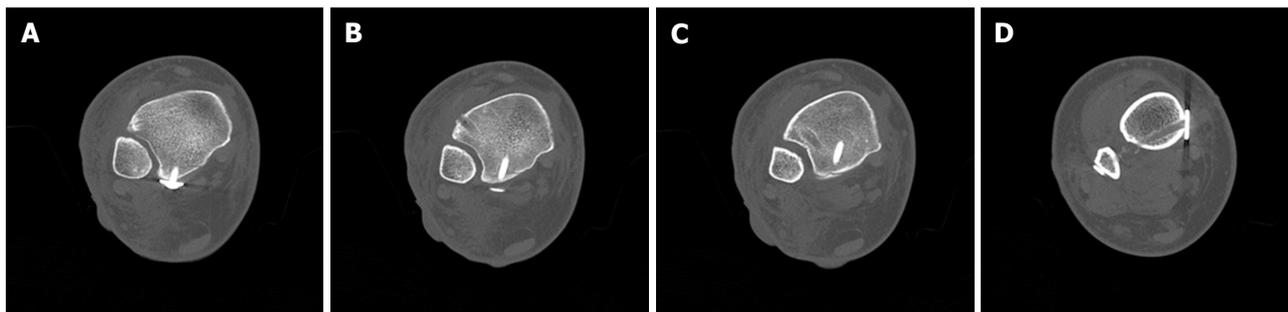


Figure 7 Syndesmotic *InternalBrace*™ for triple stabilization. The posterior malleolus was first directly refixed with a lag screw (A), then the anterior syndesmosis was augmented with an *InternalBrace*™ under direct view (B, C), and finally the posterolateral screw fixation was augmented by a slightly posteriorly directed *TightRope*® resulting in a perfect anatomical positioning of the highly unstable distal fibula (D).

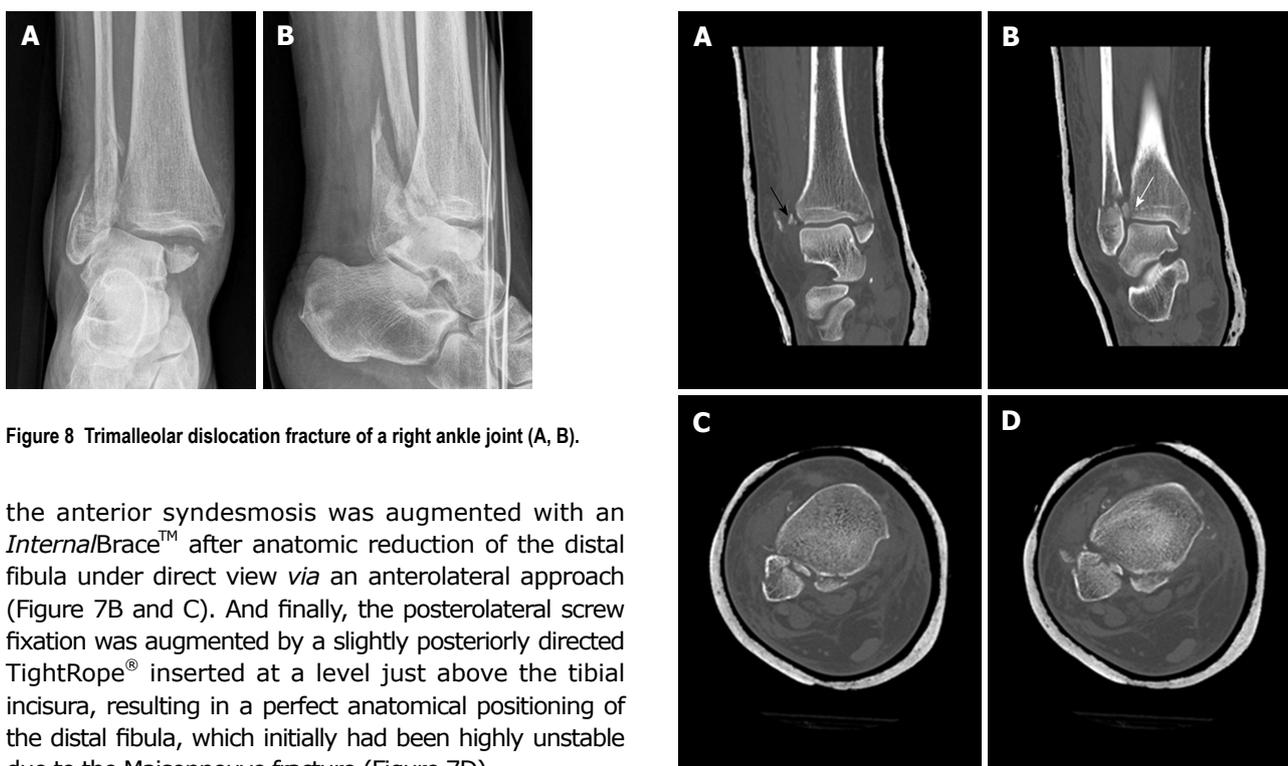


Figure 8 Trimalleolar dislocation fracture of a right ankle joint (A, B).

the anterior syndesmosis was augmented with an *InternalBrace*™ after anatomic reduction of the distal fibula under direct view *via* an anterolateral approach (Figure 7B and C). And finally, the posterolateral screw fixation was augmented by a slightly posteriorly directed *TightRope*® inserted at a level just above the tibial incisura, resulting in a perfect anatomical positioning of the distal fibula, which initially had been highly unstable due to the Maisonneuve fracture (Figure 7D).

Moreover, we found that the syndesmotic *InternalBrace*™ technique is quite suitable for anatomic refixation and stabilization of displaced bony avulsion fragments too small for screw fixation. For example, Figure 8 shows X-rays of a 43-year-old male patient who sustained a trimalleolar dislocation fracture of the right ankle joint during a motor bike accident. After immediate closed reduction and cast immobilization, CT scans of the ankle showed tibial avulsion of the anterior tibiofibular ligament with dislocation of a bone fragment (black arrow) too small for screw fixation (Figure 9A). Furthermore, complete closed reduction was not possible due to a small bone fragment (white arrow) interposed between distal tibia and fibula (Figure 9B). Figure 9C and d reveal a displaced avulsion of a small fragment of the posterolateral malleolus. Due to the fracture pattern the patient was treated by open surgery (Figure 10).

The distal fibula and the anterolateral ankle joint were exposed by a lateral approach. Note the small

Figure 9 Computed tomography scans of the ankle from Figure 8 showing tibial avulsion of the anterior tibiofibular ligament with dislocation of a bone fragment (black arrow) too small for screw fixation (A), complete closed reduction was not possible due to a small bone fragment (white arrow) interposed between distal tibia and fibula (B), displaced avulsion of a small fragment of the posterolateral malleolus (C, D).

bony tibial avulsion fragment of the anterior tibiofibular ligament (black arrow) and the corresponding avulsion site (white arrow) at the tubercule de Chaput (Figure 10A). After reduction of the avulsion fragment the whole ligament proved to be intact (Figure 10B). After insertion of a *FiberTape*® about 4 mm proximal and medial of the avulsion site (Figure 10C) with a 4.75 mm *SwiveLock*®, standard osteosynthesis of the distal fibula was performed using an anatomic preformed locking plate (*Arthrex*®, Naples, United States). The reduced tibial avulsion fragment was then stabilized with a *FiberTape*® fixed by the tibial 4.75 mm *SwiveLock*® and by knots

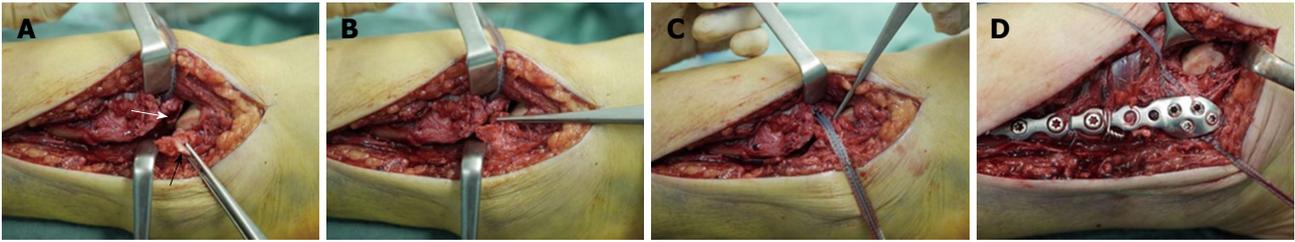


Figure 10 Surgical treatment of the patient from Figure 8. Note the small bony tibial avulsion fragment of the anterior tibiofibular ligament (black arrow) and the corresponding avulsion site (white arrow) at the tubercle de Chaput (A). After reduction of the avulsion fragment the whole ligament proved to be intact (B). Insertion of a FiberTape® about 4 mm proximal and medial of the avulsion site with a 4.75 mm SwiveLock® (C). Standard osteosynthesis of the distal fibula was performed using an anatomic preformed locking plate (Arthrex®, Naples, United States). The reduced tibial avulsion fragment was then stabilized with a FiberTape® fixed by the tibial 4.75 mm SwiveLock® and by knots under the osteosynthesis plate (D).

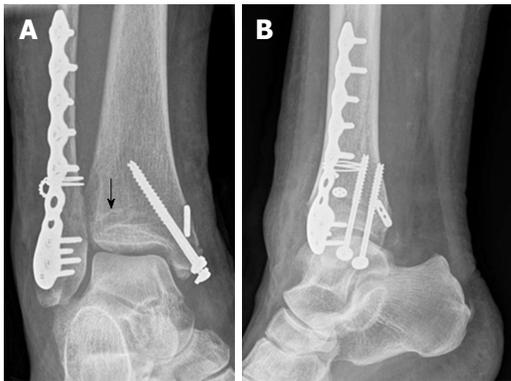


Figure 11 Postoperative X-rays of the ankle from Figure 8 showing anatomic reduction of the syndesmotic injury (A, B). The tibial bone tunnel for the *InternalBrace*™ is visible (black arrow).

under the osteosynthesis plate.

Postoperative X-rays of the ankle showed anatomic reduction of the syndesmotic injury (Figure 11). The tibial bone tunnel for the *InternalBrace*™ is clearly visible (black arrow). Postoperative CT scans in Figure 12 revealed anatomic reduction of the tibial avulsion (white arrows) of the anterior tibiofibular ligament (Figure 12A and C) as well as anatomic reduction of the ankle mortise (Figure 12D). The tibial bone tunnel (black arrows) for the *InternalBrace*™ is clearly visible (Figure 12A and B).

In the field of surgical treatment for unstable syndesmotic injuries, intraoperative testing of the stability of the syndesmosis still remains a major problem, and a normal classical hook test is not sufficient to exclude a clinically relevant syndesmotic instability^[31]. Figure 13 shows an example of an intraoperative testing of syndesmotic stability after distal fibula plating of a type B ankle fracture: The classical hook test (Figure 13A and B) shows no lateral translation of the distal fibula while pulling the distal fibula laterally and pushing the distal tibia medially, indicating a normal result without syndesmotic instability. However, the same ankle joint shows relevant rotational instability of the anterior tibiofibular ligament (Figure 13C and D) indicating the need for surgical stabilization. Intraoperative testing of syndesmotic rotational stability under direct visualization after distal fibula plating using a mounted drill bit for locking screws is shown in Figure 14. The ankle joint

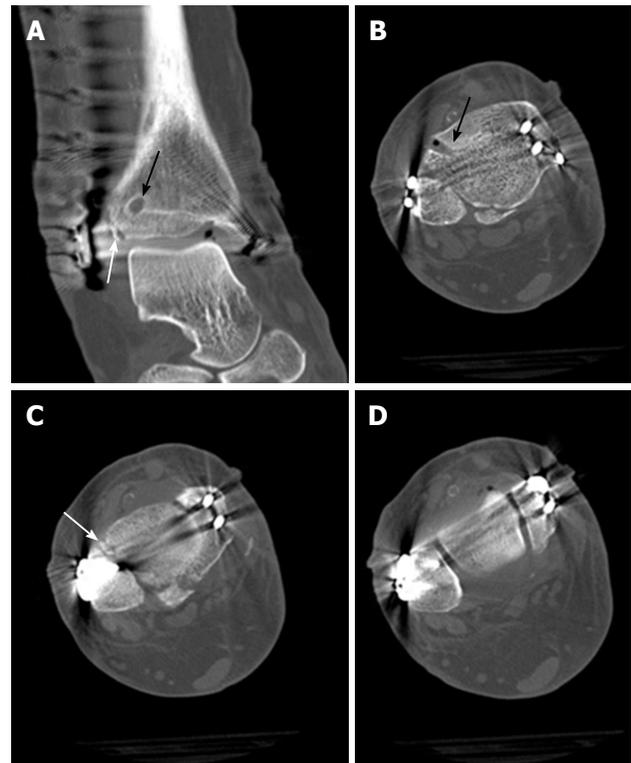


Figure 12 Postoperative computed tomography scans of the ankle from Figure 8 showing anatomic reduction of the tibial avulsion (white arrows) of the anterior tibiofibular ligament (A, C) as well as anatomic reduction of the ankle mortise (D); the tibial bone tunnel (black arrows) for the *InternalBrace*™ is clearly visible (A, B).

shows relevant external rotational instability of the anterior tibiofibular ligament (Figure 14B) indicating the need for surgical stabilization. Note the clear opening of the star figure (white arrow) normally built by the tibiofibular, tibiotalar and talofibular joint lines (black arrow) by external rotation of the distal fibula (Figure 14B). Due to the well-known problems of fluoroscopic intraoperative stability testing of the syndesmosis reported in the current literature, an open visualization of the syndesmosis during the reduction maneuver and stability testing has recently been recommended^[31]. Disadvantages of the described procedures are higher costs of implants and may be an increased surgical time compared to using classical syndesmotic screws.

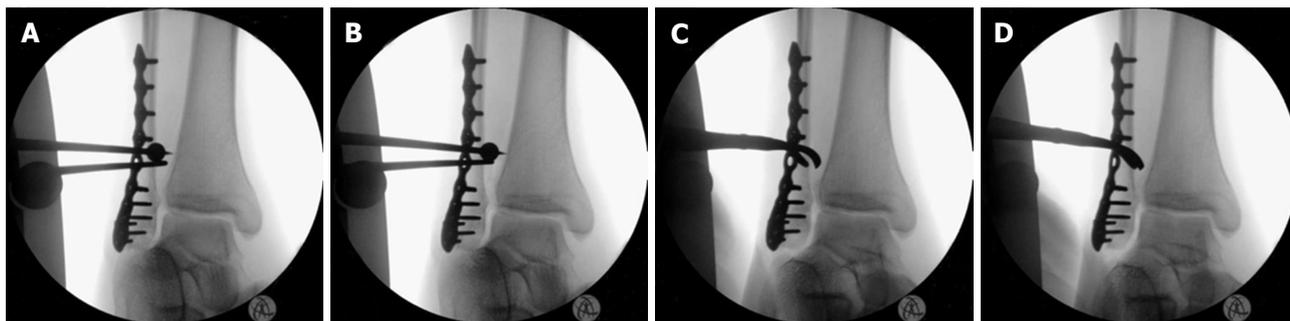


Figure 13 Intraoperative testing of syndesmotic stability after distal fibular plating: The classical hook test (A, B) shows no lateral translation of the distal fibula while pulling the distal fibula laterally and pushing the distal tibia medially, indicating a normal result without syndesmotic instability, however, the same ankle joint shows relevant rotational instability of the anterior tibiofibular ligament (C, D) indicating the need for surgical stabilization.

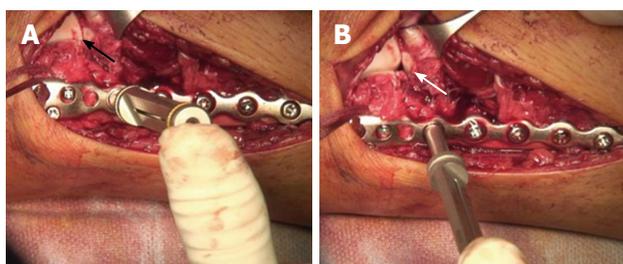


Figure 14 Intraoperative testing of syndesmotic stability after distal fibular plating using a mounted drill bit for locking screws: The ankle joint shows relevant external rotational instability of the anterior tibiofibular ligament (B) indicating the need for surgical stabilization. Note opening (white arrow in B) of the star figure (black arrow in A) normally built by the tibiofibular, tibiotalar and talofibular joint lines by external rotation of the distal fibula (B).

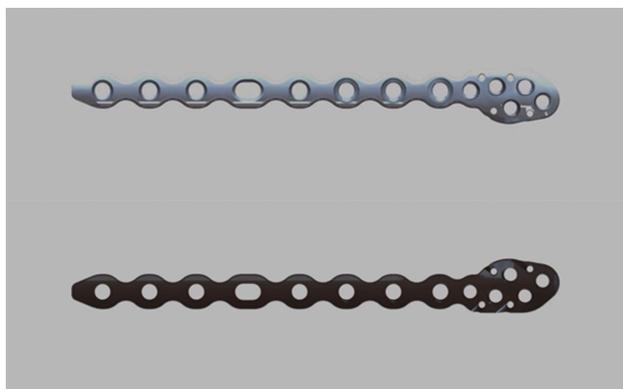


Figure 15 Prototype of a new syndesmotic plate (Arthrex, Naples, United States) with suture holes especially designed for augmentation of the anterior and posterior syndesmosis.

OVER THE HORIZON

Our preliminary clinical results indicate that anatomic reconstruction with rotational stabilization of the syndesmosis can be realized regularly by use of the reported new syndesmotic *InternalBrace*™ technique. A clinical trial for prospective evaluation of the functional outcomes has just been started at our hospital.

And - based on our positive results - a new syndesmotic plate is currently developed with added suture holes for easier mounting of the *FiberTapes*® for performing a syndesmotic *InternalBrace*™.

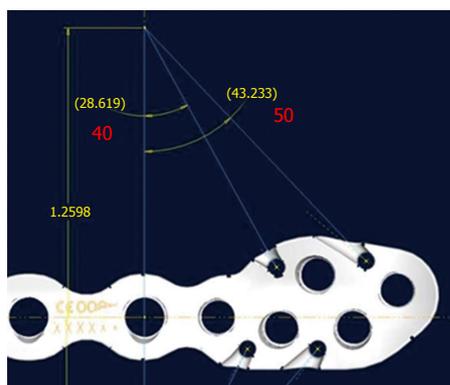


Figure 16 Prototype of a new syndesmosis plate with four suture holes, each combined with a specially designed notch at the inside surface exactly in line with the potential course of the inserted and tensioned *FiberTape*®.

Figure 15 shows the current prototype of the new syndesmotic plate (Arthrex®, Naples, United States) with suture holes at the distal part especially designed for augmentation of the anterior and posterior syndesmosis. The four suture holes are combined with a specially designed notch at the inside surface (Figure 16) exactly in line with the potential course of the inserted and tensioned *FiberTape*® to avoid impaired fitting of the plate to the distal fibula. As expected, this new syndesmotic plate will provide another step for improving anatomical stabilization of syndesmotic injuries.

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Basic Study

Posterior interosseous nerve localization within the proximal forearm - a patient normalized parameter

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Author contributions: Kamineni S and Deane AS designed the research; Kamineni S, Norgren CR and Davidson EM performed the research; Kamineni S and Kamineni EP analyzed the data; Kamineni S, Norgren CR, Kamineni EP and Davidson EM wrote the paper; all authors performed dissection.

Institutional review board statement: The study was exempt by the University of Kentucky Institutional Review Board, since it does not involve patients or clinical data.

Conflict-of-interest statement: None.

Data sharing statement: None.

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Abstract**AIM**

To provide a "patient-normalized" parameter in the proximal forearm.

METHODS

Sixty-three cadaveric upper extremities from thirty-five cadavers were studied. A muscle splitting approach was utilized to locate the posterior interosseous nerve (PIN) at the point where it emerges from beneath the supinator. The supinator was carefully incised to expose the midpoint length of the nerve as it passes into the forearm while preserving the associated fascial connections, thereby preserving the relationship of the nerve with the muscle. We measured the transepicondylar distance (TED), PIN distance in the forearm's neutral rotation position, pronation position, supination position, and the nerve width. Two individuals performed measurements using a digital caliper with inter-observer and intra-observer blinding. The results were analyzed with the Wilcoxon-Mann-Whitney test for paired samples.

RESULTS

In pronation, the PIN was within two confidence intervals of 1.0 TED in 95% of cases (range 0.7-1.3 TED); in neutral, within two confidence intervals of 0.84 TED in 95% of cases (range 0.5-1.1 TED); in supination,

within two confidence intervals of 0.72 TED in 95% of cases (range 0.5-0.9 TED). The mean PIN distance from the lateral epicondyle was 100% of TED in a pronated forearm, 84% in neutral, and 72% in supination. Predictive accuracy was highest in supination; in all cases the majority of specimens (90.47%-95.23%) are within 2 cm of the forearm position-specific percentage of TED. When comparing right to left sides for TEDs with the signed Wilcoxon-Mann-Whitney test for paired samples as well as a significance test (with normal distribution), the *P*-value was 0.0357 (significance - 0.05) indicating a significant difference between the two sides.

CONCLUSION

This "patient normalized" parameter localizes the PIN crossing a line drawn between the lateral epicondyle and the radial styloid. Accurate PIN localization will aid in diagnosis, injections, and surgical approaches.

Key words: Posterior interosseous nerve; Radial nerve; Transepicondylar distance; Radial tunnel syndrome; Supinator syndrome

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Core tip: We present a "patient normalized" parameter that localizes posterior interosseous nerve (PIN) crossing point with a line interconnecting the lateral epicondyle and the radial styloid, with the "70-85-100" rule. The mean PIN distance from the lateral epicondyle was 100% of transepicondylar distance (TED) in a pronated forearm, 85% in neutral, and 70% in supination; in all cases the majority of specimens (90.47%-95.23%) are within 2 cm of the forearm position-specific percentage of TED. Non-invasive accurate PIN localization will aid in diagnosis, injections, surgical approaches, and understanding neurological symptoms in the forearm.

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INTRODUCTION

The radial nerve's localization has been the subject of much concern due to the potential for pathologic^[1,2], traumatic^[3,4], and iatrogenic^[5-7] injuries. Radial nerve localization has been described relative to a distance from various bony landmarks: The acromion and lateral epicondyle^[8] proximal to the elbow and the bicipital tuberosity distal to the elbow^[9]. The deep radial nerve [posterior interosseous nerve (PIN)] has proven more

difficult to localize distal to the elbow. Accurately localizing PIN in the proximal forearm is important when diagnosing nerve compression with physical examination, placing injections at the site of the nerve, accurately exposing the nerve during a surgical exposure^[10], and reducing the incidence of iatrogenic nerve injury during surgical interventions^[11-17]. Specifically, the surgical repair of open and closed injuries to the elbow/forearm, relief of entrapment neuropathies, and implantation of fixation devices for fracture stabilization all require intimate knowledge of PIN anatomy^[8,10,13,17,18]. The general course of PIN has previously been described in detail in relation to muscular anatomy and by using absolute measurement from a bony landmark^[8,9,11,14,16,19,20]. These descriptors serve a useful function for the general anatomic understanding of PIN location, but have their limitations. They are limited because muscular anatomy must be defined first, which limits its usefulness to surgical interventions with this capacity, such as open surgical dissection. Descriptors utilizing a specific measurement from a bony landmark can be difficult to use clinically due to body habitus or because the bony landmark is outside of the surgical field. An absolute measurement does not normalize for a particular individual and can lead to erroneous localization. This latter issue is based on the wide range of variability in body sizes. Thus, localization of PIN in the proximal forearm utilizing a patient-normalized parameter is advantageous when dealing with an individual person.

Surgical landmarks traditionally used to localize PIN in the forearm (such as the bicipital tuberosity, articular surface of the posterior supinator head, and the entry and exit points of the supinator muscle) require invasive surgical exploration of the area for accurate use of the parameter^[9,11,14,20,21]. The establishment of a non-invasive parameter using external anatomical landmarks would be beneficial by localizing PIN without invasive dissection and could potentially reduce the incidence of iatrogenic PIN injury.

We propose that the transepicondylar distance (TED) are, utilized as a body size descriptor and normalizing feature, can be used as a non-invasive parameter for PIN localization in the proximal forearm. In this study, we calculate PIN distance from the lateral humeral epicondyle as a percentage of TED and examine the predictive accuracy of this parameter in localizing PIN in three forearm positions: Pronation, supination, and neutral. We expect this information will be useful to guide surgical techniques in a more patient-specific manner, which may ultimately reduce surgical morbidities.

MATERIALS AND METHODS

Approval was obtained from the Department of Anatomy in the College of Medicine at our University to collect morphometric data describing PIN position from cadavers. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

Cadaver preparation

Skin was removed from 35 cadavers utilizing 63 upper extremities. A muscle splitting approach was utilized to locate PIN at the point where it emerges from beneath the supinator. The supinator was carefully incised to expose the midpoint length of the nerve as it passes into the forearm while preserving the associated fascial connections, thereby preserving the relationship of the nerve with the muscle.

Measurements

TED: The medial and lateral epicondyles of the humerus were palpated to identify the maximum medial and lateral extensions of the humeral epicondyles. The distance between these points was measured using Mituyoto digital calipers. Maximum TED was measured on three separate occasions by two separate observers for a total of six measurements.

PIN distance: The distance between the lateral humeral epicondyle apex and the proximal and distal borders of PIN were recorded for each cadaver with the forearm in a pronated, supinated and neutral position along an interconnecting line between the lateral epicondyle and radial styloid tip ("epi-styloid line"). PIN position was measured by establishing the position of the lateral humeral epicondyle and then extending a length of inelastic string (0.5 mm diameter) from that point to the radial styloid process, following the surface contour of the forearm. Distances were recorded from the lateral epicondyle to the proximal intersection of PIN with the string and between the lateral epicondyle and the distal intersection of PIN with the guide string. Proximal and distal PIN positions were each measured on three separate occasions by two observers for a total of six proximal and six distal PIN measurements. PIN distance from the epicondyle was recorded as the distance from the epicondyle to the midpoint between the proximal and distal intersection of PIN with the guide string.

PIN width: The total difference between the proximal and distal intersection of PIN with the guide string.

Summary descriptive statistics (*i.e.*, mean, standard deviation, range) were calculated for all individual PIN distance measurements and for all individual PIN distance measurements when calculated as a percentage of TED. We conducted the signed Wilcoxon-Mann-Whitney test for paired samples as well as a significance test (with normal distribution) for paired samples in order to compare difference between right and left sides of TED lengths, pronated position, supinated position, and neutral position. The distances of PIN from the lateral epicondyle, with respect to TED, were plotted with 95% CIs, using normal, long normal, Weibull, and Gamma distributions.

RESULTS

The mean TED for all elbows was 63.59 mm (range

53.0-80 mm). The mean left elbow TED was 62.92 mm (range 53-80 mm), and the mean right TED was 63.97 mm (range 54-77 mm). When comparing right to left sides for TEDs with the signed Wilcoxon-Mann-Whitney test for paired samples as well as a significance test (with normal distribution), the *P*-value was 0.0357 (significance - 0.05) indicating a significant difference between the two sides. However, when comparing the measurements by different observers, as a measure of inter-observer differences of measurements taken, all *P*-values were greater than 0.29 indicating no significance was detected.

Mean radial nerve distances from the lateral epicondyle were greatest when the forearm was in a pronated position [63 mm (range 34.5-80.6 mm)] and least when the forearm was in a supinated position [45.7 mm (33-61.9 mm)]. Mean radial nerve distances when the forearm was in a neutral position [53.5 mm (34.3-70.6 mm)] was intermediate to the values reported for the pronated and supinated forearm (Figure 1).

We calculated the location of PIN along the epi-styloid line as a percentage of TED for that same specimen. In neutral forearm rotation the radial nerve was located at 85% of TED [range 65% (4.1 cm) to 105% (6.6 cm) TED]. In supination it was located at 70% of TED [range 50% (3.15 cm) to 90% (5.7 cm) TED], and in pronation was 100% of TED [range 70% (4.4 cm) to 120% (7.6 cm) TED] (Figure 2).

Radial nerve width (*i.e.*, the distance between the proximal and distal intersection of the nerve with the guide string) was observed to vary across cadavers. Figure 3 represents boxplots of sample median, standard deviation and range for all forearm positions in both the left and right upper limb (Figure 3).

Mean PIN distance as a percentage of TED was greatest when the forearm is pronated (98.7%-101.4%) and least when the forearm was supinated (71.7%-72.6%). Mean PIN distance as a percentage of TED when the forearm was in a neutral position (84.4%-84.7%) were intermediate to the values reported for the pronated and supinated forearm.

PIN distances recorded when the forearm was pronated, supinated, and in neutral rotation were used to predict PIN position relative to the lateral epicondyle. The mean distance between the lateral epicondyle and proximal intersection of PIN and guide string was used to establish predictive lengths for each of the three forearm positions. When the forearm was pronated the mean PIN distance was 100% of TED. In the supinated position the mean PIN distance was 70% of TED. When the arm is in a neutral position the mean posterior interosseous distance was approximately 85% of TED. These percentages were applied to the individual cadavers to establish a "Predictive Value" for PIN localization.

When the arm was pronated PIN was located within 1.5 cm of 1.0 × TED in 71.43% of the specimens and within 2 cm in 90.47% of specimens. The predictive accuracy was highest when the arm was supinated. PIN was identified within 1 cm of 0.7 × TED in 73.01% of

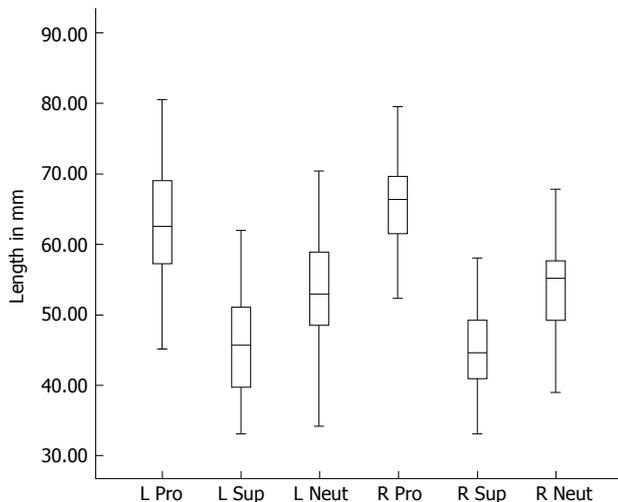


Figure 1 Boxplots of the distance from the humeral epicondyle to the midpoint of the radial nerve (mm) for the left and right forearm in pronated, supinated and neutral positions. Cross bars represent the median value for each group, while the boxes show the 50% confidence interval and the whiskers extend to the highest and lowest values. L: left; R: Right; Pro: Pronated; Sup: Supinated; Neut: Neutral.

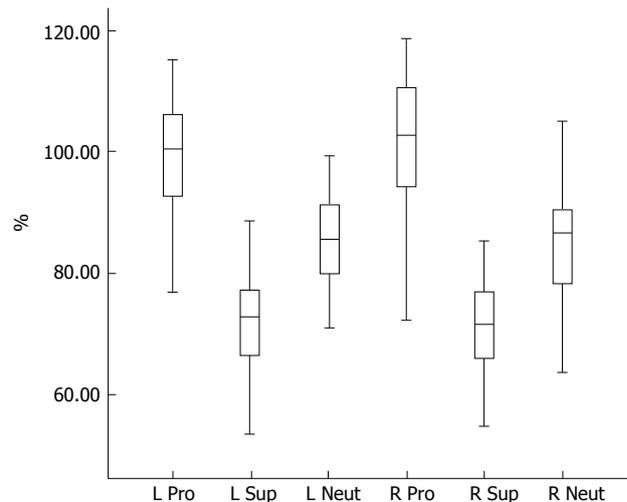


Figure 2 Boxplots of the distance from the humeral epicondyle to the midpoint of the radial nerve (mm) for the left and right forearm in pronated, supinated and neutral positions as expressed as a percentage of transepicondylar distance breadth. Crossbars represent the median value for each group, while the boxes show the 50% confidence interval and the whiskers extend to the highest and lowest values. L: left; R: Right; Pro: Pronated; Sup: Supinated; Neut: Neutral.

cadavers, and within 1.5 cm in 85.7% of cadavers and within 2 cm in 95.23% of cadavers. When the forearm was in neutral rotation PIN was within 1 cm of $0.85 \times$ TED in 63.5% of specimens, 1.5 cm in 84.12%, and within 2 cm in 93.7% of proximal forearms.

DISCUSSION

Our study introduces a non-invasive, patient-normalized parameter for localizing PIN in the proximal forearm within 2 cm of the predicted distance from the lateral humeral epicondyle with 90%-95% accuracy in three positions of forearm rotation. TED has previously been utilized to normalize radial nerve localization proximal to the elbow, to help prevent radial nerve injury when placing pins/screws^[22], as has the bicapital tuberosity^[9] distal to the elbow. We have demonstrated that the mean PIN distance relative to TED is approximately 85% in neutral (Figure 4), 70% when supinated (Figure 5), and 100% when pronated (Figure 6).

There are several potential limitations to consider when evaluating this "70-85-100" guideline. These issues include the use of cadavers, variable branching patterns, inter-individual differences, and the value of this parameter compared to using absolute values for localization of PIN.

Anatomical investigations often use cadavers for data collection, but some studies use formalin-embalmed cadavers while others use fresh specimens. While it is unclear how the embalming process would significantly alter anatomical relationships, Artico *et al.*^[8] postulated that differences in the distances of PIN to various landmarks in their study vs other literature can be explained by the use of either fresh cadaver specimens or formalin-embalmed cadavers. While fresh cadaver

specimens likely preserve normal anatomy more accurately than embalmed ones, we believe the relatively large sample size of our study ($n = 63$) increases the power of our data such that the correlations we have found are true. However, future research with fresh cadaver specimens may be valuable in supporting or refuting our findings.

There were significant variations in the branching patterns of the deep PIN within the supinator muscle that made localization less precise even though care was taken during the dissection to preserve as much surrounding fascial tissue as possible with minimal disruption of anatomical relationships. This is reflected by the wide ranges of PIN widths (Figure 3) as determined by the distance from the lateral epicondyle to the proximal and distal edges of where the guide string crossed PIN. The inclusion of some, but not all, branches as part of the main PIN trunk led to some subjective interpretation of which branches were "too far" or "too small" to include. Variability in nerve sizes and branching patterns contributed to a wide range of widths which could affect the calculated mean distances of the "midpoint" of the nerve to the lateral epicondyle. A suggestion for future research would be to focus on the "safe zone" of where surgical incisions are less likely to damage PIN or any of its branches as opposed to direct PIN localization.

Intra-individual variation between right and left upper extremities is not well predicted by our "70-85-100" rule. Despite the fact that most people have similar right and left TED's, this does not necessarily mean that their PINs have symmetric courses. Benham *et al.*^[23] found that there were significant intra-individual differences between the right and left limb in the distance from the

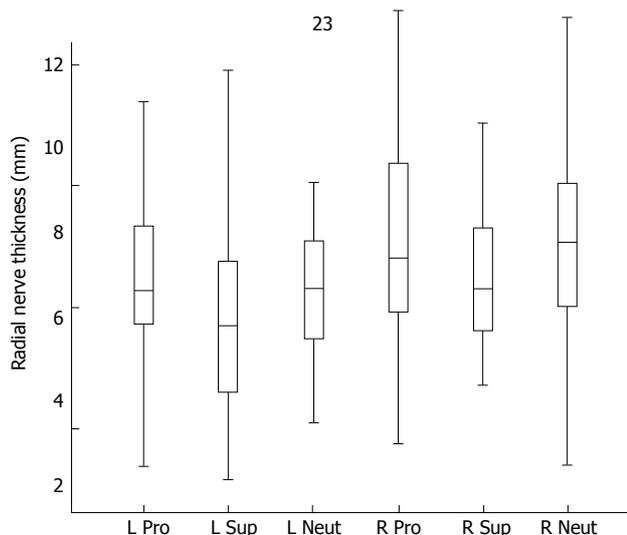


Figure 3 Boxplots of the distance from the proximal to the distal intersection of the radial nerve and the guide string for the left and right forearm in pronated, supinated and neutral positions. Crossbars represent the median value for each group, while the boxes show the 50% confidence interval and the whiskers extend to the highest and lowest values. L: left; R: Right; Pro: Pronated; Sup: Supinated; Neut: Neutral.

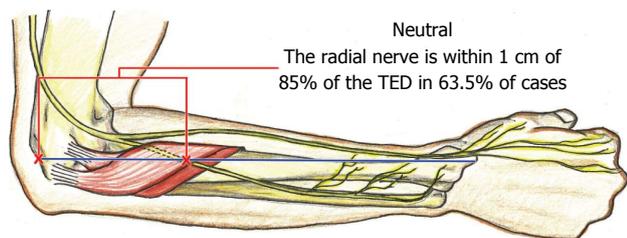


Figure 4 Pictorial depiction of the location of the posterior interosseous nerve, along the longitudinal line drawn from the lateral epicondyle to the radial styloid, at 85% transepicondylar distance, with the forearm in neutral rotation. TED: Transepicondylar distance.

lateral epicondyle to the bifurcation point of PIN into its superficial and deep branches. While this finding may have important clinical implications, it may not be relevant for deep PIN localization because their study uses a different point of measurement and our study found no significant difference between the right and left measurements in any of the three forearm positions. While intra-individual variation may exist at the bifurcation point of the superficial and deep PIN branches, it does not likely play a role in the localization of the deep PIN within the supinator muscle.

TED was measured after skin removal, which resulted in an over-estimation when assessing PIN *in situ*. However, our method provides a good estimation of PIN localization as the effect of skin thickness is likely negligible when using the parameter non-surgically (skin intact state).

Although our proposed localizing parameter is patient-normalized using TED, it may not be any more specific than using the absolute values provided by previous research. It is important to note that our "70-85-100" rule

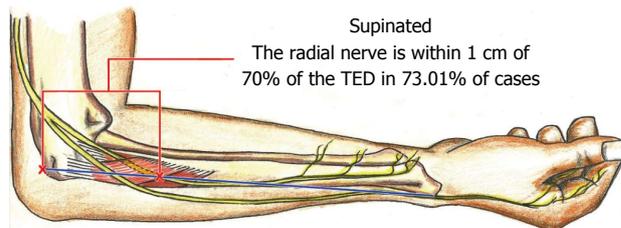


Figure 5 Pictorial depiction of the location of the posterior interosseous nerve, along the longitudinal line drawn from the lateral epicondyle to the radial styloid, at 70% transepicondylar distance, with the forearm in supination. TED: Transepicondylar distance.

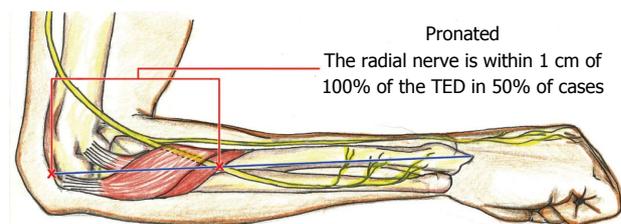


Figure 6 Pictorial depiction of the location of the posterior interosseous nerve, along the longitudinal line drawn from the lateral epicondyle to the radial styloid, at 100% transepicondylar distance, with the forearm in pronation. TED: Transepicondylar distance.

predicts the location of PIN within 1 cm in only 50% of cases when pronated, 63.5% when neutral, and 73.1% when supinated. Only when the range is increased to 2 cm does it include 90%-95% of cases, which is no more specific or accurate than the average values and ranges calculated from numerous specimens. For example, Strauch *et al*^[11] found the average distance from the posterior interosseous tuberosity to PIN is 2.3 cm with a total range of only 1.4 cm (1.8 cm-3.2 cm). Witt *et al*^[9] discovered the distance from the first branches of PIN to the articular surface of the posterior interosseous head are 6.0 cm ± 1 cm (range 4.0-8.4 cm). Thomas *et al*^[14] reported that the bifurcation of PIN into its superficial and deep branches is 8.0 cm ± 1.9 cm distal to the lateral intermuscular septum and 3.6 cm ± 0.7 cm proximal to the leading edge of the supinator (Arcade of Froshé). While these studies use different landmarks, they all have ranges of < 2 cm when reporting absolute values for localizing PIN. Therefore, our patient-normalized parameter may be no more specific or individualized than absolute values for localizing PIN, but it still has the advantage of being non-invasive.

Our study has limitations that should be considered when utilizing it in the clinical setting. These were cadaveric specimens which may differ from patients in their musculoskeletal relationships as a consequence of the preservation procedure. The line connecting the lateral epicondyle and radial styloid was not a projected straight line, but a straight line following the contour of the forearm and may be influenced by the individual bulk of the forearm, which was not investigated in this study. Previous trauma or surgical procedures in the

territory could influence this parameter.

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COMMENTS

Background

The authors describe a simple method, based on cadaveric data and corroborated in clinical practice, of locating the posterior interosseous nerve (PIN) in the proximal forearm. The location of the PIN can be simply summarized by the 70-85-100 rule. They have demonstrated that the location of the PIN from the lateral epicondyle, in terms of the patient's transepicondylar distance (TED) is approximately 70%TED with forearm supination, 85%TED in neutral forearm rotation, and 100%TED when pronated. This will help clinicians to localize the PIN when dealing with a proximal forearm painful differential diagnosis, injections around the PIN for diagnostic and therapeutic purposes, and when surgically approaching the PIN for a decompressive operation.

Research frontiers

The PIN is increasingly recognized as a differential diagnosis and a coexistent pathology in tennis elbow. The ability to locate the PIN accurately in relation to the patient's own anatomy is a very important step towards an accurate diagnosis.

Innovations and breakthroughs

The significant innovation of the study is that they are able to locate the PIN by "normalizing" their measurement to the patient's own anatomy. The authors' normalizing parameter is the TED, which can easily be measured by the clinician.

Applications

The practical application of their study is that it accurately locates the PIN, it normalizes the location of this nerve to the patient's own anatomy, helps in the diagnosis of lateral elbow and forearm pain, improves the localization of diagnostic and therapeutic injections around the PIN, and helps the surgeon decrease in the size of the incision when decompressing the PIN.

Terminology

TED: The distance between the most prominent part of the medial and lateral epicondyle.

Peer-review

This is a very well presented study.

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Basic Study

Effect of a specialized injury prevention program on static balance, dynamic balance and kicking accuracy of young soccer players

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Author contributions: Dunskey A designed and coordinated the research, and wrote the paper; Barzilay I performed the majority of experiments; Fox O analyzed the data.

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Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: No additional data are available.

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Abstract

AIM

To study the effect of balance intervention program using the "FIFA 11+" program on static and dynamic balance and kicking accuracy of young soccer players.

METHODS

Twenty young soccer players were allocated to experimental ($n = 10$) or control ($n = 10$) groups. The experimental group performed the "FIFA 11+" program three times a week for six weeks. The control group performed their normal warm-up routine. The primary outcomes were measured pre and post intervention, and assessed kicking accuracy, static balance and dynamic balance.

RESULTS

No differences were found in kicking accuracy following intervention, for both groups, however, static balance improved significantly among the experimental group with significant interaction with the control group, and with high effect size. In addition, the dynamic balance of the left leg of the experimental group, with medium effect size for interaction between groups.

CONCLUSION

The large effect size of balance improvement that was observed following six weeks of intervention sessions, implies that soccer trainers and coaches should consider the inclusion of "FIFA 11+" as components of programs aimed at improving balance ability/control in young soccer players, as improvement in balance abilities may prevent injuries.

Key words: Soccer; Injury prevention; Balance; Warm-up; Kicking accuracy

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Core tip: The implementation of "FIFA 11+" for six weeks of intervention, led to a large effect size of balance improvement among young soccer players. As improvement in balance abilities may prevent injuries, soccer trainers and coaches should consider the inclusion of "FIFA 11+" as a component of training programs in young soccer players.

Dunsky A, Barzilay I, Fox O. Effect of a specialized injury prevention program on static balance, dynamic balance and kicking accuracy of young soccer players. *World J Orthop* 2017; 8(4): 317-321 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/317.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.317>

INTRODUCTION

Soccer is a sport requiring a plethora of technical skills as well as static, semi-dynamic and dynamic balance. Most of these skills, such as passing, juggling the ball in the air, dribbling or receiving the ball, are achieved through standing on one leg. Balance plays a pivotal role in the harsh conditions, such as pushing opponents, slippery grass, changes to the ball's orbit, moving, facing footballers during a football game^[1].

Balance ability has been found to be significantly related to several performances in sport, such as shooting accuracy of archers, pitching accuracy of baseball pitchers, maximum skating speed during ice hockey, and putting accuracy of golfers^[2]. While the relationship between balance and accuracy of ball kicking in soccer is randomly reported, it is well known that good balance seems to be effective in neuromuscular control performance^[1], and is considered a distinctive characteristic of high level soccer players at the same time^[3]. In addition, soccer players have been proved to surpass basketball players in static and dynamic balance and do not differ from gymnasts or dancers^[2].

Playing soccer, as with any other sport, entails some risk of injury. With more than 240 million amateur soccer players worldwide, it has the highest participation rate in the world, and it accounts for more than 10% of sport injuries requiring medical attention in adolescents^[4,5]. Based on those facts, injury prevention programs should be of major importance for soccer coaches and trainers. Considerable reductions in the number of injured players, ranging between 30% and 70%, have been observed among the teams that implemented the FIFA 11+ program^[6].

As poor balance has been correlated to increased risk of injury in athletes^[7], it was suggested that a program

Table 1 Descriptive statistics for anthropometric data of the participants (means and standard deviations)

Variable	Experimental	Control
Age (yr)	12.91 ± 0.26	12.75 ± 0.3
Height (cm)	153.6 ± 7.58	149.7 ± 7.45
Weight (kg)	44.8 ± 6.33	40.7 ± 6.5
Right leg length (cm)	80.4 ± 4.95	76.8 ± 5.05
Left leg length (cm)	79.7 ± 4.57	77.1 ± 4.86

based on balance improvement may reduce the risk of injury^[8].

One suggested program was the "FIFA 11+", which is a complete warm-up package that combines cardiovascular activation and preventive neuromuscular exercises. The key element of the program is the promotion of proper neuromuscular control during all exercises ensuring correct posture and body control, thus it is mainly based on balance control. Recently the "FIFA 11+" was found to induced improvements in neuromuscular control in amateur football players^[8], however in another study it was found to have no significant effect on vertical jump tests, sprint running and soccer skill tests in comparison to control condition^[9].

To the best of our knowledge, no studies have examined the changes in accuracy of ball kicking among young soccer players induced by the "FIFA 11+". Therefore, the main aim of this study was to examine whether implementing the "FIFA11+" for six weeks as a routine warm-up can improve kicking accuracy as well as static and dynamic balance abilities in young soccer players.

MATERIALS AND METHODS

The study was approved by the Zinman College of Physical Education and Sport Sciences Institutional Review Board.

Participants

Twenty young soccer players who agreed to participate, and had confirmation from their parents, were selected to take part in the study, and were allocated into two groups by their football group for convenience of training routine.

Inclusion criteria for the players were: (1) male amateur players competing in the Official Amateur Championships of the Israeli Football Federation; (2) supervised training 3 times a week for 90 min; (3) no major recent injuries; and (4) good physical condition for completing the baseline measurements.

Descriptive statistics for the group are presented in Table 1.

Intervention

Experimental group: The players completed "The FIFA 11+" (for details see the manual and instructions freely

1	3	1
3	5	3
1	3	1

Figure 1 Scoring grid for the kicking-accuracy protocol.

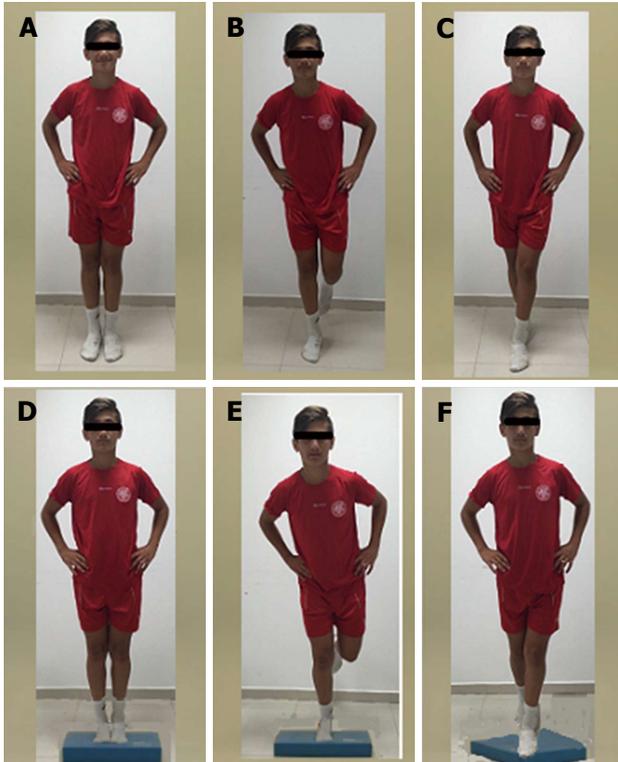


Figure 2 Stances used in Balance Error Scoring System. A: Double-leg stance; B: Single-leg stance; C: Tandem stance; D: Double-leg stance with foam; E: Single leg on foam; F: Tandem stance on foam.

available on the official website: <http://f-marc.com/fifa-11-kids/>) three times a week for six weeks substituting their normal warm-up routine. In brief, the protocol includes three parts: 8 min of running exercises, 10 min of strength, plyometric and balance exercises, and 2 min of explosive running exercises. From week one to two players performed the level 1, from week three to four they performed the level 2 and from week five to six they performed the level 3.

Control group: The control group received a normal warm-up routine while matching the duration of the "FIFA 11+" (20-25 min). This routine involved a combination of running, stretching, technical exercises with the ball and small-sided games.

The guidance of both groups were performed by the fitness coach who is familiar with the "FIFA 11+".

Assessments

Kicking accuracy: This test was performed based on Currell *et al.*^[10]. A goalmouth was split into nine equal targets by a series of ropes. Each target was allocated a different score: The center was worth 5 points, around

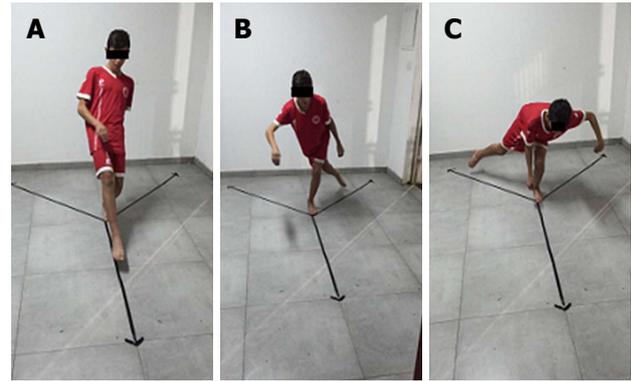


Figure 3 Postures used in the Y Balance Test. A: Y-balance anterior reach; B: Y-balance posteromedial reach; C: Y-balance posterolateral reach.

the center 3 points and the corners 1 point (Figure 1). Participants had 10 attempts from 16 m away, using their preferred foot and with the ball being stationary. On the completion of one kick the next immediately followed.

Balance ability: Static balance - Balance Error Scoring System^[11]. This test consists of three stances: Double-leg stance (hands on the hips and feet together), single-leg stance (standing on the non-dominant leg with hands on hips), and a tandem stance (non-dominant foot behind the dominant foot) in a heel-to-toe fashion (Figure 2). The stances are performed on a firm surface and on a foam surface with the eyes closed, with errors counted during each 20-s trial. An error is defined as opening eyes, lifting hands off hips, stepping, stumbling or falling out of position, lifting forefoot or heel, abducting the hip by more than 30°, or failing to return to the test position in more than 5 s. Dynamic balance - The Y Balance Test (YBT) assesses range of motion (ROM), strength, and neuromuscular control of the lower extremity and was chosen to assess the participants' lower limb balance as prior studies have demonstrated its utility as a clinical test to assess for lower limb balance deficits in the athletic population^[12]. The participant reaches with one foot in the anterior, posteromedial, and posterolateral directions while standing on the other foot on a centralized stance platform. The test is performed barefoot with both left and right limbs (Figure 3). Following the protocol, each participant was required to perform six practice trials before the three data-collection trials. With the stance-foot toes immediately behind the start line, the participant was instructed to reach as far as he could while maintaining his balance. Each participant was instructed that any of the following activities would constitute a failed attempt, after which an additional trial would be performed: (1) touching the reach foot down before returning to the stance platform under control; or (2) losing balance before returning under control to bilateral stance. The reach distance in each direction was normalized to the limb length (*i.e.*, inferior anterosuperior iliac spine to inferior medial malleolus). The sum of three normalized reach distances was then averaged and

Table 2 Means, standard deviations and analysis of variance comparing performance for kicking accuracy, static balance and dynamic balance

Variable	Experimental		Control		Cohen's <i>d</i>
	Pre	Post	Pre	Post	
kicking accuracy	2.69 ± 0.54	3.06 ± 0.72	2.5 ± 0.51	2.82 ± 0.38	0.11
Static balance - BESS	3.52 ± 0.78	3.35 ± 1.04	1.72 ± 0.66	2.94 ± 1.17 ¹	1.92
Dynamic balance - YBT-R	0.98 ± 0.07	1.03 ± 0.07	0.97 ± 0.06	1.00 ± 0.04	0.31
Dynamic balance - YBT-L	0.98 ± 0.08	1.04 ± 0.07 ²	0.97 ± 0.06	1.01 ± 0.04	0.32

¹Significant interaction ($F_{1,18} = 21.05, P < 0.01$); ²Significant improvement ($t = 1.78, P = 0.05$). BESS: Balance Error Scoring System; YBT-R: Y Balance Test Right leg; YBT-L: Y Balance Test Left leg.

multiplied by 100 to generate a composite score^[3].

Statistical analysis

A repeated measures ANOVA model was employed in order to determine possible statistically significant differences between the measurements and between the experimental and control group.

RESULTS

Both groups showed excellent adherence during the intervention period. More specifically, participants of the experimental group expressed their high enthusiastic about the "FIFA 11+" program, and asked their coach to continue with it.

The differences in kicking accuracy and balance assessments between pre and post intervention for the experimental group and the control group are presented in Table 2. No differences were found in kicking accuracy following intervention, for both groups, however, static balance improved significantly among the experimental group with significant interaction with the control group, and with high effect size. In addition, the dynamic balance of the left leg of the experimental group, with medium effect size for interaction between groups.

DISCUSSION

The results of this study show that the integration of "FIFA 11+" program for six weeks improved both static as well as dynamic balance ability, among young soccer players, but it did not improve the accuracy of kicking. The "FIFA 11+" has been developed for improving neuromuscular control^[8], which explains the improvement in balance control among the experimental group in the current study, and also in other studies^[8,13]. In addition, the implementation of "FIFA 11+" led to reductions in the number of injured players, ranging between 30% and 70%^[6].

Improvement in balance control as measured by the YBT is considered to be important for soccer players, since it is based on the combination of ROM, movement abilities, strength, and proprioception^[3]. Thus, improvements found in that assessment may imply better performances during soccer game.

In addition, some researchers investigated the effects of balance training on injury rates reduction concerning soccer players, since soccer is a contact sport associated with a large number of injuries involving adult as well as young players^[14]. In that matter, it was found that balance training was associated with reduced number of injuries among soccer players^[15,16]. However, Malliou *et al.*^[15] suggested that for better results of injury prevention, proprioceptive training should be incorporated with the balance training. It is important to mention in this matter, that the prevention of muscular injuries seems multifactorial and would imply nutrition and hydration to optimize performances and recovery, type of grounds, climatic conditions, or still stretching and strengthening protocols to restore limbs muscle imbalance^[17], thus, the possibility to predict injuries or to prevent injuries may still considered to be inconclusive.

The fact that the accuracy of kicking was not changed significantly may be explained by the short duration of the intervention, since we found some improvement in that variable, however it was not significant. It is possible that longer period of intervention would lead to significant improvement in kicking accuracy, based on the fact that kicking requires control and exploitation of large reactive forces while the performer preserves stability over a narrow base of support^[18].

Another possible explanation for the lack of changes in kicking accuracy is based on the "FIFA 11+" protocol. It is possible that if training protocols were designed to not just prevent injuries but also increase performance, they would lead to higher potential for athlete compliance^[9]. The "FIFA 11+" does not contain specific accuracy exercises, however based on the correlations that were found between kicking accuracy and single-leg balance^[18], it was suggested that improved balance would lead to improved accuracy. Still, no significant improvement was seen in kicking accuracy among the experimental group in comparison to the control group.

In the current study, the large effect size of balance improvement that was observed following six weeks of intervention sessions implies that soccer trainers and coaches should consider the inclusion "FIFA 11+" as components of programs aimed at improving balance ability/control in young soccer players, as improvement in balance abilities may prevent injuries.

COMMENTS

Background

Playing soccer entails some risk of injury and it accounts for more than 10% of sport injuries requiring medical attention in adolescents. As poor balance has been correlated to increased risk of injury in athletes, it was suggested that a program based on balance improvement might reduce the risk of injury.

Research frontiers

The "FIFA 11+", which is a complete warm-up package that combines cardiovascular activation and preventive neuromuscular exercises, was found to induce improvements in neuromuscular control in amateur football players. The key element of the program is the promotion of proper neuromuscular control during all exercises ensuring correct posture and body control, thus it is mainly based on balance control.

Innovations and breakthroughs

To the best of our knowledge, no studies have examined the changes in both balance as well as accuracy of ball kicking among young soccer players induced by the "FIFA 11+". The major result of the study implies a large effect size of balance improvement following six weeks of intervention sessions, with no significant change in kicking accuracy.

Applications

The large effect size of balance improvement that was observed following six weeks of intervention sessions, implies that soccer trainers and coaches should consider the inclusion of "FIFA 11+" as components of programs aimed at improving balance ability/control in young soccer players, as improvement in balance abilities may prevent injuries.

Terminology

The "FIFA 11+" program - A warm-up program that includes three parts: 8 min of running exercises, 10 min of strength, plyometric and balance exercises, and 2 min of explosive running exercises.

Peer-review

The review has a good level of quality and it is very interesting and adequate.

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Case Control Study

Abnormal ground reaction forces lead to a general decline in gait speed in knee osteoarthritis patients

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Author contributions: Wiik AV and Cobb J designed the study; Wiik AV collected the clinical data; Wiik AV and Brevadt M analysed the data; Wiik AV, Aqil A, Brevadt M, Jones G and Cobb J interpreted and wrote the report.

Institutional review board statement: Ethical approval was sought and gained prior to commencement of the trial through the research ethics committee (10/H0807/101). All investigations were conducted in conformity with ethical principles of research, and informed consent for participation in the study was obtained. This work was performed at, Imperial College London, Charing Cross Campus, United Kingdom.

Informed consent statement: All study participants provided informed written consent prior to study enrolment.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: Extended dataset available from the corresponding author.

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Abstract**AIM**

To analyse ground reaction forces at higher speeds using another method to be more sensitive in assessing significant gait abnormalities.

METHODS

A total of 44 subjects, consisting of 24 knee osteoarthritis (OA) patients and 20 healthy controls were analysed. The knee OA patients were recruited from an orthopaedic clinic that were awaiting knee replacement. All subjects had their gait patterns during stance phase at top walking speed assessed on a validated treadmill instrumented with tandem force plates. Temporal measurements and ground reaction forces (GRFs) along with a novel impulse technique were collected for both limbs and a symmetry ratio was applied to all variables to assess inter-limb asymmetry. All continuous variables for each group were compared using a student *t*-test and χ^2 analysis for categorical variables with significance set at $\alpha = 0.05$. Receiver operator characteristics curves were utilised to determine best discriminating ability.

RESULTS

The knee OA patients were older (66 ± 7 years vs $53 \pm$

9 years, $P = 0.01$) and heavier (body mass index: 31 ± 6 vs 23 ± 7 , $P < 0.001$) but had a similar gender ratio when compared to the control group. Knee OA patients were predictably slower at top walking speed (1.37 ± 0.23 m/s vs 2.00 ± 0.20 m/s, $P < 0.0001$) with shorter mean step length (79 ± 12 cm vs 99 ± 8 cm, $P < 0.0001$) and broader gait width (14 ± 5 cm vs 11 ± 3 cm, $P = 0.015$) than controls without any known lower-limb joint disease. At a matched mean speed (1.37 ± 0.23 vs 1.34 ± 0.07), ground reaction results revealed that push-off forces and impulse were significantly ($P < 0.0001$) worse (18% and 12% respectively) for the knee OA patients when compared to the controls. Receiver operating characteristic curves analysis demonstrated total impulse to be the best discriminator of asymmetry, with an area under the curve of 0.902, with a cut-off of -3% and a specificity of 95% and sensitivity of 88%.

CONCLUSION

Abnormal GRFs in knee osteoarthritis are clearly evident at higher speeds. Analysing GRFs with another method may explain the general decline in knee OA patient's gait.

Key words: Gait; Treadmill; Ground reaction forces; Symmetry; Osteoarthritis; Knee

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Core tip: Top walking speed may unmask significant abnormalities which would not be seen at slower walking speeds. The use of impulse rather than solitary peaks in the analysis of ground reaction forces may be more sensitive in detecting significant abnormalities in gait.

Wiik AV, Aqil A, Brevadt M, Jones G, Cobb J. Abnormal ground reaction forces lead to a general decline in gait speed in knee osteoarthritis patients. *World J Orthop* 2017; 8(4): 322-328 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/322.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.322>

INTRODUCTION

Difficulty walking is one of the principal symptoms reported by patients with knee osteoarthritis (OA). Analysis of gait symmetry between right and left legs has been shown useful in identifying lower limb joint disease, particularly osteoarthritis^[1]. Such data may be useful as a trigger for clinical intervention, given that significant asymmetry may lead to falls, injury to other joints and declining walking activity^[2,3].

Previous studies analysing gait symmetry in OA are arguably limited in value by their use of slow speed gait protocols^[4], with more recent studies demonstrating that slower speeds are employed as a protective mechanism by the patient, and can disguise the significant gait abnormalities apparent at higher speeds^[5]. Furthermore,

analysis at faster walking speeds may provide insight into why self-selected walking speed is reduced in knee OA patients, which is of particular interest given that a slow walking speed has been associated with decreased life expectancy^[6].

Biomechanical (obesity, joint instability and malalignment) factors play an important role in the development of OA^[7,8], and the vertical ground reaction force (GRF) measured in gait laboratories is a useful non-invasive surrogate of internal joint loading^[9]. Although repeatable and well described, GRF results are surprisingly variable in the published literature, which is likely due to the uncontrolled variation in walking speed during assessments^[5]. Analysing GRF symmetry offers a potential method of removing the effect introduced by variations in speed, given that the patient's normal limb acts as a control when compared to the diseased contralateral limb. Moreover, most studies only use single "peak" data points for GRF during the gait cycle^[10], which may fail to capture the variation between subjects afforded by a more detailed analysis.

The aim of the study was to: (1) assess the gait patterns and symmetry of patients with knee OA at top walking speed with the aid of an instrumented treadmill; and (2) apply a new method of assessing ground reaction force symmetry. The null hypothesis was that top walking speed and a new method of analysis would show no differences.

MATERIALS AND METHODS

Participants

A total of 44 subjects, consisting of 24 knee OA patients and 20 healthy controls, were included in this study ethically approved by the joint research office (10/H0807/101). Patients with unilateral symptomatic knee OA awaiting knee arthroplasty were recruited from an orthopaedic knee clinic. All subjects had primary knee osteoarthritis and were cardio-vascularly fit, with no further lower limb or joint disease. Standard pre-operative knee radiographs of the OA patient group were used to assess disease severity using Kellgren and Lawrence (KL) grading^[11]. In order to aid validity and interpretation of subsequent data, patients with neurological, medical or other lower limb conditions were excluded, as these variables may also have affected walking ability. This study utilised a control group comprising of healthy staff members, who were free from neurological or joint problems. Test subjects were recruited by a single research assistant. Gait analysis was undertaken using a blinded assessor to avoid testing bias.

Gait analysis and data collection

Gait analysis was performed using a validated treadmill instrumented with tandem piezo-electric force plates (Kistler Gaitway®, Kistler Instrument Corporation, Amherst NY). All participants gave informed consent before treadmill testing began. After an acclimatisation period at 4 km/h, speed was increased incrementally until top

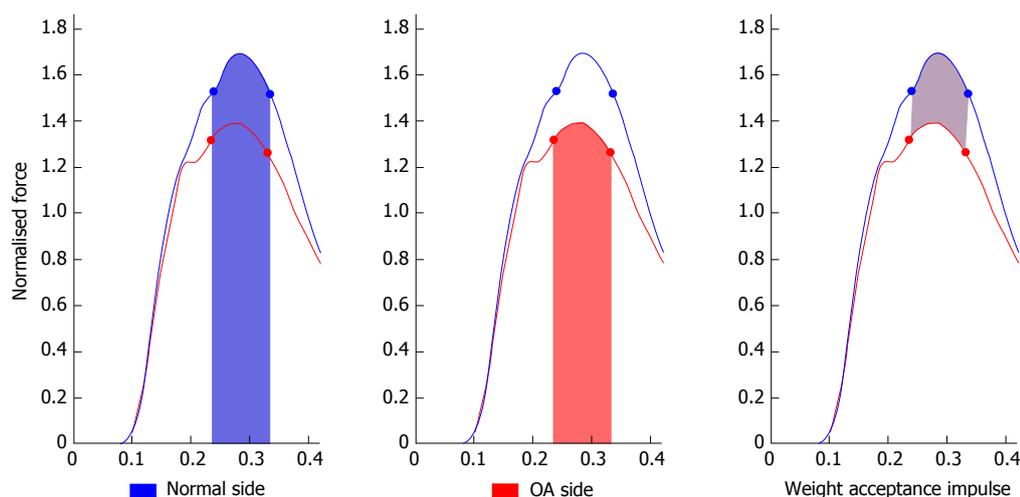


Figure 1 Impulse analysis during weight acceptance: Comparing the knee osteoarthritis limb to the contralateral normal side. OA: Osteoarthritis.

walking speed (TWS) performance had been attained. TWS was defined as the fastest speed a subject could walk without running. All walking measurements were collected without the aid of any props using a standardised testing protocol^[12]. Vertical ground reaction forces, centre of pressure (COP) and temporal measurements were collected for both limbs with a sampling frequency of 100 Hz over 10 s. Gait data was subject to averaging by a custom written MATLAB software script as a 10 s interval normally recorded a minimum of 5 steps for each limb. A validated body weight normalising (BWN) was applied to the force results to correct for mass differences^[13].

BWN force = Ground reaction force/(body mass × gravity)

The data was further divided into affected (A)/unaffected (UA) limb for the OA group, and right/left limb for the healthy controls. A previously described and validated symmetry ratio (SR)^[14], was applied to all variables.

$$SR = [(XA/XUA) - 1] \times 100\%$$

SR values describe the percentage difference between limbs, with zero indicating complete symmetry. Negative values indicated worsening asymmetry with respect to the affected limb in the OA group and the right limb in the control group.

Impulse values were calculated from the vertical GRF data. Impulse takes into account both the magnitude of loading and duration of stance phase of a limb. The total and each phase peak of impulse was assessed on the “M” pattern force curve, comprising weight acceptance (WA) and push-off (PO) impulse. These peaks were identified using a MATLAB script to segment the data, with the limits of integration defined as 5% of force time either side of the maximum value. Figure 1 illustrates the calculation of weight acceptance impulse during stance phase between right and left legs. The same technique was also used for push-off and total impulse used the

entire curve.

Statistical analysis

Statistical analysis was performed with SPSS (IBM SPSS Statistics, version 20). For continuous variables between the groups an independent *t*-test was used and for categorical variable (gender), a χ^2 test was used. A significance level of $\alpha = 0.05$ was employed throughout. Shapiro-Wilk test showed the gait variables to be normally distributed. Variable data is presented as means with standard deviations.

Receiver operating characteristics (ROC) curves were utilised to determine which gait symmetry variables had the best discriminating ability. Categorisation of the area under the curve (AUC) was performed, with AUC above 0.7 determined as fair, above 0.8 good and above 0.9 as excellent discriminating ability^[15].

OA patients’ top walking speed results were predictably slower than the healthy group, and were hence also compared to the healthy group’s preferred walking speed, which was more comparable.

RESULTS

Patient and control characteristics are provided in Table 1. The most common disease severity grade of OA was 2 using Kellgren and Lawrence system. Nineteen patients had medial tibiofemoral OA with an element of patellofemoral OA. Two patients had lateral tibiofemoral OA and remaining three had primarily patellofemoral OA. None of the patients had significant joint bone deformity and an intermediate grade of knee OA can be concluded.

Preferred and top walking speed for the knee OA patients was predictably and significantly slower ($P < 0.0001$) than the controls (1.09 m/s vs 1.34 m/s and 1.37 m/s vs 2.00 m/s respectively). Step length was also reduced at TWS (79 cm vs 99 cm, $P < 0.0001$), with a broader gait width (14 cm vs 11 cm, $P = 0.015$) as seen in Table 2. As ground reaction forces are partly speed dependent^[16] (Figure 2), analysis comparing the knee OA

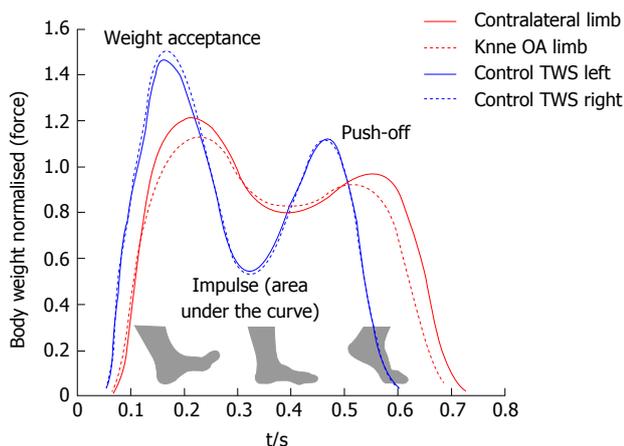


Figure 2 Mean gait patterns during stance phase of controls (blue) and knee osteoarthritis patients (red) at their top walking speed. OA: Osteoarthritis; TWS: Top walking speed.

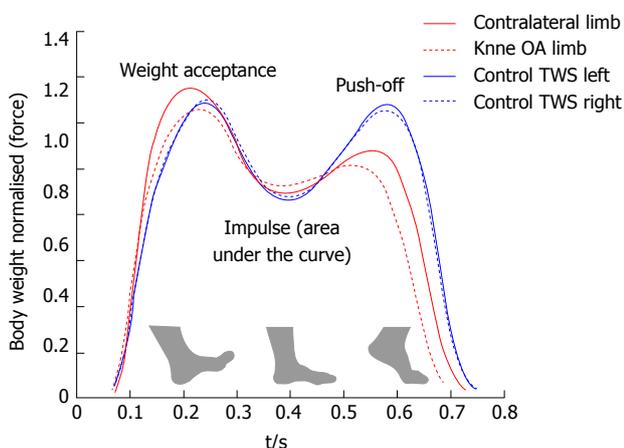


Figure 3 Mean gait patterns during stance phase of controls (blue) and knee osteoarthritis patients (red) at similar speeds. OA: Osteoarthritis; TWS: Top walking speed.

results to the control group's preferred walking speed was done given that they were similar (1.34 m/s vs 1.37 m/s $P = 0.56$). Push-off force and total impulse were significantly ($P < 0.0001$) less (22% and 12% respectively) than the controls (Table 2 and Figure 3). This was also seen at the knee OA preferred walking speed, but became more pronounced at top walking speed. The knee OA patients were also significantly more asymmetrical than the healthy controls, with the greatest difference between limbs (Table 2) seen during single limb stance time (8%, $P = 0.001$), push-off impulse (7%, $P = 0.050$) and total impulse (7%, $P < 0.0001$). ROC analysis of the gait symmetry variables (Table 3) at TWS demonstrated that total impulse (Figure 4) was the best discriminator of symmetry with an AUC of 0.902, with a cut-off of -3% and a specificity of 95% and sensitivity of 88%.

DISCUSSION

By analysing gait ground reaction forces and symmetry at top walking speed, this study set-out to determine

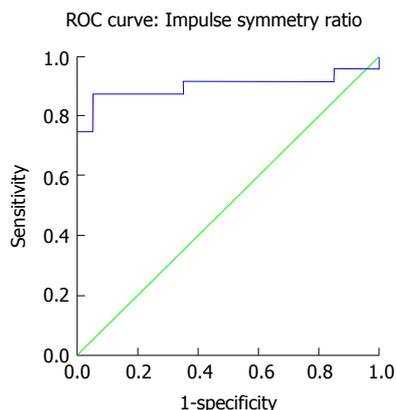


Figure 4 Receiver operating characteristics graph: Displaying the discriminating ability of total impulse symmetry ratio. ROC: Receiver operating characteristics.

Table 1 Subject characteristics		
Subject	Control	Knee OA
Sex M:F	7:13	8:16
Age (yr)	52.5 (8.8)	65.5 (7.2) ¹
BMI	23.2 (6.6)	31.2 (6.1) ¹
Leg length (cm)	89.3 (5.6)	85.1 (5.9) ¹
Height (cm)	168.5 (7.5)	164.1 (7.9)
Total KL score	NA	2.5 (1.1)

¹Significant difference between OA group vs control at PWS ($P < 0.05$). OA: Osteoarthritis; NA: Not available; PWS: Preferred walking speed; KL: Kellgren and Lawrence; BMI: Body mass index.

the changes in gait associated with the general decline in walking speed seen in patients with knee OA. In accordance with previous studies^[17,18], compared to healthy controls the OA group walked more slowly and asymmetrically, with a wider based gait, and a shorter step length. Furthermore the study demonstrated that testing at top walking speed elicited differences in gait which would not ordinarily be detected at slower walking speeds.

Of most interest was that the OA patients had a significantly lower, and less symmetrical, push-off force and push-off impulse compared to healthy controls - suggesting a weakness during the terminal stance phase is a factor causing slower walking speeds. This may be secondary to loss of muscle power around the joint, a theory supported by Baert *et al*^[19]'s finding of a 37% decrease in isometric knee extension power in early OA, and a 56% decrease in established OA patients, when compared to a matched control group. This loss may also be due to pain and the progressive attrition of muscle power due to the decreasing activity found in a biomechanically faulty knee. Nevertheless Bytyqi *et al*^[20] demonstrated 11.6 degree loss during knee flexion/extension during comfortable walking in patients with OA when compared to controls which would further explain the importance of power and improved knee kinematics to achieve faster walking speed. This is of clinical value to surgeons and patients alike, given that it reinforces

Table 2 Temporospatial and normalised ground reaction results

Variable	Knee OA PWS		Symmetry ratio %		Control PWS		Symmetry ratio %		Knee OA TWS		Symmetry ratio %		Control TWS		Symmetry ratio %	
	Affected (n = 24)	Unaffected (n = 24)	Mean (SD)	Mean (SD)	Right (n = 20)	Left (n = 20)	Mean (SD)	Mean (SD)	Affected (n = 24)	Unaffected (n = 24)	Mean (SD)	Mean (SD)	Right (n = 20)	Left (n = 20)	Mean (SD)	Mean (SD)
Speed (m/s)	1.09 ¹ (0.14)	113 (7)	NA	NA	1.34 (0.07)	114 (10)	NA	NA	1.37 ² (0.23)	123 ^{1,2} (9)	NA	NA	2.00 (0.20)	137 (11)	NA	NA
Cadence (step/min)	113 (7)	14.6 (4.2) ¹	NA	NA	11.2 (3.2)	11.2 (3.2)	NA	NA	14.2 ^{1,2} (4.5)	11.2 (3.0)	NA	NA	11.2 (3.0)	11.2 (3.0)	NA	NA
Gait width (cm)	1.07 ¹ (0.08)	1.12 ¹ (0.10)	-4.0 ¹ (5.7)	1.18 (0.07)	1.18 (0.08)	1.18 (0.07)	0.7 (2.0)	1.18 ² (0.14)	1.26 ^{1,2} (0.16)	1.55 (0.12)	1.55 (0.12)	1.55 (0.12)	1.52 (0.12)	1.52 (0.12)	2.6 (3.3)	2.6 (3.3)
Weight acceptance (BWN)	1.00 ¹ (0.06)	1.02 (0.06)	-2.6 (5.2)	1.15 (0.09)	1.15 (0.09)	1.16 (0.08)	-1.5 (1.6)	0.95 ^{1,2} (0.07)	1.00 ^{1,2} (0.07)	1.16 (0.12)	1.16 (0.12)	1.16 (0.12)	1.17 (0.10)	1.17 (0.10)	-0.9 (3.5)	-0.9 (3.5)
Push-off (BWN)	0.53 (0.05)	0.57 (0.04)	-5.9 ¹ (5.6)	0.55 (0.05)	0.55 (0.05)	0.55 (0.05)	-0.2 (1.8)	0.49 ^{1,2} (0.04)	0.53 ^{1,2} (0.04)	0.46 (0.04)	0.46 (0.04)	0.46 (0.04)	0.46 (0.04)	0.46 (0.04)	-0.1 (1.6)	-0.1 (1.6)
Total impulse (BWN/s)	0.104 ¹ (0.008)	0.108 (0.010)	-3.4 ¹ (6.3)	0.112 (0.007)	0.112 (0.007)	0.112 (0.007)	0.9 (3.1)	0.113 ² (0.014)	0.120 ² (0.015)	0.146 (0.010)	0.146 (0.010)	0.146 (0.010)	0.142 (0.011)	0.142 (0.011)	3.5 (4.2)	3.5 (4.2)
Weight acceptance impulse (BWN/s)	0.098 ¹ (0.008)	0.098 ¹ (0.011)	0.6 (13.4)	0.111 (0.009)	0.111 (0.009)	0.114 (0.008)	-2.9 (2.6)	0.091 ^{1,2} (0.008)	0.098 ^{1,2} (0.007)	0.110 (0.011)	0.110 (0.011)	0.110 (0.011)	0.111 (0.009)	0.111 (0.009)	-2.9 (4.7)	-2.9 (4.7)
Push off impulse (BWN/s)	68 ¹ (10)	67 ¹ (9)	2.6 (6.5)	79 (6)	79 (6)	78 (5)	1.7 (2.5)	79 (12) ²	78 (11) ²	99 (8)	99 (8)	99 (8)	98 (8)	98 (8)	1.0 (1.9)	1.0 (1.9)
Step length (cm)	0.53 (0.05)	0.54 (0.04)	-1.2 (7.5)	0.53 (0.05)	0.53 (0.05)	0.53 (0.04)	0.3 (3.1)	0.48 ^{1,2} (0.03)	0.50 ² (0.05)	0.44 (0.04)	0.44 (0.04)	0.44 (0.04)	0.44 (0.04)	0.44 (0.04)	-0.2 (3.5)	-0.2 (3.5)
Step time (s)	0.72 (0.05)	0.73 (0.05)	-2.4 ¹ (3.8)	0.68 (0.06)	0.68 (0.06)	0.69 (0.06)	-0.3 (1.7)	0.65 ^{1,2} (0.05)	0.67 ² (0.07)	0.56 (0.05)	0.56 (0.05)	0.56 (0.05)	0.56 (0.05)	0.56 (0.05)	-0.3 (1.5)	-0.3 (1.5)
Contact time (s)	0.33 ¹ (0.04)	0.36 (0.04)	-7.0 ¹ (9.3)	0.38 (0.04)	0.38 (0.04)	0.38 (0.04)	-0.4 (3.5)	0.32 ¹ (0.02)	0.34 ¹ (0.03)	0.33 (0.04)	0.33 (0.04)	0.33 (0.04)	0.33 (0.04)	0.33 (0.04)	-0.3 (3.1)	-0.3 (3.1)
Single limb stance time (s)																

The values are indicated as means ± standard deviation; ¹Significant difference between OA group vs control at PWS (P < 0.05); ²Significant difference between OA group vs control at TWS (P < 0.05). PWS: Preferred walking speed; NA: Not available; TWS: Top walking speed; BWN: Body weight normalised; OA: Osteoarthritis.

the need for replacement surgery to be combined with physiotherapy aimed at restoring muscle strength and range of motion, and is consistent with the finding that gait and function can improve over time^[21].

Another important study finding was the results of weight acceptance and weight acceptance impulse in the knee OA patients. Weight acceptance is the period during early stance phase at which the knee is fully extended and accepting the full weight. Whilst the weight acceptance of the affected limb in knee OA patients was comparable to healthy controls (1.18 vs 1.18 BWN/s respectively), they were in fact abnormal when compared to the unaffected leg in the same patient (1.18 vs 1.26 BWN and 0.113 vs 0.112 BWN/s respectively). This likely indicates that these patients inherently have loaded their arthritic knee joint beyond than what would be expected at that speed at which now they are limping and trying to reduce load on it. Furthermore considering that the patient's body mass index (BMI) were 35% higher than the controls, the normalised force results underestimates the true gross force which is traveling through the OA patient's knee during walking. These findings may partly explain why their knee joints wore out in the first instance. Furthermore they are consistent with a study reporting significantly increased knee joint loads during walking in subjects with knee OA^[22]. These observations may be of practical value, as a tool for measuring intervention which aim to retrain gait, avoid high weight acceptance forces and theoretically prevent further joint arthrosis from occurring.

The second main aim of the study was to assess the use of an area (impulse) below ground reaction force peaks, rather than just solitary points on the peak, as a novel method of assessing symmetry. In this regard, after single limb stance time, total impulse and push-off impulse displayed the largest asymmetries in knee OA patients. And ROC analysis identified the total impulse symmetry ratio as the best variable to discriminate between groups, with an AUC of 0.902 which is considered excellent. Weight acceptance impulse also proved to be a good discriminating measure, with an AUC of 0.852. Hodt-Billington recommended a 10% asymmetry criterion for pathological gait from their work comparing hip OA patients with healthy controls^[1], whilst our results suggest a symmetry ratio criterion as low as 5% for total impulse. Nevertheless a 10% criterion should generally be recommended for parametric data as recommended by multiple studies^[1,23,24]. Our results also demonstrate that healthy gait has a range of asymmetry which is parameter dependent and varies statistically depending on its confidence interval.

The limitation of this study relates to the control group, who were significantly lighter and younger, and walked with a significantly faster top speed. Fortunately, the

Table 3 Area under curve results with confidence intervals demonstrating the discriminating ability of different variables

SR at TWS	AUC	CI	Significance
WA	0.898	0.800, 0.996	< 0.001
PO	0.683	0.521, 0.846	0.038
TI	0.902	0.797, 1.000	< 0.001
WAI	0.852	0.736, 0.968	< 0.001
POI	0.654	0.491, 0.817	0.081
ST	0.650	0.484, 0.816	0.090
CT	0.767	0.628, 0.905	0.003
SLST	0.767	0.628, 0.906	0.003

AUC: Area under curve; CI: Confidence intervals; SR: Symmetry ratio; WA: Weight acceptance; PO: Push-off; TI: Total impulse; WAI: Weight acceptance impulse; POI: Push-off impulse; ST: Stance time; CT: Contact time; SLST: Single limb stance time.

control group’s preferred walking speed was similar to the OA group’s top walking speed with identical step length (79 cm vs 79 cm), allowing for a fair and better comparison. Additionally the intended objective was not to determine which group was faster but rather, which factors caused them to be slower. Nevertheless a previous 3-D kinematic gait study looking at knee movements did not observe a difference in fast walking speed in knee OA patients despite them being almost 10 years older than the health controls^[25]. And as previously discussed, by looking at asymmetry, in effect patients act as their own controls if they have one healthy, un-affected, knee. In common with many other gait studies, our OA group were significantly heavier than controls, which is unsurprising given that high BMI is a perhaps the greatest known risk factor for OA^[5,25]. However, all ground reaction forces were normalised for body weight to minimise the bias introduced by this difference between groups. Lastly this is a cross-sectional study and it would have been interesting to see whether interventions such as physiotherapy, foot orthotics, or knee surgery could restore normal ground reaction forces and symmetry while walking.

In conclusion, this paper reconfirms the gait abnormalities seen with knee OA, but for the first time using ground reaction forces at top walking speed and a novel method of analysis. Reduced push-off and overall loading (impulse) are key factors in limiting the top walking speed of patients with OA. Higher than expected weight acceptance loads are potential causes for patients wearing out their joints. Furthermore OA patients demonstrate significant asymmetry in almost all parameters of gait biomechanics, with ROC analysis identifying total impulse as the variable with the best discriminating ability. Longitudinal studies are required, but these features may be useful in the screening and rehabilitation of patients at risk of developing, or with early knee arthrosis.

COMMENTS

Background

Knee osteoarthritis is an increasingly common condition. Understanding the

loading characteristics of patients with knee osteoarthritis may help prevent or delay this condition from occurring.

Research frontiers

The gait assessment of patients with knee osteoarthritis has primarily been completed using slower speed protocols. The use of faster speeds on an instrumented treadmill has allowed us to better understand the loading patterns of patients with knee osteoarthritis.

Innovations and breakthroughs

This study demonstrated that faster speed detected differences which would not be seen at slower speed. Impulse and weight acceptance were the variables with the best discriminating ability.

Applications

Faster walking speed is recommended during gait analysis for patients with knee osteoarthritis.

Terminology

Ground reaction forces are the stance phase loading characteristics of the foot during gait.

Peer-review

This is an interesting paper that aims to evaluate the gait patterns in osteoarthritis patients at top walking speed. This is a well-designed and organized study that uses validated measurements and produces some important findings. The methodology used is appropriate and well presented.

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Retrospective Study

Variability in conflict of interest disclosures by physicians presenting trauma research

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Abstract

AIM

To quantify the variability of financial disclosures by authors presenting orthopaedic trauma research.

METHODS

Self-reported authorship disclosure information published for the 2012 American Academy of Orthopaedic Surgeons (AAOS) and Orthopaedic Trauma Association (OTA) meetings was compiled from meeting programs. Both the AAOS and OTA required global disclosures for participants. Data collected included: (1) total number of presenters; (2) number of presenters with financial disclosures; (3) number of disclosures per author; (4) total number of companies supporting each author; and (5) specific type of disclosure. Disclosures made by authors presenting at more than one meeting were then compared for discrepancies.

RESULTS

Of the 5002 and 1168 authors presenting at the AAOS and OTA annual meetings, respectively, 1649 (33%) and 246 (21.9%) reported a financial disclosure ($P < 0.0001$). At the AAOS conference, the mean number of disclosures among presenters with disclosures was 4.01 with a range from 1 to 44. The majority of authors with disclosures reported three or more disclosures ($n = 876$, 53.1%). The most common cited disclosure

was as a paid consultant (51.5%) followed by research support (43.0%) and paid speaker (34.8%). Among the 256 physicians with financial disclosures presenting at the OTA conference, the mean number of disclosures was 4.03 with a range from 1 to 22. Similar to the AAOS conference, the majority of authors with any disclosures at the OTA conference reported three or more disclosures ($n = 140$, 54.7%). Most authors with a disclosure had three or more disclosures and the most common type of disclosure was paid consulting. At the OTA conference, the most commonly cited form of disclosure was paid consultant (54.3%) followed by research support (46.1%) and paid speaker (42.6%). Of the 346 researchers who presented at both meetings, 112 (32.4%) authors were found to have at least one disclosure discrepancy. Among authors with a discrepancy, 36 (32.1%) had three or more discrepancies.

CONCLUSION

There were variability and inconsistencies in financial disclosures by researchers presenting orthopaedic trauma research. Improved transparency of conflict of interest disclosures is warranted among trauma researchers presenting at national meetings.

Key words: Conflict of interest; Financial disclosures; Ethics; American Academy of Orthopaedic Surgeons; Orthopaedic Trauma Association

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Core tip: Previous studies have demonstrated discrepancies in financial conflict of interest disclosures among physicians presenting research. The purpose of this study was to quantify the variability of self-reported financial disclosures by authors presenting at multiple trauma conferences during the same year. The disclosures published for the 2012 annual meetings of the American Academy of Orthopaedic Surgery and Orthopaedic Trauma Association were tabulated and disclosures made by authors presenting at both meetings were compared for discrepancies. Our results demonstrate variability in reported disclosures by authors presenting at multiple conferences within the same year. Further work is warranted to improve transparency of disclosures.

Wong K, Yi PH, Mohan R, Choo KJ. Variability in conflict of interest disclosures by physicians presenting trauma research. *World J Orthop* 2017; 8(4): 329-335 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/329.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.329>

INTRODUCTION

Private industry has become an increasingly significant source of funding for physicians conducting research in recent years^[1-3]. As industry investment in medical

research grows however, conflict of interest (COI) has become a controversial topic in orthopaedic surgery. Many studies have suggested that close ties between industry and physicians may negatively influence the quality and integrity of clinical studies^[4-6]. For example, industry funding is one of the strongest predictors for a favorable result in a product being studied^[7-11]. Although industry funding has a potential to create bias, it has also been essential in achieving many advances in diagnosis and treatment in medicine^[12], and as a result balancing the benefits and risks of industry relationships has become a divisive reality to deal with within the orthopaedic community.

Disclosures of conflict of interest have been called for by the American Academy of Orthopaedic Surgeons (AAOS) and other medical organizations in order to maintain research integrity^[13-16]. Unfortunately, differences in what constitutes a COI as well as ambiguity between disclosure guidelines between different organizations can make it difficult for physicians to know exactly what to disclose^[15,17]. Previous studies have shown variability in the COI disclosures by researchers presenting on spine surgery and sports medicine, possibly due to variability in disclosure policies^[18,19]. In fact, some evidence suggests that inaccuracies in COI disclosure can be found throughout the field of orthopaedics as a whole^[20]. To date, however, there has been no previous analysis of COI discrepancies within the subspecialty of orthopaedic trauma.

The purpose of the present study was: (1) to describe the COI disclosures of authors presenting research at both the AAOS and the OTA annual meetings; and (2) to quantify variability in COI disclosures of authors who presented orthopaedic trauma research. We hypothesized that there would be variability in the disclosure of physicians presenting research at the two conferences in the same given year.

MATERIALS AND METHODS

We recorded the disclosures from all authors who presented trauma research at two orthopedic conferences. The two conferences included in the study were the 2012 annual meeting for the AAOS and the 2012 annual meeting for the Orthopaedic Trauma Association (OTA). Self-reported disclosure data from the authors for each conference was collected from the printed meeting information, which is available online^[21,22]. Since the 2012 AAOS abstract deadline was in June 2011 while the 2012 OTA conference abstract deadline was in February 2012, it is possible that industry support and COI for some authors may have changed during the time between the two conferences. However, it is common for industry sponsorships to last for years, especially when these partnerships involve clinical research^[23,24]. Thus, for the purposes of this current study, it was assumed that changes, if any, would be minimal given the relatively short time between the two conference deadlines.

The disclosure policies for the AAOS and OTA con-

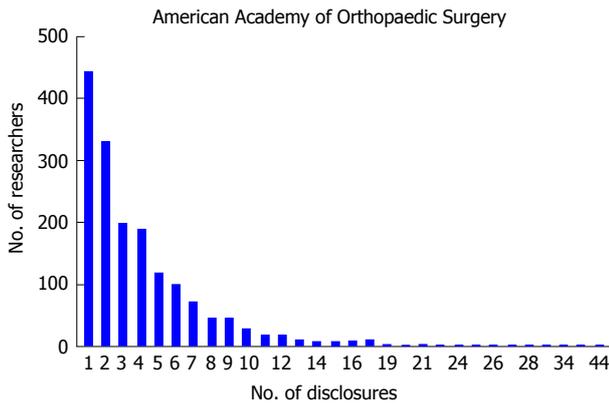


Figure 1 Total number of researchers reporting disclosures at the American Academy of Orthopaedic Surgery decreases as the total number of disclosures increases.

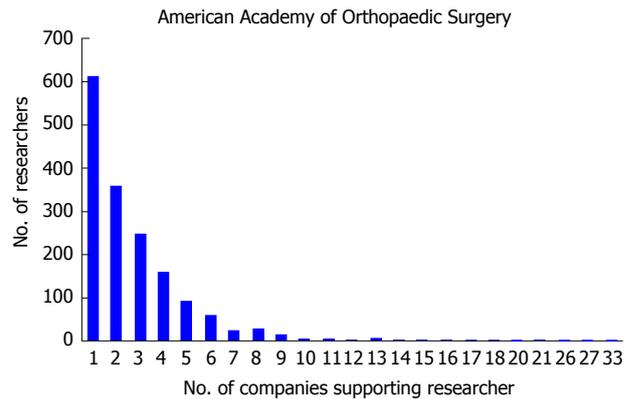


Figure 2 Number of researchers disclosing company/entity support at the American Academy of Orthopaedic Surgery decreases as the number of disclosures increases.

ferences were obtained from the AAOS and OTA websites^[25]. Both the AAOS and OTA conferences required global disclosure (*i.e.*, presenters were required to disclose all financial relationships, regardless of relevance to their presentation). Because the guidelines between these two conferences were equivalent, we were able to compare the financial relationships reported by authors who attended both conferences in order to quantify any discrepancies present in the author's disclosures. Only authors who presented at both conferences were included in the present study for a total of 346 individuals. Researchers who presented at only one of the conferences were excluded from the study.

Pertinent characteristics recorded from each conference included: (1) total number of presenters; (2) number of presenters with financial disclosures; (3) number of disclosures per author (among authors with disclosures); (4) total number of companies/entities supporting each author (among authors with disclosures); and (5) percentage breakdown of each type of disclosure into 9 specific categories (*i.e.*, royalties, paid speaker, employee, paid consultant, nonpaid consultant, stock options, research support, other support, and publishers).

After recording disclosure data from each conference for eligible authors, the disclosures between the two conferences were then compared. First, the total number of authors with and without consistent number of disclosures was recorded. Next the individuals with inconsistent disclosures were categorized into two categories: (1) those who disclosed at least one financial relationship at one conference but no financial relationships at the other conference; and (2) those who disclosed at both conferences but with different number and type of disclosures.

RESULTS

The total number of research presenters at the AAOS annual meeting was 5002, and out of those who presented, 1649 (33.0%) had financial disclosures. The total number of presenters at the OTA annual meeting was 1168 and a total of 256 (21.9%) authors at the OTA

meeting had financial disclosures. In total there were 6613 disclosures reported at the AAOS meeting and 1033 disclosures reported at the OTA meeting.

At the AAOS conference, the mean number of disclosures among presenters with disclosures was 4.01 with a range from 1 to 44. The majority of authors with disclosures reported three or more disclosures ($n = 876$, 53.1%); in contrast, only 443 (26.9%) researchers reported one disclosure and 330 (20.0%) of researchers reported two disclosures. Although the majority of authors reported three or more disclosures, the number of researchers reporting increasing number of disclosures progressively decreases (Figure 1). The mean number of companies/entities supporting researchers among those with disclosures was 2.88 with a range from 1 to 33 companies. Of those authors with support from companies, 612 (37.1%) researchers received support from only one company, 358 (21.7%) received support from two companies, and 679 (41.2%) received support from three or more companies. Similar to the total number of disclosures, the number of researchers disclosing company/entity support decreases as the number of disclosures increases (Figure 2). Among authors who provided specific types of disclosures, the most common cited disclosure was as a paid consultant (51.5%) followed by research support (43.0%) and paid speaker (34.8%). In descending order, the remaining disclosures include royalties (29.1%), stock options (27.9%), publisher (17.5%), unpaid consultant (11.7%), other support (11.0%), and employee (5.15%).

Among the 256 physicians with financial disclosures presenting at the OTA conference, the mean number of disclosures was 4.03 with a range from 1 to 22. Similar to the AAOS conference, the majority of authors with any disclosures reported three or more disclosures ($n = 140$, 54.7%), a total of 61 (23.8%) presenters reported only one disclosure and 55 (21.5%) of presenters reported two disclosures. Although the majority of authors who reported any disclosures at the OTA conference reported three or more financial affiliations, the number of re-

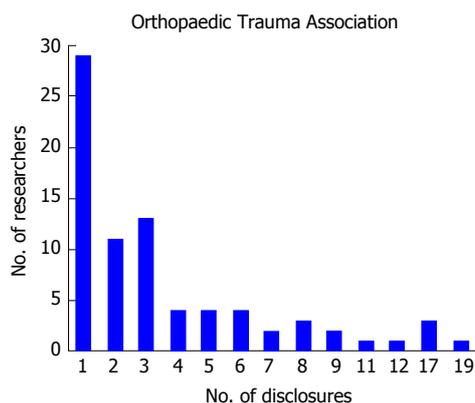


Figure 3 Total numbers of researchers reporting disclosures at the Orthopaedic Trauma Association decreases as the total number of disclosures increases.

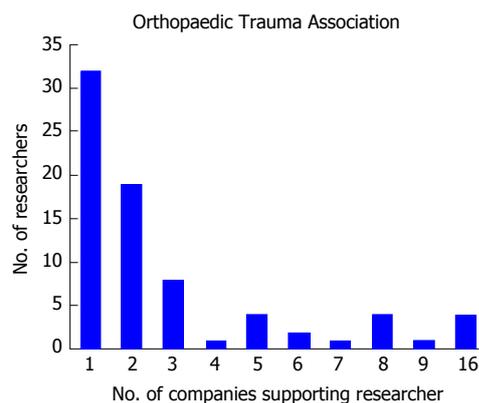


Figure 4 Number of researchers disclosing company/entity support at the Orthopaedic Trauma Association decreases as the number of disclosures increases.

searchers reporting sequentially increasing number of affiliations decreases (Figure 3). The mean number of companies/entities supporting researchers who reported disclosures was 3.09 with a range from 1 to 22 companies. Of those presenters who received support from companies, 78 (30.5%) researchers received support from only one company, 69 (27.0%) researchers received support from two companies, and 109 (42.6%) researchers received support from three or more companies. The number of physicians disclosing support from companies decreases at successively higher numbers of company support (Figure 4). Among presenters who provided specific types of financial disclosures, the most commonly cited form of disclosure was paid consultant (54.3%) followed by research support (46.1%) and paid speaker (42.6%). In descending order, the remaining disclosures include stock options (23.4%), royalties (19.5%), publisher (16.8%), other support (13.3%), unpaid consultant (12.1%), and employee (6.25%).

In total, 346 physicians presented at both the AAOS and OTA conferences in 2012. The number of co-presenters with discrepancies in financial disclosure was 112 (32.4%) with a mean of 2.47 and a range from 1 to 16 discrepancies. Among the co-presenters with disclosures, 55 (49.1%) had one discrepancy between the AAOS and OTA conferences, 21 (18.8%) of co-presenters had two discrepancies between the two conferences, and 36 (32.1%) of co-presenters had three or more discrepancies between the two conferences (Figure 5). Of the 112 co-presenters with discrepancies, 38 (33.9%) made zero disclosures at one conference but disclosed at least one financial relationship at the other conference while 74 (66.1%) of co-presenters with discrepancies disclosed at both conferences (Figure 6). The remaining 67.6% of physicians who presented at both conferences were found to have no discrepancies between their disclosures.

nificantly towards private industry^[26], addressing COI has become an important topic for orthopaedic surgeons. Although previous studies have demonstrated disclosure inconsistencies by physicians presenting sports medicine and spine surgery at various orthopaedic conferences^[18,19], no previous study has assessed the variability of COI disclosures by physicians presenting orthopaedic trauma research. The purpose of this study was to evaluate disclosures by physicians presenting at the 2012 AAOS and OTA annual meetings in order to quantify COI discrepancies. Overall, we found a high prevalence of disclosure discrepancies. Nevertheless, specific types of disclosures were similar between presenters at both the AAOS and OTA conferences; furthermore, the most common disclosure types were paid consulting, research support, and paid speaker. Finally, we found that the majority of physicians with discrepancies had more than one discrepancy, and a large portion of physicians with discrepancies disclosed nothing at one conference despite disclosing at least one COI at the other conference.

There was a high prevalence of disclosure discrepancies by physicians who presented at both the 2012 AAOS and OTA conferences with a total of about one third of all physicians with at least one discrepancy. This is consistent with previous reports in sports medicine and spine, which have also shown high discrepancy rates among researchers presenting in these fields. There are several possible explanations for this high number of discrepancies. First, it is possible that discrepancies between the two conferences can be explained simply by natural changes in industry affiliations that occurred between the two conferences; however the period of only a few months between conference abstract submission deadlines makes this explanation unlikely. A second possibility is that the discrepancies simply result from physician carelessness. Current penalties for inaccurate disclosure are fairly limited and leave researchers considerable discretion in what they decide to disclose^[16,27]; lack of sufficient repercussion may decrease the effort some authors make in order to check or verify disclosure policies, leading to disclosure errors.

DISCUSSION

As funding for biomedical research has shifted sig-

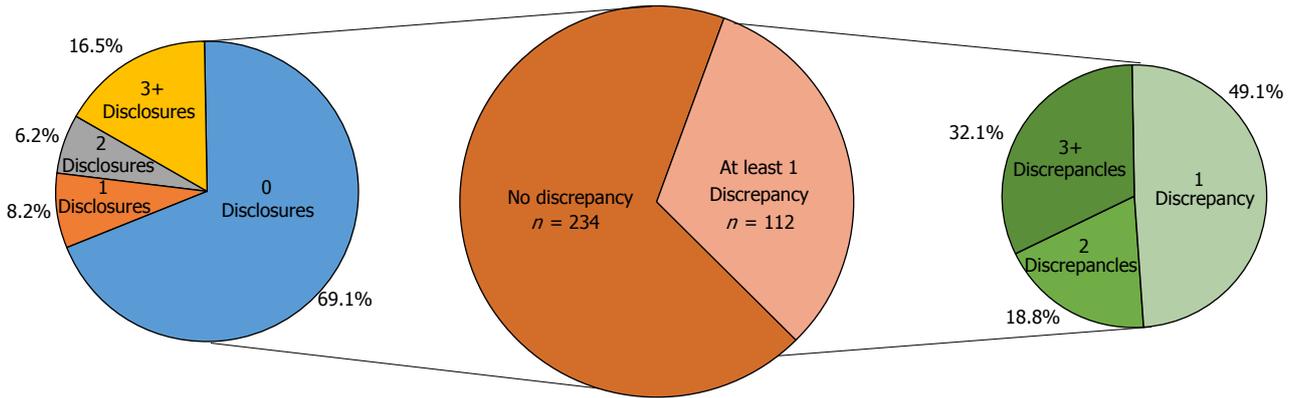


Figure 5 Number of disclosure discrepancies by physicians who disclosed at both the American Academy of Orthopaedic Surgery and Orthopaedic Trauma Association conferences.

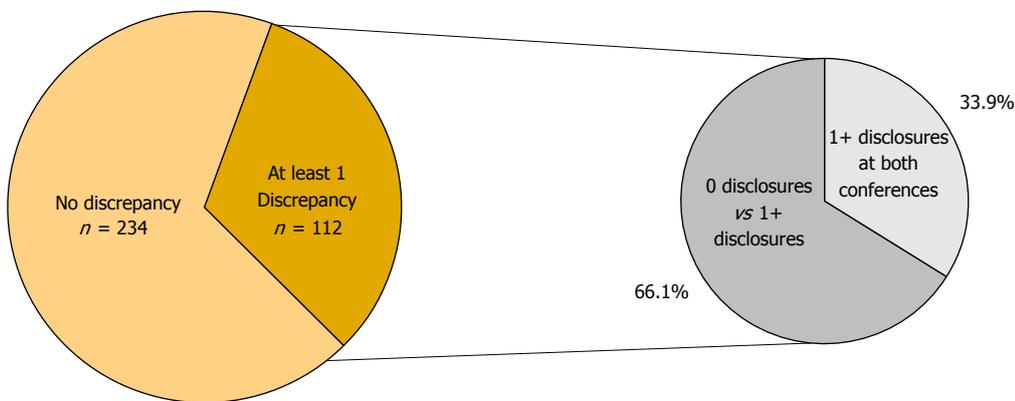


Figure 6 Disclosure patterns among researchers with disclosure discrepancies.

This carelessness might also explain the difference in total disclosures between the AAOS and OTA conferences: The AAOS is a larger conference, and hosts not only a higher number of attendees, but also features a larger number of orthopaedic topics including but not limited to trauma^[28]. While it is possible that some physicians correctly assumed a global disclosure policy at the AAOS conference given the larger scope of the conference, when these same physicians presented at the OTA conference - a conference focused on a more niche topic - they may have erroneously assumed that they only needed to disclose project-specific industry relationships without checking for the true OTA global disclosure policy. This possibility is consistent with our data, which showed an increase in the proportion of physicians reporting disclosures at the AAOS conference compared to the OTA conference.

The three most common types of disclosures in descending order were paid consultant, research support, and paid speaker. These observations are consistent with previous studies within the fields of spine surgery, sports medicine, and pediatric orthopaedics, which have also been shown to have the same three most frequent financial relationships^[29]. General trends in paid consultancies are also commonplace in total joint arthroplasty, with manufacturers often paying physicians

to serve as experts^[30]. These findings demonstrate that industry funding has become such a consistent factor in orthopaedic research that even the type of disclosures remains steady between orthopaedic trauma and other orthopaedic specialties. However the prevalence of industry funding within orthopaedic research is not necessarily detrimental. As we have already mentioned, industry funding in itself does not automatically decrease the credibility or validity of research. Secondly, the presence of industry funding in multiple orthopaedic specialties may actually be beneficial by providing an opportunity to compare rates of disclosure discrepancies between specialties and identify areas with lower discrepancies. This would ultimately be beneficial for orthopaedic trauma research by allowing researchers to adopt successful strategies to reduce COI discrepancies within this field.

Meaningful research requires more than proper technique and procedure, it also requires proper disclosure of conflicts of interest^[31,32]. The inability of current disclosure guidelines to facilitate uniform and accurate physician disclosure regarding orthopaedic trauma research is demonstrated by the high variability in both the number and type of disclosure inconsistencies. Our data has shown that the majority of physicians with discrepancies in disclosure presented with more than one

discrepancy. Furthermore, over a third of physicians who reported at least one disclosure at one conference failed to report any COI at the other conference. Proper disclosure is crucial to inform the audience and allow readers to draw their own conclusions about the objectivity of the research^[33]. At a time when the public is often cautious and even skeptical towards medical research, disclosure inconsistencies may negatively impact the integrity of research, and it is therefore important that orthopaedic surgeons hold themselves to a high standard of accuracy and decrease the inconsistencies in both the number and type of disclosures.

There were several limitations to our study. As previously mentioned, the AAOS and OTA conferences occurred during different months so there may have been changes in financial affiliations during that time. The disclosure deadline for the 2012 AAOS conference was June 2011 while the disclosure deadline for the 2012 OTA conference was February 2011. In these nine months, we predicted that there would only be minor changes, if any, in disclosures by anyone presenting at both conferences. Another limitation to our study was the fact that only two orthopaedic conferences were examined in this study. For this reason, the sampling of physician disclosures may not be representative of the total population of disclosures in orthopaedic trauma research, nor can the findings be generalized towards non-orthopaedic research. Nevertheless, we believe that our data does provide accurate insight into the realities of two of the most prominent venues for the presentation of orthopaedic trauma research in the world, and as such is relevant to the discussion of COI in orthopaedics.

In our study, we found substantial variability in disclosures from physicians presenting orthopaedic trauma research at the 2012 AAOS and OTA conferences. The origin of financial relationships between researchers and industry arise from multiple sources, and there is variability in both the number and type of discrepancies involved in trauma research. The large proportion of disclosure inconsistencies currently found in physicians presenting trauma research may be explained by factors such as physician carelessness, unclear disclosure instructions, or inadequate repercussions by the AAOS and OTA for failure to accurately disclose. Because the current system presents with a high number of disclosure discrepancies within orthopaedic trauma, we recommend adjusting current guidelines to be more clear and uniform as a first step in promoting accurate COI disclosure as well as research transparency and accountability.

COMMENTS

Background

Private industry has become an increasingly significant source of research funding. Financial relationships may create biases that compromise the integrity and objectivity of industry-sponsored medical research. To improve transparency, multiple orthopaedic organizations have developed specific disclosure policies. Unfortunately, current guidelines vary between organizations

and are often not clearly explained to researchers. The purpose of this study was to quantify the variability of financial disclosures by authors presenting orthopaedic trauma research.

Research frontiers

Previous studies in sports medicine, spine surgery, and arthroplasty have shown that researchers presenting at separate national meetings within the same academic year have discrepancies in the financial disclosures they make.

Innovations and breakthroughs

This is the first study to our knowledge that has investigated: (1) the prevalence and characteristics of financial relationships; and (2) quantified discrepancies in conflict of interest disclosures by researchers presenting orthopaedic trauma research. The results of their study demonstrate that many authors reported financial disclosures at American Academy of Orthopaedic Surgeons and Orthopaedic Trauma Association, with a relatively high number of discrepancies.

Applications

Clearer instructions for authors regarding financial disclosures should be established in order to help make conflict of interest disclosures a more reliable and appropriate measure.

Terminology

A "conflict of interest" is defined as a situation in which a person or organization is involved in multiple personal or financial interests that may corrupt or otherwise influence the motivation and decision-making abilities of that individual.

Peer-review

The paper is an excellent paper with very important topic: Variability in conflict of interest disclosures by physicians presenting trauma research.

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Retrospective Study

Associations among pain catastrophizing, muscle strength, and physical performance after total knee and hip arthroplasty

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Informed consent statement: All the participants provided written informed consent.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at hayashi.k@med.nagoya-u.ac.jp.

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Abstract**AIM**

To investigate whether reductions in pain catastrophizing associated with physical performance in the early period after total knee arthroplasty (TKA) or total hip arthroplasty (THA).

METHODS

The study group of 46 participants underwent TKA or THA. The participants were evaluated within 7 d before the operation and at 14 d afterwards. Physical performance was measured by the Timed Up and Go (TUG) test, and 10-m gait time was measured at comfortable and maximum speeds. They rated their knee or hip pain using a visual analog scale (VAS) for daily life activities. Psychological characteristics were measured by the Pain Catastrophizing Scale (PCS). Physical characteristics were measured by isometric muscle strength of knee extensors and hip abductors on the operated side. The variables of percent changes between pre- and post-operation were calculated by dividing post-operation score by pre-operation score.

RESULTS

Postoperative VAS and PCS were better than pre-operative for both TKA and THA. Postoperative physical performance and muscle strength were poorer than

preoperative for both TKA and THA. The percent change in physical performance showed no correlation with preoperative variables. In TKA patients, the percent change of PCS showed correlation with percent change of TUG ($P = 0.016$), 10-m gait time at comfortable speeds ($P = 0.003$), and 10-m gait time at maximum speeds ($P = 0.042$). The percent change of muscle strength showed partial correlation with physical performances. The percent change of VAS showed no correlation with physical performances. On the other hand, in THA patients, the percent change of hip abductor strength showed correlation with percent change of TUG ($P = 0.047$), 10-m gait time at comfortable speeds ($P = 0.001$), and 10-m gait time at maximum speeds ($P = 0.021$). The percent change of knee extensor strength showed partial correlation with physical performances. The percent change of VAS and PCS showed no correlation with physical performances.

CONCLUSION

Changes in pain catastrophizing significantly associated with changes in physical performance in the early period after TKA. It contributes to future postoperative rehabilitation of arthroplasty.

Key words: Gait; Hip arthroplasty; Knee arthroplasty; Osteoarthritis; Pain; Pain management; Postoperative care

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Core tip: This clinical trial investigated whether reductions in pain catastrophizing are associated with physical performance in the early period after total knee arthroplasty (TKA) or total hip arthroplasty (THA). We found that changes in pain catastrophizing were significantly associated with physical performance in the early period after TKA. These findings may contribute to future postoperative rehabilitation of the arthroplasties in lower limbs. Treatment based on cognitive-behavioral therapy might be useful in the early period, particularly after TKA.

Hayashi K, Kako M, Suzuki K, Hattori K, Fukuyasu S, Sato K, Kadono I, Sakai T, Hasegawa Y, Nishida Y. Associations among pain catastrophizing, muscle strength, and physical performance after total knee and hip arthroplasty. *World J Orthop* 2017; 8(4): 336-341 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/336.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.336>

INTRODUCTION

Osteoarthritis leads to considerable morbidity in terms of pain, functional disability, lowered quality of life, and psychological problems^[1]. Total knee arthroplasty (TKA) and total hip arthroplasty (THA) improve pain

and physical performance in participants with end-stage arthritis^[1]. The number of TKA and THA procedures performed is increasing worldwide^[1]. Early postoperative recovery is important in particularly rehabilitation; however, uncertainty exists about effective rehabilitation methods for physical performance.

Pain treatment has targeted not only pain intensity, but also pain catastrophizing, which has been conceptualized as a negative cognitive-affective response to pain^[2]. The patients with high pain catastrophizing suggest that cognitive-behavioral intervention should incorporate in treatment^[2]. Recently systematic review concludes better outcome associates with greater reduction in pain catastrophizing during treatment in low back pain^[3]. The review shows a mediating effect is found in all studies assessing the impact of a decrease in catastrophizing during treatment^[3]. In addition, some studies have reported pain catastrophizing associated with physical performance than pain intensity, in low back pain^[4,5]. On the other hand, the impact of reduction in pain catastrophizing on outcome has not investigated in patients with TKA or THA, although pain catastrophizing has investigated only at baseline^[6-11]. In changes of pain related variables, the changes in postoperative pain intensity associate with changes in physical performance within 16 d after either TKA or THA^[12]. It has not investigated whether pain intensity or pain catastrophizing have mediating effect of physical performance.

The purpose of the present study is to determine whether reductions in pain catastrophizing are associated with physical performance in the early period after TKA or THA.

MATERIALS AND METHODS

Participants

A total of 46 participants were enrolled. Twenty-three underwent initial TKA, and 23 underwent initial THA between September 2014 and April 2015 at Nagoya University Hospital (Table 1). Exclusion criteria were that the participant (1) was diagnosed with cognitive impairment; and (2) had pain in other body parts that was more severe than in the operative site. All participants underwent a baseline preoperative visit prior to their operation and received standardized in-participant treatment including usual rehabilitation, following either a primary total hip or total knee care pathway.

This cross sectional study was approved by the Ethics Committee of Nagoya University Hospital (No. 328). All the participants provided written informed consent.

Measures

Demographic data including age, sex, height, body weight, and body mass index were measured. The participants were evaluated within 7 d before the operation and at 14 d afterwards. Physical performance was measured

Table 1 Participant characteristics

	THA	TKA
Sex (male/female)	4/19	9/14
Age	61.17 ± 10.32	69.65 ± 8.52
Height (cm)	155.84 ± 8.34	153.01 ± 10.37
Body weight (kg)	58.66 ± 13.75	60.78 ± 12.87
Body mass index (kg/m ²)	24.05 ± 4.30	25.80 ± 4.25

Data for age, height, body weight, and body mass index are presented as mean ± SD. THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

by the Timed Up and Go (TUG) test, and 10-m gait time was measured at comfortable and maximum speeds^[13,14]. Participants were allowed to use a walking aid, based on walking ability. They rated their knee or hip pain using a visual analog scale (VAS) for daily life activities. Psychological characteristics were measured by the Pain Catastrophizing Scale (PCS)^[15,16]. Physical characteristics were measured by isometric muscle strength of knee extensors and hip abductors on the operated side^[17-22].

Physical performance: The 10-m gait test was used to measure the time it took the participant to walk 10 m at comfortable and maximum speeds. Timing at each of the two speeds was measured twice. Participants were timed using a stopwatch as they moved along a 10-m walkway. Participants stood directly behind the start line and were clocked from the moment the first foot crossed the start line until the lead foot crossed the finish line. Participants were instructed to continue at least 2 m past the finish line to eliminate the deceleration effects from stopping the gait. Gait speeds were then expressed as meters per second^[13]. For the comfortable-gait speed trial, participants were instructed to walk at their normal comfortable speeds. For the maximum-speed trials, they were asked to walk as fast as they could safely do so without running. Each participant performed two valid trials, and the higher-speed trial was used for analysis.

The TUG test is a measure frequently used to assess function in older individuals^[14]. Subjects were given verbal instructions to stand up from a chair, walk 3 m as quickly and as safely as possible, cross a line marked on the floor, turn around, walk back, and sit down. Each participant performed two valid trials, and the higher-speed trial was used for analysis.

Psychological measures: For the 13-item PCS, participants rate how frequently they have experienced various cognitions or emotions^[15,16]. The PCS comprises three subscales: rumination (*e.g.*, "I keep thinking about how much it hurts"), magnification (*e.g.*, "I wonder whether something serious may happen"), and helplessness (*e.g.*, "There is nothing I can do to reduce the intensity of the pain")^[15,16]. The total score range is 0-52^[15,16]. Several findings support this scale's validity as a measure of PCS^[15,16].

Isometric muscle strength: The isometric muscle strength of the hip abductors and knee extensors was measured using a hand-held gauge meter (μ -Tas F-100; Anima, Tokyo, Japan). The strength of the hip abductors was measured in the supine position with both lower limbs in neutral position. The transducer was placed at the lateral femoral condyles^[17]. The strength-testing position of the knee extensors was confirmed using a goniometer at a hip angle of 90° and knee flexed to 60°. If necessary, the feet were supported by a small bench^[18-22]. A strap was attached between the examination couch and a point on the participant's ankle, 5 cm above the lateral malleolus. The transducer was then placed at the front of the ankle under the strap to measure the extension strength. The participants were asked to push maximally against the force transducer for 5 s. Participants performed two contractions separated by a 60-s interval. The highest value was used for analysis. Muscle strength was expressed as the maximum voluntary torque with use of the external lever-arm length. The lever-arm length was the distance from the trochanter major to the center of the dynamometer for hip abductors and from the lateral femoral epicondyle to the center of the dynamometer for knee extensors.

Statistical analysis

All data are expressed as mean ± SD. The variables of percent changes between pre- and post-operation were quantified. It was calculated dividing post-operation score by pre-operation score^[18]. Their resultant data were analyzed by paired *t*-test. The correlation of physical performance with psychological and physical variables was analyzed by the Pearson *r* rank test. The data were analyzed with SPSS software (version 20.0 for Microsoft Windows; SPSS, Chicago, IL, United States). A value of *P* < 0.05 was considered statistically significant.

RESULTS

Pre- and post-operative data are shown in Table 2. The mean ± SD of VAS in THA and TKA were at preoperative of 37.87 ± 24.20, and 41.91 ± 27.09, and postoperative at 14-d of 17.61 ± 20.29, and 25.22 ± 20.41. The mean ± SD of PCS in THA and TKA were at preoperative of 28.70 ± 9.28, and 28.26 ± 11.90, and postoperative at 14-d of 18.70 ± 11.19, and 20.26 ± 10.72. Postoperative VAS and PCS were better than preoperative for both TKA and THA. Postoperative physical performance and muscle strength were poorer than preoperative for both TKA and THA.

The correlations between physical performance and other variables are shown in Table 3. The percent change in physical performance showed no correlation with preoperative variables. In TKA patients, the percent change of PCS showed correlation with percent change of TUG (*P* = 0.016), 10-m gait time at comfortable speeds (*P* = 0.003), and 10-m gait time at maximum speeds (*P* = 0.042). The percent change of muscle strength showed

Table 2 Pre- and postoperative data according to site of replacement

	THA			TKA		
	Preoperative	Postoperative at 14-d	P-value	Preoperative	Postoperative at 14-d	P-value
TUG (s)	11.51 ± 3.82	13.67 ± 5.65	0.004 ^a	12.22 ± 4.33	16.42 ± 9.09	0.004 ^a
10 m gait speeds at comfortable (m/s)	0.97 ± 0.23	0.92 ± 0.20	0.187	0.99 ± 0.24	0.77 ± 0.23	0.000 ^a
10 m gait speeds at maximum (m/s)	1.28 ± 0.34	1.11 ± 0.32	0.005 ^a	1.19 ± 0.34	0.95 ± 0.32	0.000 ^a
VAS	37.87 ± 24.20	17.61 ± 20.29	0.001 ^a	41.91 ± 27.09	25.22 ± 20.41	0.004 ^a
PCS	28.70 ± 9.28	18.70 ± 11.19	0.000 ^a	28.26 ± 11.90	20.26 ± 10.72	0.003 ^a
Muscle strength (kgf*m)						
Hip abductor strength (operated side)	2.62 ± 1.63	2.04 ± 1.36	0.026 ^a	3.49 ± 2.06	2.10 ± 1.63	0.001 ^a
Knee extensor strength (operated side)	4.78 ± 3.19	3.99 ± 1.59	0.240	4.46 ± 2.82	2.55 ± 2.13	0.001 ^a

These data were analyzed with paired *t*-tests. Data for TUG, 10-m gait speeds, VAS, PCS, and muscle strength are presented as mean ± SD. ^a*P* < 0.05. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TUG: Timed Up and Go; VAS: Visual analog scale; PCS: Pain Catastrophizing Scale.

Table 3 Correlation between percent changes from pre- to post-operative physical performance and other variables

	THA			TKA		
	ΔTUG (s)	Δ10 m gait speeds at comfortable (m/s)	Δ10 m gait speeds at maximum (m/s)	ΔTUG (s)	Δ10 m gait speeds at comfortable (m/s)	Δ10 m gait speeds at maximum (m/s)
Preoperative				Preoperative		
VAS	<i>r</i> = 0.184 <i>P</i> = 0.402	0.083 0.707	-0.025 0.908	VAS	<i>r</i> = 0.237 <i>P</i> = 0.276	-0.177 0.419
PCS	<i>r</i> = 0.270 <i>P</i> = 0.213	0.021 0.923	-0.119 0.588	PCS	<i>r</i> = -0.184 <i>P</i> = 0.400	0.122 0.579
Hip abductor strength (operated side, kg f)	<i>r</i> = 0.063 <i>P</i> = 0.774	-0.165 0.452	-0.161 0.464	Hip abductor strength (operated side, kg f)	<i>r</i> = -0.168 <i>P</i> = 0.444	0.142 0.517
Knee extensor strength (operated side, kg f)	<i>r</i> = 0.044 <i>P</i> = 0.842	-0.235 0.281	-0.278 0.199	Knee extensor strength (operated side, kg f)	<i>r</i> = -0.077 <i>P</i> = 0.726	0.070 0.751
Percent changes				Percent changes		
ΔVAS	<i>r</i> = 0.225 <i>P</i> = 0.302	-0.093 0.672	-0.212 0.332	ΔVAS	<i>r</i> = 0.085 <i>P</i> = 0.699	-0.265 0.221
ΔPCS	<i>r</i> = 0.117 <i>P</i> = 0.594	-0.042 0.849	-0.047 0.831	ΔPCS	<i>r</i> = 0.495 <i>P</i> = 0.016 ^a	-0.583 0.003 ^a
ΔHip abductor strength (operated side, kg f)	<i>r</i> = -0.418 <i>P</i> = 0.047 ^a	0.642 0.001 ^a	0.479 0.021 ^a	ΔHip abductor strength (operated side, kg f)	<i>r</i> = -0.333 <i>P</i> = 0.121	0.373 0.079
ΔKnee extensor strength (operated side, kg f)	<i>r</i> = -0.247 <i>P</i> = 0.257	0.434 0.038 ^a	0.530 0.009 ^a	ΔKnee extensor strength (operated side, kg f)	<i>r</i> = -0.389 <i>P</i> = 0.066	0.474 0.022 ^a

These data were analyzed by the Pearson *r* rank test, with the *r* value as the correlation coefficient; ^a*P* < 0.05. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TUG: Timed Up and Go; VAS: Visual analog scale; PCS: Pain catastrophizing scale.

partial correlation with percent change of physical performances. The percent change of VAS showed no correlation with percent change of physical performances. On the other hand, in THA patients, the percent change of hip abductor strength showed correlation with percent change of TUG (*P* = 0.047), 10-m gait time at comfortable speeds (*P* = 0.001), and 10-m gait time at maximum speeds (*P* = 0.021). The percent change of knee extensor strength showed partial correlation with percent change of physical performances. The percent change of VAS and PCS showed no correlation with percent change of physical performances.

DISCUSSION

The present study showed that changes in pain cata-

strophizing significantly associated with changes in physical performance in the early period after TKA, but not after THA. Changes in muscle strength significantly associated with changes in physical performance in the early period after TKA and THA. Quantification of early postoperative changes and their potential relationships to physical performance can reveal responsible mechanisms and contribute to future postoperative rehabilitation.

The importance of assessing pain catastrophizing has been highlighted in preoperative TKA or THA patients^[6-11]. Pain catastrophizing associated with physical performance, more so than was pain intensity in low back pain^[4,5]. In addition, better physical performance associated reduction in pain catastrophizing during treatment than scores at baseline in low back pain^[3]. Some reports in low back pain showed pain catastrophizing at baseline was no

predictive for disability at follow-up^[3]. This study, first, showed reductions in pain catastrophizing associated with physical performance in the early period after TKA. It is important in early postoperative treatment outcome, at least after TKA. For example, treatment that incorporates a cognitive-behavioral intervention can lead to reduction in pain catastrophizing concurrent with reduction in pain-related activity interference and disability among persons with persistent pain^[2]. The intervention targeted a decrease in maladaptive behaviors, an increase in adaptive behaviors, identification, and correction of maladaptive thoughts and beliefs, and an increase in self-efficacy for pain management^[23]. It was introduced to reduce pain and psychological distress and to improve physical and role function^[23]. Medical staff should expand their evaluations beyond traditional demographics and medical status variables to include pain-related psychological constructs when addressing perioperative participants.

The present study showed that, in the early period after THA, changes in physical performances were not significantly associated with changes in pain catastrophizing. The VAS and PCS at postoperative at 14-d in THA was less than in TKA, consistent with previous study^[24]. In general, pain-related disability might be resolved at an earlier stage than 14 d after THA. However, a recent systematic review concluded that there is no evidence for psychological factors as an influence on outcome after THA^[8]. Further investigation is needed to assess longitudinal changes after THA.

Preoperative and postoperative muscle weakness is a major contributor to poor physical performance after TKA and THA^[25-27]. The present study showed changes in physical performance were associated with changes in muscle strength.

There are several limitations in this study. We included only a small number of participants from a single medical center, so our observations must be interpreted with caution. The present study investigated only the early postoperative period; these findings should be considered preliminary for TKA and THA, although other studies have considered physical function in the early period after TKA and THA^[12,18,24]. Scores on the preoperative PCS in the present study were higher than those reported in previous TKA studies^[9-11]. This finding might be confined to the patients with high pain catastrophizing. A larger and long-term study to investigate further the association among changes in pain catastrophizing, muscle strength, and physical performance is required.

Changes in levels of pain catastrophizing were associated with changes in physical performance in the early period after TKA; and changes in muscle strength were associated with changes in physical performance in this period after both TKA and THA. These findings may contribute to future postoperative rehabilitation of lower-limb arthroplasties. Treatment based on cognitive-behavioral therapy might be useful in the early period, at least after TKA.

COMMENTS

Background

Pain treatment has targeted not only pain intensity, but also pain catastrophizing, which has been conceptualized as a negative cognitive-affective response to pain. The changes in postoperative pain intensity associate with changes in physical performance after total knee arthroplasty (TKA) or total hip arthroplasty (THA). On the other hand, the impact of changes in pain catastrophizing on outcome has not investigated in patients with TKA or THA.

Research frontiers

The purpose of the present study is to determine whether reductions in pain catastrophizing are associated with physical performance in the early period after TKA or THA.

Innovations and breakthroughs

This study, first, showed reductions in pain catastrophizing associated with physical performance in the early period after TKA.

Applications

The findings may contribute to future postoperative rehabilitation of lower-limb arthroplasties. Treatment based on cognitive-behavioral therapy might be useful in the early period, at least after TKA.

Peer-review

It is an interesting manuscript on investigating and comparing physical performance, pain ratings, pain catastrophizing, and muscle strength. This study is definitely worth publishing.

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Clinical Trials Study

RANK-ligand and osteoprotegerin as biomarkers in the differentiation between periprosthetic joint infection and aseptic prosthesis loosening

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Abstract**AIM**

To assess serum levels of RANK-ligand (RANKL) and osteoprotegerin (OPG) as biomarkers for periprosthetic joint infection (PJI) and compare their accuracy with standard tests.

METHODS

One hundred and twenty patients presenting with a painful total knee or hip arthroplasty with indication for surgical revision were included in this prospective clinical trial. Based on standard diagnostics (joint aspirate, microbiological, and histological samples) and Musculoskeletal Infection Society consensus classification, patients were categorized into PJI, aseptic loosening, and control groups. Implant loosening was assessed

radiographically and intraoperatively. Preoperative serum samples were collected and analyzed for RANKL, OPG, calcium, phosphate, alkaline phosphatase (AP), and the bone-specific subform of AP (bAP). Statistical analysis was carried out, testing for significant differences between the three groups and between stable and loose implants.

RESULTS

All three groups were identical in regards to age, gender, and joint distribution. No statistically significant differences in the serum concentration of RANKL ($P = 0.16$) and OPG ($P = 0.45$) were found between aseptic loosening and PJI, with a trend towards lower RANKL concentrations and higher OPG concentrations in the PJI group. The RANKL/OPG ratio was significant for the comparison between PJI and non-PJI ($P = 0.005$). A ratio > 60 ruled out PJI in all cases (specificity: 100%, 95%CI: 89, 11% to 100.0%) but only 30% of non-PJI patients crossed this threshold. The positive predictive value remained poor at any cut-off. In the differentiation between stable and loose implants, none of the parameters measured (calcium, phosphate, AP, and bAP) showed a significant difference, and only AP and bAP measurements showed a tendency towards higher values in the loosened group (with $P = 0.09$ for AP and $P = 0.19$ for bAP).

CONCLUSION

Lower RANKL and higher OPG concentrations could be detected in PJI, without statistical significance.

Key words: Aseptic loosening; Diagnostic; RANK-ligand; Periprosthetic joint infection; Biomarker; Osteoprotegerin

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Core tip: No statistically significant differences in the serum concentration of RANK-ligand (RANKL) and osteoprotegerin (OPG) were found between aseptic loosening and periprosthetic joint infection (PJI) with a certain trend of lower concentrations in the PJI group. Nevertheless, a RANKL/OPG ratio > 60 ruled out PJI in all cases. In the differentiation between a stable and loose implant the parameters measured showed no significant difference, which led to the conclusion that the sole use of these parameters for differentiating PJI and aseptic loosening cannot be recommended. RANK and OPG may have utility as a conformation test but are not an effective screening parameter for the discrimination of PJI and AL.

Friedrich MJ, Wimmer MD, Schmolders J, Strauss AC, Ploeger MM, Kohlhof H, Wirtz DC, Gravius S, Randau TM. RANK-ligand and osteoprotegerin as biomarkers in the differentiation between periprosthetic joint infection and aseptic prosthesis loosening. *World J Orthop* 2017; 8(4): 342-349 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/342.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.342>

INTRODUCTION

Periprosthetic joint infection (PJI) after total joint replacement still remains one of the most serious complications and is a key challenge in orthopedic surgery. A precise and rapid diagnosis of implant failure is mandatory for treatment success. The differentiation between PJI and aseptic loosening can, in particular, be unyielding or controversial, and misdiagnosis can lead to serious and permanent impairment. As the treatment of PJI is completely different from the treatment of aseptic loosening, its correct and timely diagnosis is crucial for successful therapy and relies in part on the use of molecular markers. Nevertheless, establishing a definite diagnosis of PJI prior to surgical intervention is at times difficult. Numerous researchers have focused on the development of novel and more accurate molecular methods^[1-5]. However, there is no diagnostic gold standard so far. Various definitions have been proposed and current recommendations are based on several pre-, intra-, and postoperative parameters^[6,7].

Previous studies have suggested osteoprotegerin (OPG) and receptor activator of nuclear factor- κ B ligand (RANK Ligand, RANKL) as markers of periprosthetic osteolysis^[8,9]. RANKL and its receptor RANK and OPG play an important role in osteoclastogenesis as final effectors of bone resorption. RANKL, which expresses on the surface of osteoblast, stromal cells and activated T-lymphocytes, binds to RANK on osteoclast precursors cells or mature osteoclasts, and thereby promotes osteoclastogenesis and bone resorption. OPG, which is expressed by osteoblasts and stromal cells, strongly inhibits bone resorption by binding to its ligand RANKL, and thereby preventing it from binding to its receptor, RANK. The RANKL/RANK/OPG system regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling^[10,11]. Therefore, the balance between OPG and RANKL is essential to regulate bone remodeling, by controlling the activation state of RANK on osteoclasts^[12].

In cases of aseptic loosening, it has been demonstrated that the accumulation of wear debris around the joint leads to an activation of mononuclear cells and T-lymphocytes, resulting in a multinuclear cell giant cell reaction. This causes an osteoclast activation and bone resorption^[13]. Periprosthetic membranes retrieved from patients with aseptic loosening contain fibroblasts, macrophages, and T lymphocytes^[14], as well as osteoclasts and multinucleated foreign body giant cells^[15]. This periprosthetic tissue produces a variety of factors including tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6 and other peptides that stimulate osteoclasts through the induction of RANKL^[16,17]. TNF in turn directly stimulates the production of RANKL by stromal cells, T-lymphocytes, and endothelial cells. Indirect stimulus of RANKL expression works the TNF-induced up regulation of prostaglandins, IL-1 or IL-17, resulting in an advanced expression of RANKL as well. The dominant form of this

response is due to innate reactivity to implant debris through danger associated molecular pattern signaling and inflammatory responses^[18].

Correspondingly, in the pathogen-associated molecular patterns in PJI, bacterial toxins and parts of the pathogen's cell membrane seem to induce infiltration with mainly neutrophil granulocytes and macrophages. Though the trigger is a different one, the final result with bone loosening and prosthesis failure is the same. So far, there are no investigations concerning the exact role of interleukins and RANKL/OPG signaling in PJI-associated prosthesis failure. The role of the RANKL/RANK/OPG system has not yet been examined in the differentiation between PJI and aseptic prosthesis loosening. In this study, therefore, we defined the sensitivity, specificity, and accuracy of RANKL and OPG in patients with PJI vs aseptic loosening and compared these results to current standards of diagnostic testing. Total joint replacement without signs of PJI or aseptic loosening served as the control group. Furthermore, we tested whether there is a difference between loosened and stable implants in the serum levels of these and other parameters.

Our hypothesis was that the measured serum levels of RANKL and OPG correlate positively: (1) with the presence of PJI; and (2) with implant loosening. Secondly, we investigated if the serum levels of calcium (Ca^{2+}), phosphate (PO_4), and alkaline phosphatase (AP) would be different in stable or loosened implants.

MATERIALS AND METHODS

This prospective study was approved by the local Institutional Review Board and Ethics committee with informed consent obtained in compliance with the declaration of Helsinki prior to being enrolled in the study. Between 2010 and 2011 we included 120 consecutive patients presenting with a painful total hip or total knee arthroplasty undergoing revision arthroplasty surgery for (1) PJI; (2) aseptic failure (AL); or (3) aseptic revision causes without PJI or aseptic loosening. Any patient scheduled to undergo revision surgery of a hip or knee arthroplasty were included. After signing of informed consent, all patients underwent standardized diagnostics as outlined in literature^[19]. Preoperative serum samples were collected and joint aspiration was performed under strictly aseptic conditions for cell count, cell differentiation, and microbiological analysis.

White blood cell count was determined from the blood samples, and serum samples were analyzed for C-reactive protein (CRP) (Dimension Vista, Siemens Medical Solutions Diagnostics GmbH, Eschborn, Germany), RANKL, and OPG (Sandwich ELISA, Fa. BioVendor GmbH, Heidelberg, Germany); Serum Ca^{2+} , serum PO_4 , AP and the bone-specific subform of the AP (bAP) were also analyzed in serum (Immunolite, Siemens, Eschborn, Germany). Ratio of RANKL/OPG was calculated from the determined values.

Intraoperatively, tissue specimens were taken for microbiological and histological analysis^[20], and the intrao-

perative aspect was recorded. Assessment of relevant implant instability is a routine for the experienced arthroplasty surgeon and part of many revision algorithms. If in the surgeon's view at least one implant component with bony contact could be removed with ease after debridement, the implant was considered "loosened"^[19]. Also, radiographic signs of loosening were taken into account where implant migration or dislocation could clearly be seen preoperatively.

Depending on the results of the laboratory diagnostics, including serum CRP as well as cell count and differentiation of the aspirate, microbiologic assessment of aspirate and intraoperative cultures, as well as histopathology of the intraoperative samples, the diagnosis of PJI was considered proven following the criteria according to the Musculoskeletal Infection Society (MSIS) consensus paper by Parvizi *et al*^[7], independent of the implant being loose or stable. Those who did not meet the criteria for a diagnosis of PJI and required a revision due to loosening were assigned as aseptic loosening (AL) group. Those without signs of PJI or loosening were assigned as controls (control group). For subanalysis of loosening, the PJI group was divided for those presenting with a macroscopically loosened implant vs those with stable implants. Demographic data (age, sex, body mass index, type of prosthesis [total hip arthroplasty (THA)/total knee arthroplasty (TKA)]) were collected for comparative analysis.

Data were collected in Microsoft Excel (Microsoft Corporation, Richmond, United States), and statistical analysis was carried out using GraphPad Prism 5.04 (GraphPad Software, La Jolla, CA, United States), testing for statistical significance between the three groups with Kruskal-Wallis-ANOVA without assuming normal distribution and with Dunn's post-hoc test. To test for significance between PJI vs non-PJI or stable vs loose, Mann-Whitney *t*-tests were used, and Receiver-Operator-Characteristic (ROC) curves were calculated to assess the discriminatory strength on the basis of the area under the curve (AUC) and to determine optimal cut-off. Nonparametric Correlation (Spearman) was calculated between selected parameters. According to the "Standards for Reporting of Diagnostic Accuracy", probabilistic measures, such as sensitivity, specificity, likelihood ratios, and their confidence limits for individual values and combinations were calculated^[21]. For calculating the geometric coefficient of variation (GCV), data was log-transformed and coefficient of variation calculated from the transformed data set.

RESULTS

One hundred and twenty patients were enrolled into our prospective cohort study. In all groups, there were no differences with regard to age, gender, or joint distribution. In the PJI group (26 THA, 54%) and in the aseptic loosening group (35 THA, 69%), more THA were recruited, while the control group included more TKA (13 TKA, 62%). The patient demographics and details are

Table 1 Patient demographics

Group	Total (n)	Mean age (\pm SD)	Sex (W:M)	Joint (hip:knee)
PJI	48	69.5 yr (\pm 12.1 yr)	27 female 21 male	22 TKA 26 THA
Aseptic loosening	51	68 yr (\pm 11.1 yr)	33 female 18 male	16 TKA 35 THA
Control	21	64.05 yr (\pm 11.9 yr)	13 female 8 male	13 TKA 8 THA
All	120	67.94 (\pm 11.7)	73 female 47 male	51 TKA 69 THA
P		0.2686	0.8611	0.1110

One hundred and twenty consecutive patients were enrolled in the study prospectively. Group assignment was done according to the criteria as mentioned above. There was no statistical difference in patient age, gender, or distribution of joints in the groups. More women than men were enrolled in total and in all groups. There was a lower number of total hip arthroplasties (THA) than total knee arthroplasties (TKA) only in the control group. PJI: Periprosthetic joint infection.

given in Table 1. In our collective, 31 out of 48 patients (64%) in the PJI group had consistent findings in two or more positive microbiology cultures, matching the "major" MSIS criterion for microbiology; another five patients had one positive culture, and the remaining 12 patients were "culture negative" PJIs.

Statistical analysis was completed to compare the means of laboratory values between the three groups. The results are summarized in Figure 1A and B. We found no significant differences in the mean values of PJI, AL, or the control group in the serum concentration of RANKL ($P = 0.16$) or OPG ($P = 0.45$) with a certain trend of lower RANKL concentrations and higher OPG concentrations in the PJI group. The "geometric" coefficients of variation were within a tolerable range. For RANKL, we calculated GCV as 10.65% (PJI), 18.6% (AL), and 15.85% (Control), for OPG we calculated GCV as 21.46% (OPG), 19.33% (AL) and 19.65% (Control). To assess discriminatory strength of these parameters, we pooled the AL and control group into a larger non-PJI group and calculated ROC with AUC, and a non-parametric *t*-test (Figure 1C-F). Neither RANKL nor OPG showed a significant difference ($P = 0.26$ for RANKL and $P = 0.3$ for OPG), and discriminatory strength was poor (AUC: 0.57 ± 0.05 for RANKL and 0.56 ± 0.06 for OPG). Since the aforementioned trend was still visible, we calculated sensitivity and specificity for different cut-offs and found the best, yet still poor likelihood ratio to detect a PJI for RANKL at < 188.9 pmol/L [sensitivity: 93.94%, 95% confidence interval (95%CI): 79.77% to 99.26%; specificity: 32.47%, 95%CI: 22.23% to 44.10%, likelihood ratio: 1.39], and for OPG at > 9.38 pmol/L (sensitivity: 28.13%, 95%CI: 13.75% to 46.75%; specificity: 89.33%, 95%CI: 80.06% to 95.28%, likelihood ratio: 2.64).

To determine if the parameters were independent of each other, we calculated the Spearman correlation, which showed an *r* of 0.01 (95%CI: 0.18 to 0.21, $P = 0.88$) stating that there was neither a positive nor a negative correlation between OPG and RANKL.

We therefore calculated the RANKL/OPG ratio as an additional parameter, to make use of possible synergistic effects. Though this parameter also remained without statistical significance between all three groups ($P = 0.1$), the comparison between PJI and non-PJI (Figure 1G and H) was significant (with $P = 0.005$) and the discriminatory strength was much enhanced (AUC: 0.7 ± 0.05). A ratio > 60 ruled out PJI in all cases (specificity: 100%, 95%CI: 89.11% to 100.0%) but only 30% of non-PJI patients crossed this threshold (95%CI: 21.67% to 40.29%), while the positive predictive value remained poor at any cut-off.

Both groups, PJI and non-PJI included patients where parts of the prosthesis were loosened. We therefore assessed whether or not any of the parameters would correlate with the bony integration and a stable interface of the prosthesis. None of the parameters measured showed a significant difference in this analysis (Figure 2), and only the AP and bAP measurements showed a tendency towards higher values in the loosened group (with $P = 0.09$ for AP and $P = 0.19$ for bAP). No other trends were visible, and no further statistics were calculated.

DISCUSSION

The accurate diagnosis of PJI is difficult, as the clinical symptoms often resemble those of aseptic loosening, with nonspecific pain and swelling of the joint. Though both entities share a common final pathway, leading to osteolysis and implant failure, their exact pathomechanisms remain unclear. Analyzing the available evidence and existing published data on the definition of PJI, a workgroup convened by the MSIS presented a summary of recommendations concerning a new definition for PJI^[7]. These recommendations are based on clinical findings, laboratory parameters, sterile joint aspiration for synovial leucocyte count, and microbiological analysis as well as tissue sampling for histopathology. Nevertheless, because of the inconsistent data, even the MSIS cannot provide general recommendations in interpretation of single aspects (e.g., different cut-off values of CRP or leukocyte count in synovial tests). Consequently, there is a need for further research and development into new methods aimed at improving diagnostic accuracy and speed of detection.

Several studies have attempted to assess the clinical relevance of RANKL and OPG levels in a variety of human diseases characterized by local or systemic changes in bone remodeling^[8,17,22,23]. The essential role of the OPG/RANK/RANKL pathway in regulating bone remodeling around orthopedic implants is well recognized, but the clinical usefulness of circulating OPG and RANKL levels in the differentiation between PJI and aseptic loosening is unknown.

Our hypothesis was therefore that the measured serum levels of RANKL and OPG correlate positively: (1) with the presence of PJI; and (2) with implant loosening. Secondly, we investigated if the serum levels of calcium, phosphate, and alkaline phosphatase would be different

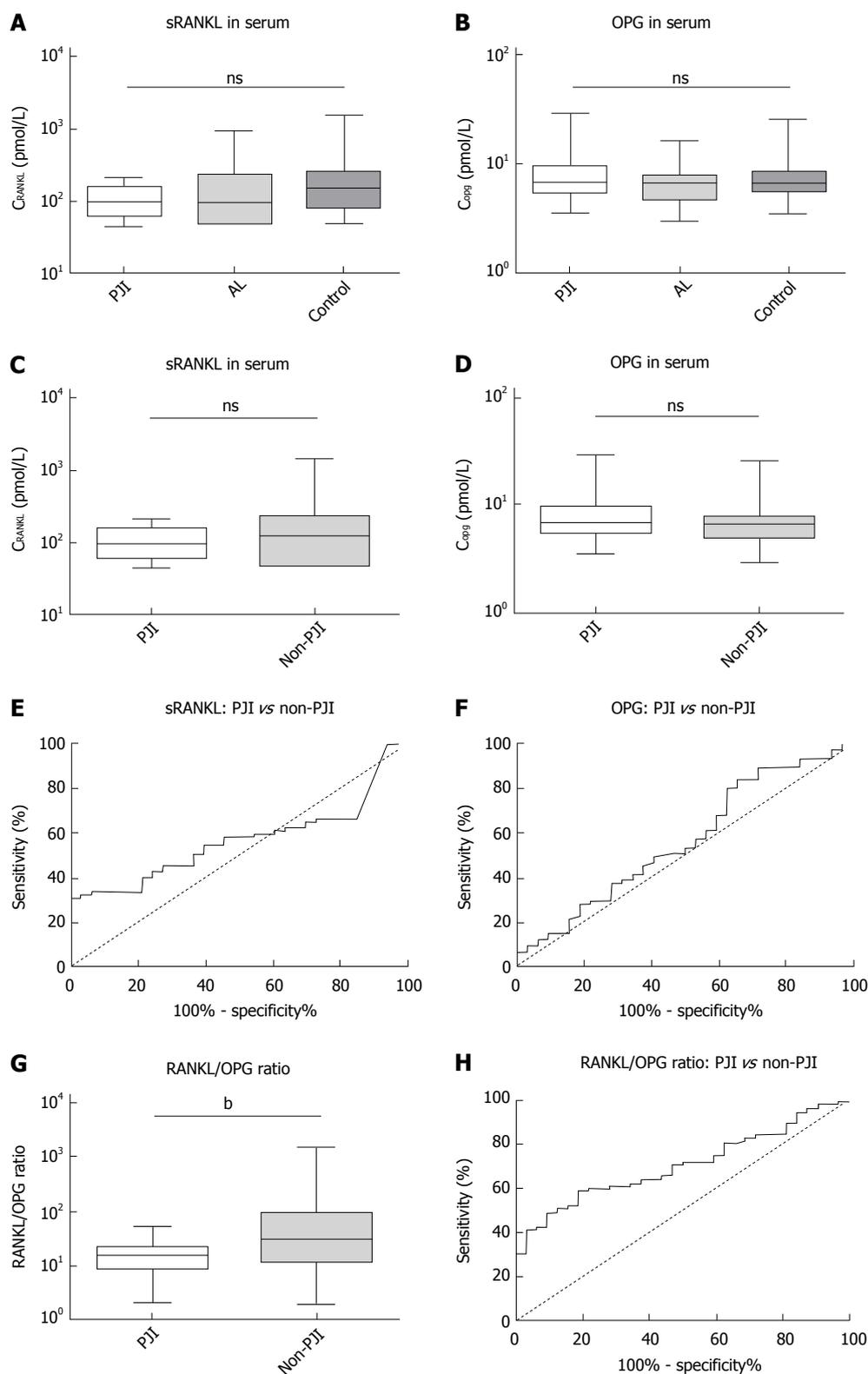


Figure 1 sRANKL and osteoprotegerin in serum, periprosthetic joint infection vs non-periprosthetic joint infection. Analysis of variance (Kruskal-Wallis-ANOVA) without assuming normal distribution with Dunn's *post-hoc* test. RANKL and OPG serum levels showed no significant (ns) differences in the mean values between periprosthetic joint infection (PJI) and aseptic loosening (AL) and between PJI and control (A and B). ANOVA for a pooled group of non-PJI (AL + control) vs PJI did not show a significant difference for either RANKL or OPG ($P = 0.26$ for RANKL and $P = 0.3$ for OPG) (C and D). The receiver-operating characteristic (ROC) curve of RANKL and OPG showed a poor discriminatory strength (AUC: 0.57 ± 0.05 for RANKL and 0.56 ± 0.06 for OPG) (E and F). ANOVA for the RANKL/OPG ratio showed a significant difference between PJI and non-PJI (G), and the discriminatory strength was enhanced with an AUC of 0.7 ± 0.05 (H); ^b $P < 0.001$. RANKL: RANKL-ligand; OPG: Osteoprotegerin.

in stable or loosened implants.

According to the results, we had to discard our above

mentioned hypotheses, as we found no significant differences in the mean values of circulating RANKL and

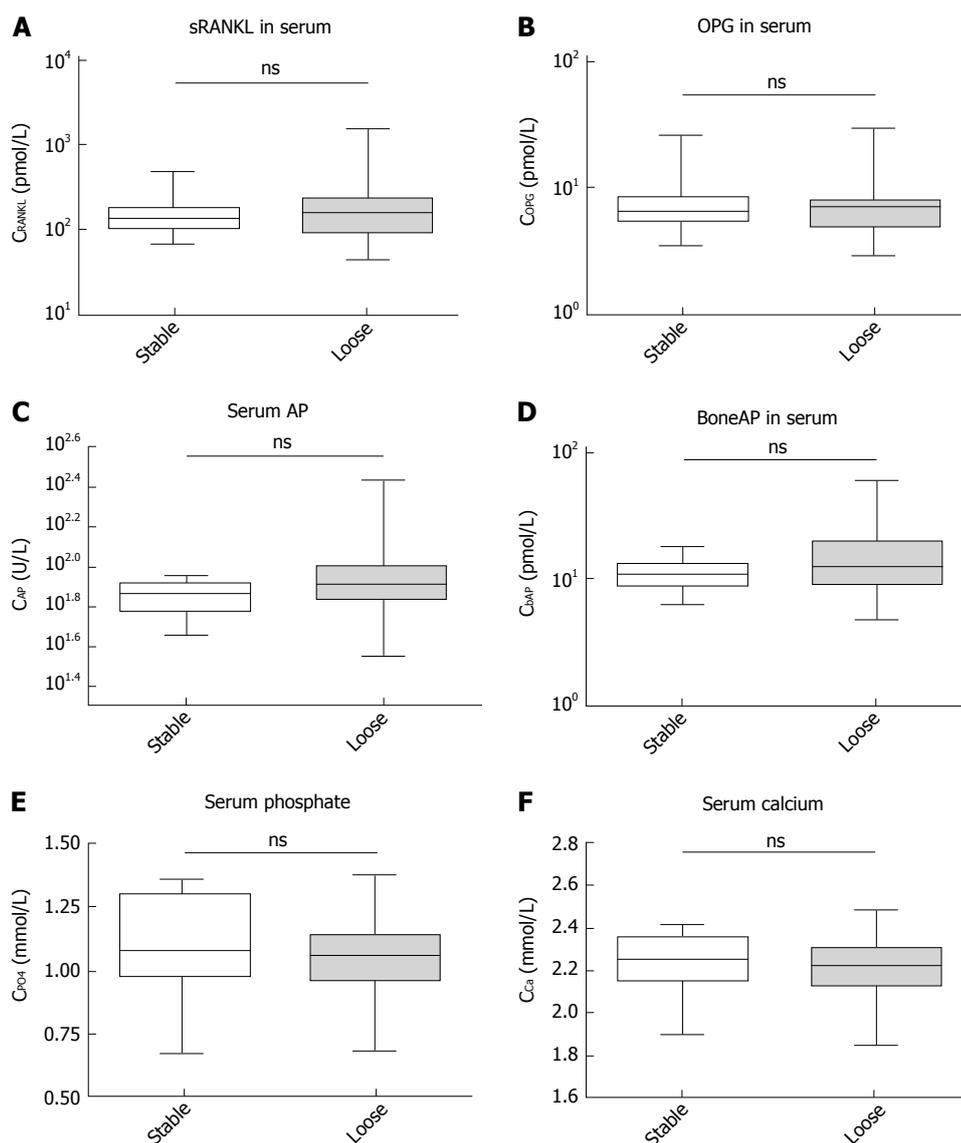


Figure 2 Serum parameters, loosened vs stable implants. Analysis of variance (Kruskal-Wallis-ANOVA) without assuming normal distribution with Dunn's *post-hoc* test. RANKL and OPG serum levels showed no significant (ns) differences in the mean values between a stable and loose implant (A and B), nor did the other parameters as alkaline phosphatase (AP), boneAP, and serum phosphate (C-F). RANKL: RANKLigand; OPG: Osteoprotegerin.

OPG in PJI vs AL or control groups, but found a certain trend of lower RANKL concentrations and higher OPG concentrations in the PJI group.

Granchi *et al*^[8] tried to evaluate whether serum levels of OPG and RANKL could be different in patients with aseptic loosening compared to patients with stable implants. While the serum levels of RANKL and the OPG-to-RANKL ratio showed no significant changes with the clinical condition or status of the implant, an increased serum level of OPG provides good diagnostic accuracy in detecting implant failure due to aseptic loosening with a sensitivity of 92%, a specificity of 75%, and a positive likelihood ratio of 7.1^[8]. These findings are in accordance with the results of He *et al*^[24] who analyzed multiple biomarkers for the detection of aseptic loosening in total hip arthroplasty. They found elevated plasma levels of OPG in failed THA and an increase of OPG plasma level from stable healthy patients to early aseptic loosening

to late aseptic loosening, stating that OPG may reflect a protective mechanism of the skeleton to increased bone resorption thereby inhibiting osteoclast formation and bone resorbing activity in aseptic loosening. These findings are in contrast to our observations, as we could not see any significant differences of OPG and RANKL plasma levels in the subanalyses between stable and loose implants. Only the AP and bAP measurements showed a tendency towards higher values in the loosened group. On the other hand, we successfully evaluated and confirmed that the RANKL/OPG ratio as an additional parameter may help in the differentiation between aseptic loosening and PJI as a ratio > 60 ruled out PJI in all cases. These results suggest that osteolysis inside the periprosthetic interface of artificial joints is not associated with a significant systemic elevation of the RANKL/RANK/OPG system.

The current paradigm to explain aseptic loosening involves an inflammatory response to wear debris par-

ticles produced by prosthetic implants. These particles are phagocytosed by macrophages adjacent to the implant resulting in cell activation and the release of cytokines as well as in a localized inflammatory response. By examination of periprosthetic tissues of 59 patients undergoing hip replacement revision for aseptic loosening Veigl *et al.*^[25] could show that RANKL is present only in tissues with a large amount of wear debris and predominantly in cases involving loosened cemented implants. Gehrke *et al.*^[9] examined the presence and distribution of RANKL, RANK and OPG in the periprosthetic interface in cases of septic and aseptic loosening by immunohistochemistry and immunoblotting. They could show a different histopathologic pattern as well as a difference in grade of inflammatory infiltrate. The inflamed periprosthetic tissue produces a variety of factors including TNF α , IL-1, IL-6 and prostaglandin stimulating osteoclast to resorb bone through the induction of RANKL. However, none of these cytokines represents a final common pathway for the process of particle-induced osteoclast differentiation and maturation. While many of these biomarkers are established in the differentiation between aseptic loosening and PJI, to the best of our knowledge, the role of the RANKL/RANK/OPG system has not yet been examined.

We acknowledge that our study has limitations. It must be considered that group definition is difficult in revision arthroplasty. The MSIS has defined a "gold standard" in PJI diagnostics. But they also acknowledge that infection may be present even without major or minor criteria being fulfilled. We therefore cannot guarantee that patients with low-grade infections and low virulence would not be misclassified into the "aseptic loosening" or control group. Also, the sample size is low for a study investigating arthroplasties. The inhomogeneity of the patients investigated is both a weakness and strength of the paper. We did not exclude patients with systemic or inflammatory diseases that may also interfere with the parameters investigated. Patients with PJI are complex and difficult to compare, but this represents day-to-day clinical experience. Eventually, new biomarkers and a further modification of the therapy algorithm may become necessary.

COMMENTS

Background

Periprosthetic joint infection (PJI) after total joint replacement still remains one of the most serious complications and is a key challenge in orthopedic surgery. A precise and rapid diagnosis of implant failure is mandatory for treatment success. Especially the differentiation between PJI and aseptic loosening can be unyielding or controversial and misdiagnosis can lead to serious and permanent impairment. As the treatment of PJI is completely different to the treatment of aseptic loosening the correct and timely diagnosis is crucial for successful therapy and relies in part on the use of molecular markers. Nevertheless, establishing a definite diagnosis of PJI prior to surgical intervention is at times difficult.

Research frontiers

Numerous researchers have focused on the development of novel and more accurate molecular methods. However, there is no diagnostic gold standard

so far. Several studies have attempted to assess the clinical relevance of RANK-ligand (RANKL) and osteoprotegerin (OPG) levels in a variety of human diseases characterized by local or systemic changes in bone remodeling. The essential role of the OPG/RANK/RANKL pathway in regulating bone remodeling around orthopedic implants is well recognized, but the clinical usefulness of circulating OPG and RANKL levels in the differentiation between PJI and aseptic loosening is unknown.

Innovations and breakthroughs

No statistically significant differences in the serum concentration of RANKL and OPG were found between aseptic loosening and PJI, with a trend towards lower RANKL concentrations and higher OPG concentrations in the PJI group.

Applications

The sole use of these parameters for differentiating PJI and aseptic loosening cannot be recommended, but they may have utility as a conformation test.

Terminology

Receptor activator of nuclear factor- κ B (RANK) ligand (RANKL), its receptor RANK and OPG play an important role in osteoclastogenesis as final effectors of bone resorption. RANKL, which expresses on the surface of osteoblast, stromal cells and activated T-lymphocytes, binds to RANK on osteoclastic precursors cells or mature osteoclasts, and thereby promotes osteoclastogenesis and bone resorption. While OPG, which is expressed by osteoblasts and stromal cells, strongly inhibits bone resorption by binding to its ligand RANKL and thereby preventing it from binding to its receptor, RANK. The RANKL/RANK/OPG system regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling. Therefore, the balance between OPG and RANKL is essential to regulate bone remodeling, by controlling the activation state of RANK on osteoclasts.

Peer-review

A good study with a well stated hypothesis and methodology.

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Observational Study

T1 ρ /T2 mapping and histopathology of degenerative cartilage in advanced knee osteoarthritis

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Abstract

AIM

To investigate whether normal thickness cartilage in osteoarthritic knees demonstrate depletion of proteoglycan or collagen content compared to healthy knees.

METHODS

Magnetic resonance (MR) images were acquired from 5 subjects scheduled for total knee arthroplasty (TKA) (mean age 70 years) and 20 young healthy control subjects without knee pain (mean age 28.9 years). MR images of T1 ρ mapping, T2 mapping, and fat suppressed proton-density weighted sequences were obtained.

Following TKA each condyle was divided into 4 parts (distal medial, posterior medial, distal lateral, posterior lateral) for cartilage analysis. Twenty specimens (bone and cartilage blocks) were examined. For each joint, the degree and extent of cartilage destruction was determined using the Osteoarthritis Research Society International cartilage histopathology assessment system. In magnetic resonance imaging (MRI) analysis, 2 readers performed cartilage segmentation for T1 ρ /T2 values and cartilage thickness measurement.

RESULTS

Eleven areas in MRI including normal or near normal cartilage thickness were selected. The corresponding histopathological sections demonstrated mild to moderate osteoarthritis (OA). There was no significant difference in cartilage thickness in MRI between control and advanced OA samples [medial distal condyle, $P = 0.461$; medial posterior condyle (MPC), $P = 0.352$; lateral distal condyle, $P = 0.654$; lateral posterior condyle, $P = 0.550$], suggesting arthritic specimens were morphologically similar to normal or early staged degenerative cartilage. Cartilage T2 and T1 ρ values from the MPC were significantly higher among the patients with advanced OA ($P = 0.043$). For remaining condylar samples there was no statistical difference in T2 and T1 ρ values between cases and controls but there was a trend towards higher values in advanced OA patients.

CONCLUSION

Though cartilage is morphologically normal or near normal, degenerative changes exist in advanced OA patients. These changes can be detected with T2 and T1 ρ MRI techniques.

Key words: T1rho; Osteoarthritis; Magnetic resonance imaging; Cartilage; Knee

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Core tip: Magnetic resonance images of eleven healthy knees and five knees with advanced osteoarthritis (OA) were studied using T1 ρ and T2 mapping. Histopathologic samples were also taken from the five osteoarthritic knees following total knee arthroplasty. Our results indicate that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. This suggests that normal thickness cartilage or mild cartilage thinning in the advanced OA knee demonstrates depletion of proteoglycan or collagen content compared with similar appearing cartilage in young healthy knees. These early changes can be detected with T2 and T1 ρ MRI techniques.

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INTRODUCTION

Osteoarthritis (OA) is one of the fastest growing medical conditions worldwide, affecting at least 27 million people in the United States alone^[1,2]. It is a major contributor to functional disability and loss of autonomy in older adults^[3]. These factors represent a significant health and financial burden to the general population^[2,4]. Knee and hip OA cause the greatest burden of disability, leading to the need for prosthetic joint replacements in the most severe cases^[5]. Decreasing the need for such procedures, and costs to both the patient and society, motivates the need for research into disease prevention and early detection.

OA is characterized by the progressive loss of articular cartilage. However, significant damage to the collagen-proteoglycan matrix and elevation of cartilage water content are believed to precede the loss of cartilage and consequent symptoms of knee OA^[6,7]. Magnetic resonance imaging (MRI) techniques have been developed over the past decade that allow for the detection of these early and subtle changes to the cartilage matrix^[8-11]. Among these techniques, T1 ρ has stood out as a high sensitivity option to detect early changes without the use of contrast agents^[7].

Prior studies have already demonstrated increased cartilage T1 ρ values, a surrogate of cartilage damage, in patients with knee OA^[12-15]. Specifically, T1 ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions^[13]. While severe focal lesions are common indications for total knee replacement, patients may also be considered for joint sparing or cartilage preservation procedures. We aim to determine whether normal appearing cartilage by MRI in the non-symptomatic regions of advanced knee OA demonstrate depletion of proteoglycan and collagen content by T1 ρ and T2 mapping and to correlate these measurements with degenerative changes of cartilage by histology. We hypothesize that normal thickness cartilage or mild cartilage thinning (early staged cartilage degeneration) in advanced knee OA will demonstrate depletion of proteoglycan or collagen content, compared with similar appearing cartilage in young healthy knees.

MATERIALS AND METHODS

Study population

Five advanced OA patients scheduled for total knee arthroplasty (TKA) were enrolled in this study. A board certified orthopaedic surgeon (RS) recruited them (Kellgren-Lawrence score of 3 or 4; mean age 70 years, range 62-90 years; 2 men and 3 women). Twenty knees from 20 healthy volunteers (mean age 28.9 years, range

19-38 years; 13 men and 7 women) without any history of knee symptoms or prior knee surgery were used as an imaging control group. The study protocol was approved by the institutional review board and all subjects provided written informed consent before any study-related procedures were performed.

MRI

All MR studies were performed on a 3.0-T unit (Achieva, Philips Healthcare, Netherland) utilizing an 8-channel knee receive-only radiofrequency coil. Three sagittal MR images were acquired including fat suppressed (FS) proton density-weighted imaging (PDWI) sequence, T2 mapping sequence, and T1 ρ mapping sequence. All sagittal images were obtained without oblique angulation, parallel to the magnetic static field (B0). Parallel imaging was used on all imaging sequences utilizing Sensitivity Encoding for MRI. The acquisition parameters were as follows. FS PDWI: 2D turbo spin-echo; Repetition time (TR)/echo time (TE) = 4311/30 ms, number of excitation (NEX) = 2, and total acquisition time = 3 min 35 s. T2 mapping: 2D turbo spin-echo; TR/TE = 2700/13, 26, 39, 52, 65, 78, 91 ms, NEX = 1 and total acquisition time = 13 min 26 s. T1 ρ : 3D FS PROSET (Principle of Selective Excitation Technique); TR/TE = 6.4/3.4 ms, flip angle = 10°, echo train length = 64, NEX = 1, spin-lock frequency = 575 Hertz, time of spin-lock (TSL), 20, 40, 60 and 80 ms, and acquisition time = 4 min 9 s \times 4. All images were obtained with field of view = 140 \times 140 mm, slice thickness/gap = 3/0 mm, image matrix = 512 \times 512, number of slices = 31 and effective in-plane spatial resolution = 0.27 \times 0.27 mm. Each femoral condyle was divided into 4 areas: The medial distal condyle (MDC), medial posterior condyle (MPC), lateral distal condyle (LDC), and lateral posterior condyle (LPC). Therefore, a total of 20 areas of MRI of the femoral condyle from 5 patients with advanced OA were reviewed.

TKA

TKA was conducted as scheduled on each operative candidate. Surgically resected condyles were recovered intraoperatively and divided into 4 parts (MDC, MPC, LDC, LPC). A total of 20 specimens (bone and cartilage blocks) were histopathologically examined.

Pathology

The MDP, MPC, LDC and LDP of the distal femur removed at surgery were fixed in 10% neutral buffered formalin for at least 72 h, decalcified using dilute hydrochloric acid (Rapid Bone Decalcifier, American Master Tech Inc., Lodi CA) for two days, and post fixed in formalin for at least 2 more days. Sagittal sections across the entire mid portion of each of the condyles underwent routine paraffin embedding and staining with hematoxylin and eosin. In this way, the same region was sampled for each of the specimens, and maximum extent of the lesion could be assessed in the mid sagittal plane of

each of the condyles. Additional paraffin sections were stained with Masson's trichrome and Alcian blue. For each joint, the degree and extent of cartilage destruction was determined using the Osteoarthritis Research Society International cartilage histopathology assessment system^[16] by a pathologist with experience in bone and soft tissue pathology. For this system, the degree of cartilage destruction (OA grade) and the extent of destruction (OA stage) are multiplied to determine the OA score. The surgical edges were not assessed to avoid possible over-interpretation of surgical artifacts.

Imaging analysis

Images were transferred in Digital Imaging and Communications in Medicine format to a personal computer (Windows 7), which was used to perform all post-processing and analyses. T2 and T1 ρ analyses were performed using in-house developed and implemented software in MatLab (MathWorks, Natick, MA) (Figure 1). Manual cartilage extraction of the femoral condyle in healthy volunteers ($n = 20$) and advanced OA patients ($n = 5$) was performed on both T2 and T1 ρ images by a board-certified orthopaedic surgeon with 14 years of experience and a board-certified radiologist with 13 years of experience, independently. Images with TE = 26 in T2 and TSL = 20 in T1 ρ were chosen for segmentation due to high signal-to-noise ratio compared to the other images, based on prior studies^[17,18]. T2 and T1 ρ values were measured in a range of -10 to 20 degrees for the distal condyle and 70 to 100 degrees for the posterior condyle (Figure 2). The angle 0 is defined along B0. We calculated average T2 and T1 ρ values of two observers at each femoral condyle, and average thickness of the cartilage as pixel numbers in the segmented area at each condyle.

Statistical analysis

Differences in T2/T1 ρ values and thickness of the cartilage between normal cartilage and advanced degenerative cartilage do not conform to normal distributions. These differences were assessed using a nonparametric Mann-Whitney *U* test. Statistical review of the study was performed by a researcher with training in biomedical statistics. SPSS Statistics version 22 (IBM, Armonk, New York) was used for calculations. In all cases, a *P* value of 0.05 or less was deemed statistically significant.

RESULTS

A total of 20 areas on MRI of the femoral condyles from 5 advanced OA patients were reviewed. Eleven areas including normal or near normal cartilage thickness (2 MDCs, 2 MPCs, 4 LDCs, 3 LPCs) were selected. The average OA grade, stage, and scores of corresponding specimens (bone blocks and cartilage) were 3.82 (range: 3-4.5), 3.45 (range: 2-4), and 13.1 (range: 7-16), respectively, compatible with mild to moderate OA (Table 1). Examples of FS PDWI, hematoxylin and eosin stain, Alcian blue stain,



Figure 1 T2 and T1 ρ relaxation time measurement. T2 and T1 ρ relaxation times were measured in a range of -10 to 20 degrees for the distal condyle and 70 to 100 degrees for the posterior condyle. The angle 0 is defined along B0.

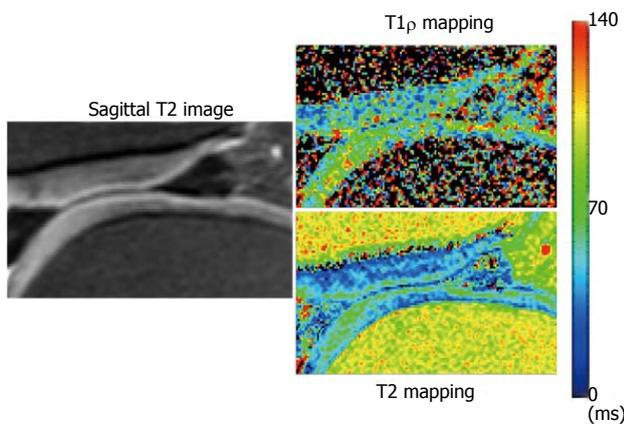


Figure 2 Example of sagittal fat suppressed proton density-weighted imaging, T1 ρ mapping and T2 mapping.

and Masson's trichrome stain are demonstrated in Figure 3.

Table 2 shows the T2/T1 ρ values and thickness of the cartilage in normal volunteers and advanced osteoarthritis patients. Although the difference of each cartilage thickness between normal volunteers and advanced OA patients was not observed, T2/T1 ρ values were significantly higher at the MPC in advanced OA patients compared to normal volunteers ($P < 0.05$). T2/T1 ρ values also tended to be higher in advanced OA patients compared to normal volunteers at the MDC, LDC and LPC without significant difference.

DISCUSSION

Knee OA is a multifactorial disease with a significant population burden^[1]. Novel strategies in the management of knee OA are based on early detection and minimally invasive procedures^[11,19]. Certain patients with focal advanced knee OA may benefit from joint preservation strategies if remaining articular cartilage is healthy. In our study we aimed to assess whether normal appearing cartilage in advanced knee OA patients demonstrate depletion of proteoglycan and collagen content by T2/T1 ρ analysis, markers of early OA. We have demonstrated that although non-osteoarthritic portions of the

femoral condyle in patients with advanced knee OA have similar morphologic characteristics compared to controls in routine MRI, there are significant changes on T2/T1 ρ mapping that can measure differences on the biomolecular level.

Many *in vivo* studies have demonstrated an association between increased T2/T1 ρ values and various stages of OA about the knee^[12-15]. T1 ρ values have been seen to increase with age, but are also higher in middle-aged populations with isolated patellofemoral and tibiofemoral compartment knee OA^[13,14,20]. T1 ρ relaxation times in particular may be elevated by as much as 30%-40% in patients with early knee OA^[14]. Furthermore, Stahl *et al.*^[13] demonstrated that patients with asymptomatic knee OA have increased T2/T1 ρ values in some compartments compared to healthy controls. These data are consistent with our findings that T2/T1 ρ values are consistently higher in multiple compartments in patients with advanced OA compared to asymptomatic controls. By isolating pathologic samples with mild or near normal pathologic changes of articular cartilage we have demonstrated a subset of patients with mild arthritic changes. Li *et al.*^[12] have already shown significantly elevated T1 ρ relaxation times in subcompartments of knee OA subjects where no prior morphologic changes were observed. This type of study demonstrates the utility of quantitative MRI sequences in detecting early biochemical changes within the articular cartilage matrix, but is limited to radiographic assessments alone. We have isolated not only radiographically similar, but pathologically similar cartilage samples to be used in this type of analysis.

This study agrees with multiple other publications that demonstrate the use of T2/T1 ρ relaxation times for the early detection of knee OA^[13,21,22]. The unique contribution is the comparison of normal or near normal imaging samples between cases and controls. Thuillier *et al.*^[23] examined patients with patellar-femoral pain but without radiographic evidence of knee OA and found significantly elevated T1 ρ values in the lateral patellar cartilage compared to controls. Several other studies have also showed that focal cartilage defects identified on arthroscopy are correlated with elevated

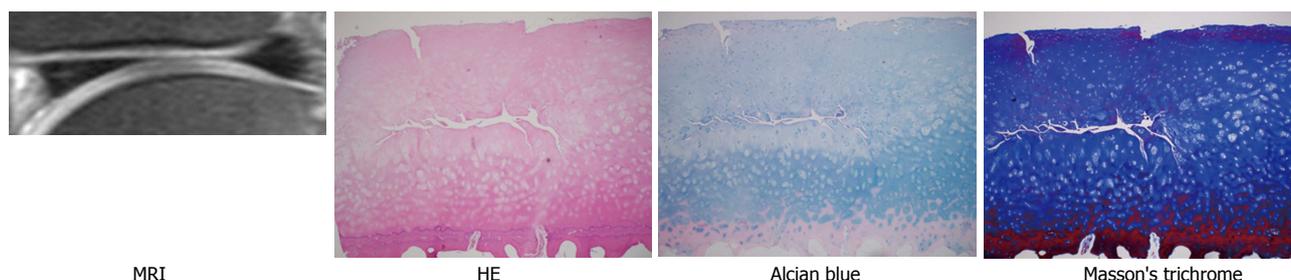


Figure 3 Example of normal thickness magnetic resonance imaging with corresponding hematoxylin and eosin, Alcian blue, and Masson trichrome stains. OA grade/stage/score in this case is 4/3/12, compatible with early OA. MRI: Magnetic resonance imaging; HE: Hematoxylin and eosin; OA: Osteoarthritis.

Table 1 Results of pathologic analysis of bone block and cartilage specimens

No.	Location	Grade	Stage	Score	Pathology comments
1	MDC	4	4	16	Superficial erosion, prominent vertical fissures and depletion of more than the upper 2/3 of proteoglycans by alcian blue staining
2	MPC	4	3	12	Focal erosion, a few small vertical clefts, depletion of the upper 1/2 to 2/3 of proteoglycans by alcian blue staining
3	LDC	3	4	12	Superficial fibrillation, small vertical clefts, minimal superficial depletion of proteoglycans by alcian blue staining
4	LDC	4.5	3	13.5	Deep erosion extending almost to bone and almost complete depletion of proteoglycans by alcian blue staining
5	MDC	4	3	12	Superficial erosion, prominent vertical and horizontal fissures and depletion of more than the upper 2/3 of proteoglycans by alcian blue staining
6	LPC	3.5	2	7	Focal superficial erosion almost complete depletion of proteoglycans by alcian blue staining
7	MPC	4	4	16	Erosion, focally deep and superficial depletion of proteoglycans by alcian blue staining over most of the surface, with complete depletion at region of deep erosion
8	LDC	3.5	4	14	Focal erosion and vertical fissures extending to mid zone with complete depletion of proteoglycans by alcian blue staining at site of fissures
9	LPC	3	4	12	Focal vertical fissures extending to mid zone with minimal depletion of proteoglycans by alcian blue staining
10	LDC	4.5	3	13.5	Focal deep erosion and superficial depletion of proteoglycans by alcian blue staining
Mean		3.82	3.45	13.09	

MDC: Medial distal condyle; MPC: Medial posterior condyle; LDC: Lateral distal condyle; LPC: Lateral posterior condyle.

MRI relaxation times^[22,24,25]. We have similarly shown that morphologically normal articular cartilage, though adjoining osteoarthritic compartments of the knee, exhibit early changes in cartilage degeneration. These early changes include articular cartilage hydration, loss of proteoglycan content, thinning and loosening of collagen fibrils. While statistically significant changes were not observed in all compartments for this small sample size, the trends are readily apparent in all groups and notably significant in the MPC.

The utility of these sequences in joint preservation or replacement remains to be seen. T2 and T1 ρ mapping have increasingly been applied with high fidelity to track outcomes after articular cartilage repair^[26]. Studies have shown significant improvements in T1 ρ relaxation times following microfracture and mosaicplasty, but values do not appear to ever return to baseline^[26-28]. The question stands as to whether focal articular cartilage defects about the knee are amenable to preservation therapies if surrounding articular cartilage exhibits degenerative changes. No doubt there is a spectrum and diversity of cartilage injuries, and only a subset are arthritic in

nature, but our data suggest that patients should be closely examined for early articular changes prior to such therapies. T2 and T1 ρ mapping may have an important role in identifying which patients may benefit from preservation strategies and which are better candidates for joint replacement. Furthermore, these strategies may be used to develop personalized, systematic recommendations for patients with articular cartilage injuries.

This study is not without limitations. Only five patients undergoing TKA were recruited for the OA arm of the study. Although T2 and T1 ρ were significantly higher in the posteromedial condylar segments, this study was underpowered to demonstrate statistically significant differences in the remaining condyles. We believe that a larger sample size would bolster our conclusions. Of note, there was a marked difference in age between the OA group and controls (70 years vs 28.9 years). Differences in T2 and T1 ρ mapping may be confounded by physiologic changes with age alone, as previously mentioned. Although the concept of morphologically normal but biochemically impaired cartilage is valid, this observation may weaken the validity of our argument

Table 2 Comparison of T2/T1 ρ values and cartilage thickness between the control cohort and advanced osteoarthritis patient

		Control (n = 20)	AOA (n = 5)	P ¹
MDC	T2-value ²	52.23	64.9	0.524
	T1 ρ -value	52.5	52.98	0.642
	T2-cartilage thickness ³	6.13	5.38	0.461
MPC	T1 ρ -cartilage thickness	5.7	6.8	0.97
	T2-value	46.83	59.3	0.016
	T1 ρ -value	57.15	73.5	0.043
LDC	T2-cartilage thickness	8.6	10.05	0.352
	T1 ρ -cartilage thickness	8.7	8.93	0.938
	T2-value	48.93	53.7	0.067
LPC	T1 ρ -value	55.85	62.55	0.371
	T2-cartilage thickness	6.58	6.4	0.654
	T1 ρ -cartilage thickness	6.2	5.75	0.587
LPC	T2-value	44.2	50.8	0.218
	T1 ρ -value	48.53	68.5	0.055
	T2-cartilage thickness	8.93	7.95	0.55
	T1 ρ -cartilage thickness	8.5	9.15	0.601

¹Mann-Whitney *U* test; ²T2 and T1 ρ values, measured in milliseconds; ³Thickness, measured in pixels. AOA: Advanced osteoarthritis; MDC: Medial distal condyle; MPC: Medial posterior condyle; LDC: Lateral distal condyle; LPC: Lateral posterior condyle.

regarding joint preservation options. Furthermore, this is a cross-sectional design with no long-term follow-up as all OA patients underwent TKA. They also were not recruited according to degree or radiographic severity of disease and there is no long-term follow-up regarding symptom development in control subjects. However, there are lessons to be learned from this work that may help in the development of personalized treatments for OA and cartilage injuries.

In conclusion, our findings lend additional support to the use of T2 and T1 ρ mapping in the diagnosis and management of OA of the knee. We have uniquely shown that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. These early changes can be detected with T2 and T1 ρ MRI techniques and consideration should be given to the use of these sequences in the early detection of OA.

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COMMENTS

Background

Characterized by the progressive loss of articular cartilage, osteoarthritis (OA) is one of the largest and fastest growing medical conditions worldwide. Significant damage to the collagen-proteoglycan matrix is believed to precede the loss of cartilage and consequent symptoms of knee OA. Among imaging techniques, magnetic resonance T1 ρ has stood out as a high sensitivity option

to detect these early changes in otherwise young, healthy joints.

Research frontiers

Prior studies have demonstrated increased cartilage T1 ρ values, a surrogate of cartilage damage, in patients with knee OA. Specifically, T1 ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions. The basic science foundation for the use of these techniques is now understood, but translating them into clinical practice is an area of current interest.

Innovations and breakthroughs

In recent years, novel strategies have been explored for the early detection of OA. Magnetic resonance T1 ρ and T2 mapping has emerged as an excellent candidate for this endeavor. The authors have uniquely shown that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. These early changes can be detected with T2 and T1 ρ magnetic resonance imaging techniques and consideration should be given to the use of these sequences in the early detection of OA.

Applications

The authors' findings lend support to the use of T2 and T1 ρ mapping in the diagnosis and management of OA of the knee. The results of this study suggest that asymptomatic individuals under consideration for knee joint preservation strategies may benefit from pre-procedure T2 and T1 ρ analysis. Future studies should build upon their results to determine specific T2 and T1 ρ parameters whereby joint preservation strategies are likely to fail.

Terminology

Standard T2 and lesser-known T1 ρ magnetic resonance pulse sequences can be used as surrogates of cartilage damage in patients with knee OA. Specifically, T1 ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions.

Peer-review

It is a well-written paper.

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Total hip arthroplasty in patients with Paget's disease of bone: A systematic review

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Abstract

AIM

To investigate the clinical and functional outcomes following total hip arthroplasty (THA) in patients with Paget's disease.

METHODS

We carried out a systematic review of the literature to determine the functional outcome, complications and revision rates of THA in patients with Paget's disease. Eight studies involving 358 hips were reviewed. The mean age was 70.4 years and follow-up was 8.3 years. There were 247 cemented THAs (69%), 105 uncemented THAs (29%) and 6 hybrid THAs (2%).

RESULTS

All studies reported significant improvement in hip function following THA. There were 19 cases of aseptic loosening (5%) at a mean of 8.6 years. Three cases occurred in the uncemented cohort (3%) at a mean of 15.3 years and 16 cases developed in the cemented group (6%) at a mean of 7.5 years ($P = 0.2052$). There were 27 revisions in the 358 cases (8%) occurring at a mean of 7 years. Six revisions occurred in the uncemented cohort (6%) at a mean of 8.6 years and 21 in the cemented cohort (9%) at a mean of 6.5 years ($P = 0.5117$).

CONCLUSION

The findings support the use of THA in patients with Paget's disease hip arthropathy. The post-operative functional outcome is largely similar to other patients; however, the revision rate is higher with aseptic loosening being the most common reason for revision. Uncemented

implants appear to be associated with a lower failure rate, however, there were no modern stem designs fixed using current generation cementing techniques used in the reported studies, and as such, caution is advised when drawing any conclusions.

Key words: Total hip arthroplasty; Paget's disease; Revision; Loosening; Heterotopic ossification

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Core tip: Patients with Paget's disease commonly develop structural bone deformities in the proximal femur, making total hip arthroplasty (THA) technically demanding. In addition, achieving adequate fixation of hip implants in the hypervascular and often sclerotic bone may prove challenging. This review has shown that, despite its challenging nature, THA can be very successful in terms of improving symptoms and restoring hip function in this unique group of patients. The failure rate, however, appears to be slightly higher than in other patients undergoing a primary total hip replacement. The most common reason for revision surgery is aseptic loosening, and using modern uncemented implants appear to reduce the risk of this occurring.

Hanna SA, Dawson-Bowling S, Millington S, Bhumbra R, Achan P. Total hip arthroplasty in patients with Paget's disease of bone: A systematic review. *World J Orthop* 2017; 8(4): 357-363 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i4/357.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i4.357>

INTRODUCTION

Paget's disease of bone (PDB) is a chronic deforming metabolic disorder characterised by increased osteoclastic bone resorption and subsequent erratic compensatory formation of new woven bone of an abnormal microstructure^[1]. British surgeon Sir James Paget first described PDB in 1877 as a chronic inflammation of bone and termed it "osteitis deformans"^[2]. The resultant bone is mechanically weaker, larger, less compact, more vascular, and more susceptible to fracture than normal adult lamellar bone^[1]. Although the exact aetiology of PDB remains unknown, both genetic and environmental factors have been suggested^[3]. PDB is more common in Europe, North America and Australasia than in Asia and Africa. It is thought to result from a slow viral infection occurring in individuals with a genetic predisposition^[4]. PDB evolves through three distinct phases: An initial osteolytic phase, a mixed phase with lytic and blastic features, and a final osteoblastic or sclerotic phase^[5]. Its prevalence has been shown to increase with age and the most commonly involved sites include the pelvis, femur, spine, skull and tibia^[5]. The pelvis and proximal femur are involved in 20%-80% of patients resulting

in disabling hip disease^[6]. A number of structural bony deformities such as coxa vara, anterolateral femoral bowing and acetabular protrusion are commonly seen in patients with advanced PDB hip arthropathy^[3]. When secondary degenerative changes occur in the hip, symptoms may be initially treated with activity and lifestyle modifications, anti-inflammatory and anti-pagetoc medications, functional bracing and physical therapy. If these measures fail, total hip arthroplasty (THA) is indicated to manage significant pain, joint stiffness and deformity. If THA is considered, preoperative treatment with bisphosphonates or calcitonin is thought to reduce the incidence of intraoperative bleeding, heterotrophic ossification and loosening, although no randomised controlled trials exist to support their use^[7]. The increased bone turnover and remodelling is associated with elevated levels of serum alkaline phosphatase (ALP), which is used to assess the activity of the PDB and the effectiveness of medical treatment by bisphosphonates^[8].

THA in the context of PDB can be a technically challenging procedure because of a number of reasons. The broad spectrum of deformities developing in the hip, including acetabular protrusion, coxa vara and femoral bowing, may hamper dislocation of the hip necessitating a neck cut *in-situ*. A trochanteric osteotomy may also be required for adequate exposure. A marked deformity of the proximal femur may require a corrective osteotomy to enable adequate femoral component alignment and fixation. The presence of dense sclerotic bone may make reaming and bone preparation extremely difficult. Bone hypervascularity may impair visualisation, require higher than usual fluid and blood replacement, and compromise cement implant fixation. Inability to achieve a dry bone bed for cement interdigitation/micro-interlock may compromise long-term implant fixation^[3], which probably explains why the published results of cemented THA in PDB patients appear to be generally poorer than results in other patients^[7]. Concerns also exist when using uncemented hip implants in patients with PDB, as the increased bone turnover is believed to predispose to failure of osseointegration and early aseptic loosening in some cases^[9].

It is estimated that approximately 3% to 4% of the population over age 50 in the United States are affected by PDB^[10]. Although the majority of these patients will not require surgical intervention, those who do, however, represent a unique subset of patients and orthopaedic pathology. When taking into account the exponential increase in the number of THAs performed annually, it can be extrapolated that arthroplasty surgeons will be faced with caring for an increasing number of patients with PDB in the future. It is, therefore, important to recognise the unique problems and challenges inherent to performing THA in patients with PDB. To this end, we therefore performed a systematic review of the literature to determine the method of fixation, failure rates, complication rates and functional outcome of THA in patients with PDB of the hip.

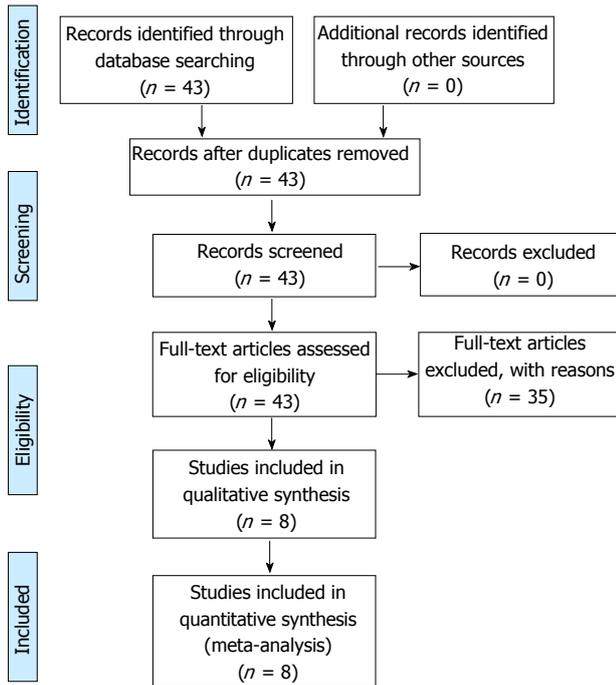


Figure 1 PRISMA flowchart illustrating the search strategy and number of records screened and included.

MATERIALS AND METHODS

Search strategy

MEDLINE and EMBASE were searched on 1/7/2016 to identify relevant studies in the English literature describing the results of THA in patients with PDB between 1980 and July 2016 in line with the PRISMA statement. Keywords used for the searches were "total hip arthroplasty" or "total hip replacement" and "Paget's disease". The bibliographies of all included studies and pertinent reviews were checked carefully for identifying additional studies. We did not contact the corresponding authors to obtain extra data.

Eligibility criteria

Inclusion criteria included all papers, which described the results of THA in patients with PDB published in the English language. Isolated case reports/series with 5 or less patients were excluded. The included articles met the PICO criteria for systematic reviews (Population, Intervention, Comparison and Outcomes).

Data extraction

One reviewer (Sammy A Hanna) extracted data through a standardized data collection form, and then another reviewer (Sebastian Dawson-Bowling) checked the data for accuracy. Any inconsistent results were handled by discussion. Data of the number of patients, follow-up period, type of implant, type of fixation, complications, re-operations, revision rate and functional outcome were extracted and entered in a spreadsheet. Figure 1 represents a PRISMA flowchart illustrating the search strategy and number of records screened and included.

Statistical analysis

Fisher's exact test was used to compare the incidence of aseptic loosening and revision THA between the uncemented and cemented groups. A P value of < 0.05 was considered statistically significant.

RESULTS

Search results

A total of 43 relevant article titles were identified. After reviewing the full text, a total of 8 studies^[7,11-17] satisfied the eligibility criteria and the search strategy illustrated in Figure 1. The excluded 35 articles did not meet the PICO criteria. The included 8 studies were small to medium size retrospective case series ($n = 19-98$). The range of follow-up was 2 to 12.3 years.

Quality assessment

All studies were small to medium size retrospective case series ($n = 19-98$) describing the outcome of THA in patients with PDB of the hip. The range of follow-up in the studies was 2 to 12.3 years.

Cohort characteristics

The studies included 358 THAs performed in patients with a mean age of 70.4 years who were followed-up for a mean of 8.3 years (0.7 to 20). There were 247 cemented THAs (69%), 105 uncemented THAs (29%) and 6 hybrid THAs (2%). The demographics of the patients in the studies are summarised in Table 1.

Outcome analysis

Functional outcome: All studies reported significant improvement in hip function and patient satisfaction following THA. The Harris Hip Score improved by a mean of 40 points post-operatively (27 to 57) in 5 studies^[12,13,15-17]. The Hospital for Special Surgery Scale improved from 18 to 30 post-operatively in one study^[11].

Aseptic loosening: Overall, there were 19 cases of aseptic loosening in 358 cases (5%) at a mean of 8.6 years (1.5 to 20). Three cases occurred in the uncemented cohort (3%) at a mean of 15.3 years (14 to 17) and 16 cases developed in the cemented group (6%) at a mean of 7.5 years (1.5 to 20) - ($P = 0.2052$). There was only one case of failure of osseointegration/early subsidence of the femoral stem in the uncemented patients (1%) occurring at 7 mo.

Revisions rate: There were 27 failures requiring revision surgery in the 358 cases (8%) occurring at a mean of 7 years (0.6 to 20). Six revisions occurred in the uncemented cohort (6%) at a mean of 8.6 years (0.6 to 17) and 21 in the cemented cohort (9%) at a mean of 6.5 years (1.5 to 20) - ($P = 0.5117$). The reasons for failure were aseptic loosening (70%, $n = 19$), septic loosening (11%, $n = 3$), periprosthetic fracture (11%, $n = 3$),

Table 1 Demographics of the patients included in the studies and summary of the results

Study and country	No. of hips	Age (yr)	Follow-up (yr)	Type of fixation	Approach	Complications (implant related)	Heterotopic ossification (%)	Revision rate (%)	Functional outcome (pre and post op)
Merkow <i>et al</i> ^[11] 1984, United States	21	68.6 (57-80)	5.2 (2-11.4)	Cemented	Direct lateral (7) Antero-lateral (14)	Aseptic loosening (2)	52%	10%	HSS scale: 18 to 30
McDonald <i>et al</i> ^[12] 1987, United States	91	69.9 (49-85)	7.2 (0.7-15)	Cemented	Direct lateral (64) Antero-lateral (27)	Aseptic loosening (12) Deep infection (2) Instability (2) Foot drop (1) Nonunion of GT osteotomy (7)	37%	15%	HHS: 39 to 83
Ludkowski <i>et al</i> ^[13] 1990, United States	37	71.5 (60-81)	7.8 (1-18.4)	Cemented	Direct lateral	Superficial infection (3)	65%	0%	HHS: 48.1 to 83.2
Sochart <i>et al</i> ^[14] 2000, United Kingdom	98	67.4 (51-79)	10.4 (5.3-20)	Cemented	Direct lateral	Stem fracture (1) Deep infection (1) Instability (1) Aseptic loosening (2) Nonunion of GT osteotomy (1) Foot drop (1) Instability (1)	29%	5%	
Kirsh <i>et al</i> ^[15] 2001, Australia	20	72 (62-82)	5.7 (4-8)	Uncemented (17) Hybrid (3)	Antero-lateral (13) Posterior (7)	Instability (1)	50%	0%	HHS: 31 to 88
Parvizi <i>et al</i> ^[16] 2002, United States	19	71.3 (54-85)	7 (2-15)	Uncemented	Posterior	Instability (1)	32%	0%	HHS: 59.8 to 86.7
Wegrzyn <i>et al</i> ^[17] 2010, France	39	74.2 (55-89)	6.6 (2-12)	Uncemented (36) Hybrid (3)	Antero-lateral (36) Posterior (3)	Intra-operative posterior column acetabular fracture (1) Periprosthetic fractures (2)	56%	0%	HHS: 54 to 89
Imbuldeniya <i>et al</i> ^[7] 2014, Australia	33	75 (63-85)	12.3 (10.3-17)	Uncemented	Posterior	Aseptic loosening/poly wear (4) Periprosthetic fracture (2)	45%	18%	

HSS: Hospital for special surgery; HHS: Harris hip score.

Table 2 Comparison of the complication rates between the cemented and uncemented groups *n* (%)

Complication	Cemented THR (<i>n</i> = 247)	Uncemented THR (<i>n</i> = 105)
Aseptic loosening	16 (6)	3 (3)
Septic loosening	3 (1)	0 (0)
Periprosthetic fracture	0 (0)	4 (4)
Intra-operative fracture	0 (0)	1 (1)

THR: Total hip replacement.

femoral stem fracture (4%, *n* = 1) and instability (4%, *n* = 1). Table 2 summarises the different complication rates between the cemented and uncemented groups.

DISCUSSION

THA appears to be a generally successful procedure in patients with PDB. The reported post-operative improvement in functional outcome and patient satisfaction is significant in all studies in this review, and is largely comparable to the outcome of THA in other patients^[17].

The overall revision rate was 8% at 7 years with aseptic loosening being the main reason for revision (70%). The revision rate was lower in the uncemented patients (6%) at 8.6 years compared with (9%) in the cemented group at 6.5 years and the incidence of aseptic loosening was higher when cemented implants were used (6%), compared with uncemented porous coated implants (3%). Both differences were not statistically significant (*P* = 0.5117 and 0.2052 respectively). Aseptic loosening also occurred much earlier in the cemented patients (7.5 years vs 15.3 years). These failure rates are slightly higher than those in other patients undergoing THA^[18]. According to the Australian National Joint Registry, a revision rate of > 7.5% at 10 years is considered higher than anticipated^[19]. It is important to note that the vast majority of cemented THAs in this review included modifications of the Charnely stem coupled with a conventional ultra high molecular weight polyethylene liner and fixed with first/second generation cementing techniques. This may have contributed to the relatively high failure rates^[20]. Cementless implants may have a theoretical advantage over cemented ones in the context of PDB. Cement penetration and interdigitation may

be limited in Pagetic bone, which is typically sclerotic and more prone to bleeding. In contrast, many authors believe that the altered bone morphology and increased turnover may hamper osseointegration of uncemented implants^[7]. Interestingly, there was only one case in the uncemented cohort (1%) where failure of bone ingrowth/osseointegration had occurred. This required revision at 7 mo post index surgery.

The overall reported incidence of heterotopic bone (HO) formation was 46% (29% to 65%). It is unclear how the surgical approach to the hip affects this. It is also unclear as to how best to prevent it in terms of dose and timing of radiation and/or chemoprophylaxis^[21,22].

Taking into account the exponential increase in the number of THAs performed annually, it can be extrapolated that arthroplasty surgeons will be faced with caring for an increasing number of patients with PDB in the future. It is, therefore, important to understand the implications of PDB on the medical management of patients, intra-operative technical considerations and the outcomes and complications associated with surgery. When planning to perform THA in a PDB patient, a systematic approach is paramount to ensure optimal outcome. The following pre, intra and post-operative considerations need to be adequately addressed.

Pre-operative considerations /requirements

Differentiating mechanical joint pain from Pagetic bone pain is important. Diagnostic injections are a useful tool to confirm the intra-articular origin of the hip pain and to rule out concurrent pathology.

Good quality imaging studies including long leg views ± computed tomography (CT) scans to assess bone morphology and extra-articular deformities. This is important to plan surgery, including the need for any extra intra-operative steps such as corrective osteotomy and to choose the appropriate implants.

Review by a cardiologist is recommended to assess cardiac function and the presence of high-output cardiac failure. This will likely have anaesthetic implications and may require optimisation prior to performing the surgery.

Preoperative treatment with bisphosphonates or calcitonin reduces intraoperative bleeding by decreasing disease activity. Anti-pagetic medications should be started at least 6 wk prior to elective surgery. Disease activity can be monitored using ALP serum levels^[23].

Pre-operative optimisation of Haemoglobin levels is important to compensate for blood loss intra-operatively. Pre-operative autologous blood donation may also be considered.

Intra-operative considerations /requirements

Effective blood salvage strategies should be employed including expeditious surgery and the administration of tranexamic acid.

Surgery should be performed through an extensile approach when necessary with liberal soft tissue releases

in patients with severe contractures.

Preparation of the femoral side must be performed with caution because standard rasps and reamers may not be effective when used in extremely sclerotic bone. A high-speed burr may be useful to aid in bone preparation. As discussed previously, sclerotic bone may compromise the interdigitation of cement, and uncemented implants may be preferred under these circumstances.

If an uncemented shell is used, it is important to achieve good peripheral rim fit and the use of acetabular screws are recommended to enhance fixation^[24].

Concurrent osteotomy to achieve satisfactory femoral component alignment can be difficult. It is advisable to perform the osteotomy in the metaphysis when possible. A previous study has shown that osteotomy performed in a metaphyseal location had a better outcome than those performed through diaphysis^[25]. However, the complex nature of the deformity in some of these patients may necessitate diaphyseal, and in some occasions multi-planar osteotomies to achieve a satisfactory correction.

Post-operative considerations /requirements

Bisphosphonate treatment should continue if the disease activity high (ALP levels).

It is advisable to administer prophylaxis against HO with preventive measures such as radiation and/or prophylactic drug regimens^[21]. The efficacy of indomethacin in preventing HO is well documented^[26]. The most common treatment is to give 25 mg three times a day for five to six weeks. Several studies have shown the efficacy of radiation therapy in reducing the incidence of HO following lower limb arthroplasty. The most appropriate dose regimen appears to be 7 to 8 Gy given as a single fraction either < 4 h pre-operatively or < 72 h post-operatively^[26].

The main limitation of this review is that it included studies dating back to 1980, with three of the eight papers included being published in 1990 or earlier. Only two articles were published in the last 10 years. This potentially has an impact the results as dated implants and techniques have poorer survivorship. However, although Paget's disease is fairly common (3%-4% of the United States population above the age of 50 are affected)^[10], very limited new information has been published on the topic. With the exponential annual increase of THAs, most arthroplasty surgeons will care for patients with Paget's disease at some point, which makes this review relevant to clinical practice, especially by highlighting the potential challenges and expected outcomes of THA in this unique group of patients.

Conclusion

The findings of this review support the use of THA to alleviate debilitating hip pain and functional limitation in PDB patients with hip arthropathy. Post-operative patient satisfaction and functional improvement is similar to other patients, however, the revision rate is higher with

aseptic loosening being the most common reason for revision. Uncemented implants appear to be associated with a lower failure rate. However, there are no studies reporting on the use of modern stem designs fixed using current generation cementing techniques in PDB patients, so caution is advised when drawing any conclusions.

COMMENTS

Background

Paget's disease is a fairly common disorder, which affects approximately 3% to 4% of the United States population over the age of 50. Although the majority of these patients will not require surgical intervention, those who do, however, represent a unique subset of patients and orthopaedic pathology. Hip involvement is common and performing total hip arthroplasty (THA) in this group of patients is technically demanding. There are three main issues the surgeon needs to address during the procedure: How to deal with the structural deformities present in the hip, how to achieve adequate implant fixation in the hypervascular and sclerotic bone, and how to manage blood loss intra-operatively. This review attempts to answer these questions based on current evidence.

Research frontiers

The optimal method of fixation of hip implants in patients with Paget's disease is frequently debated amongst hip surgeons with no clear consensus. The role of Bisphosphonate therapy peri and post-operatively in reducing blood loss is also a controversial issue.

Innovations and breakthroughs

The review supports the use of THA in patients with Paget's disease. The functional benefit after the procedure is similar to other patients undergoing a primary THA. However, the authors found a slightly higher revision rate in this group of patients, with aseptic loosening being the most common reason for revision. Although uncemented implants appear to be associated with a lower failure rate, however, they did not find any studies evaluating the role of modern polished tapered cemented stem designs in patients with Paget's disease. Caution is therefore advised when drawing any conclusions.

Applications

The results highlight the need for a structured, planned and multidisciplinary approach when managing patients with Paget's disease of bone undergoing THA in order to optimise outcome and reduce the risk of complications.

Peer-review

This is a systematic review on THA in patients with Paget's disease of bone. The introduction is well written and convincing. This systematic review seems to be highly original and no systematic review currently exists on this topic; thus, this manuscript is timely.

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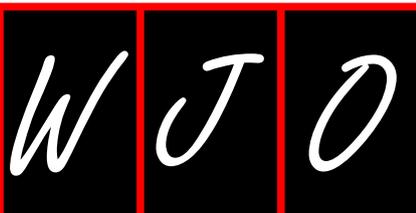
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Abstract

Hallux rigidus is a degenerative disease of the first metatarsalphalangeal (MTP) joint and affects 2.5% of people over age 50. Dorsal osteophytes and narrowed joint space leads to debilitating pain and limited range of motion. Altered gait mechanics often ensued as 119% of the body force transmit through the 1st MTP joint during gait cycle. Precise etiology remains under debate with trauma being often cited in the literature. Hallux valgus interphalangeus, female gender, inflammatory and metabolic conditions have all been identified as associative factors. Clinical symptoms, physical exam and radiographic evidence are important in assessing and grading the disease. Non-operative managements including nonsteroidal antiinflammatory drugs, intra-articular injections, shoe modification, activity modification and physical therapy, should always be attempted for all hallux rigidus patients. The goal of surgery is to relieve pain, maintain stability of the first MTP joint, and improve function and quality of life. Operative treatments can be divided into joint-sparing *vs* joint-sacrificing. Cheilectomy and moberg osteotomy are examples of joint-sparing techniques that have demonstrated great success in early stages of hallux rigidus. Arthrodesis is a joint-sacrificing procedure that has been the gold standard for advanced hallux rigidus. Other newer procedures such as implant arthroplasty, interpositional arthroplasty and arthroscopy, have demonstrated promising early patient outcomes. However, future studies are still needed to validate its long-term efficacy and safety. The choice of procedure should be based on the condition of the joint, patient's goal and expectations, and surgeon's experience with the technique.

Key words: Hallux rigidus; Cheilectomy; Arthrodiastasis; Moberg osteotomy; Arthrodesis; Interpositional arthroplasty; Arthroplasty

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Core tip: Hallux rigidus is the leading form of arthritis

of the foot. Patients experience increasing pain and decreasing motion of the first metatarsalphalangeal joint as the disease progresses, leading to significant morbidity and lower quality of life. Multiple treatment options, from cheilectomy to arthrodesis, have been utilized in treating hallux rigidus. Advances in interpositional arthroplasty and implants have introduced new opportunities in giving a more functional outcome. This review will discuss how to approach hallux rigidus in a clinical setting and examine recent evidence in the available treatment options.

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INTRODUCTION

Hallux rigidus is a degenerative disease of the first metatarsophalangeal (MTP) joint. It is the most common form of arthritis in the foot, affecting 1 in 40 people over the age of 50 with a 2:1 predilection for females^[1,2]. The first MTP joint plays an important functional role during the gait cycle as it carries approximately 119% of an individual's body weight with each step^[3]. Osteophyte formation and degeneration of the cartilage occurs dorsally in early stages of the disease and progresses to involve the entire first MTP joint. Consequently, individuals with hallux rigidus experience joint pain and decreased range of motion (ROM) in the sagittal plane. This leads to altered gait mechanics and significant reduction in activity and quality of life for patients^[4,5].

CLASSIFICATION

Multiple different classification systems have been described for hallux rigidus to evaluate and grade the severity of the first MTP joint damage. Beeson *et al*^[6] conducted a thorough review of 18 hallux rigidus classification systems reported in literature and found no consistency in the construction of the systems as they lacked reliability and scientific validity. Many of the included parameters were based on subjective clinical experience. The authors concluded that the system proposed by Coughlin and Shurnas^[7] most closely approximates a gold standard, as it is based on a combination of objective radiological and clinical findings (Table 1)^[6,7].

HALLUX RIGIDUS VS HALLUX LIMITUS

An important distinction needs to be made between hallux rigidus vs hallux limitus. Hallux rigidus is defined as pain due to an arthritic joint, whereas hallux limitus is defined as functional pain due to soft tissue tightness (*i.e.*, gastrocnemius contracture) or a long and elevated

first metatarsal. Patients with hallux limitus will typically have an increased hallux dorsiflexion when the foot is examined in plantarflexion, as this relaxes the gastrocnemius and removes the restricting factor. It must be noted, however, that hallux limitus may progress to hallux rigidus, thus there may be occasions of overlapping features of either condition.

If the contributing factor in hallux limitus is gastrocnemius tightness, then a gastrocnemius recession alone may be performed. If a long or elevated first metatarsal is responsible for the condition, then a shortening or plantarflexion osteotomy of the metatarsal head may be warranted, with or without a gastrocnemius recession.

RISK FACTORS

The etiology of hallux rigidus is not well understood. It has been reported that trauma is one of the main causes for unilateral hallux rigidus^[8]. Coughlin and Shurnas observed that hallux rigidus is associated with hallux valgus interphalangeus, and bilateral involvement is associated with a family history and female gender^[9]. Development of degenerative changes can also be secondary to repetitive stress or inflammatory or metabolic conditions such as gout, rheumatoid arthritis and seronegative arthropathies^[4,10]. Damage of the articular surface of the MTP joint due to osteochondritis dissecans has been proposed as well^[10]. Biomechanical and structural factors, such as long first metatarsal, metatarsus elevatus, and metatarsus adductus can also lead to increased risk of hallux rigidus^[10,11].

EXAMINATION

Clinical examination

Patients with hallux rigidus may present with altered gait patterns or pain on the lateral aspect of the foot. This is secondary to the attempt to reduce loading on the first MTP joint. Patients may also report limitations on wearing certain types of shoes due to dorsal osteophytes on the first metatarsal head and proximal phalanx. Concurrently, patients may experience numbness along the medial border of the great toe as the osteophytes can compress on the dorsomedial cutaneous nerve^[8].

Physical examination

The foot must be evaluated in the seated and standing positions. The standing position will provide information regarding the dynamic alignment and function of the hallux. The seated position will relax the soft tissues and help assess ROM.

The first MTP joint is often tender dorsally, with often palpable osteophytes. Since the dorsal osteophytes may compress on the dorsomedial cutaneous nerve, sensation deficits and vascular function of the foot should be recorded.

Evaluating the ROM of the first MTP joint is critical as it may be an indicator of the severity of arthritis. The

Table 1 Coughlin and Shurnas Clinical Radiographic System for Grading Hallux Rigidus

Grade	Dorsiflexion	Radiographic findings	Clinical findings
0	40° to 60° and/or 10% to 20% loss compared with normal side	Normal	No pain; only stiffness and loss of motion on examination
1	30° to 40° and/or 20% to 50% loss compared with normal side	Dorsal osteophyte is main finding, minimal joint-space narrowing, minimal periarticular sclerosis, minimal flattening of metatarsal head	Mild or occasional pain and stiffness, pain at extremes of dorsiflexion and/or plantar flexion on examination
2	10° to 30° and/or 50% to 75% loss compared with normal side	Dorsal, lateral, and possibly medial osteophytes giving flattened appearance to metatarsal head, no more than ¼ if dorsal joint space involved on lateral radiograph, mild-to-moderate joint-space narrowing and sclerosis, sesamoids not usually involved	Moderate-to-severe pain and stiffness that may be constant; pain occurs just before maximum dorsiflexion and maximum plantar flexion on examination
3	≤ 10° and/or 75% to 100% loss compared with normal side. There is notable loss of metatarsophalangeal plantar flexion as well (often ≤ 10° of plantar flexion)	Same as in grade 2 but with substantial narrowing, possibly periarticular cystic changes, more than ¼ of dorsal joint space involved on lateral radiograph, sesamoids enlarged and/or cystic and/or irregular	Nearly constant pain and substantial stiffness at extremes of range of motion but not at mid-range
4	Same as in grade 3	Same as in grade 3	Same criteria as grade 3 but there is definite pain at mid-range of passive motion

most common finding is a decreased passive and active ROM, most notably in dorsiflexion. In milder forms of hallux rigidus, pain during passive ROM usually occurs at or near the end points of flexion. However, pain in midrange motion indicates more diffuse level of arthritic change in the joint.

ROM has typically been measured clinically using a goniometer. However, clinical goniometric measurement has been proven to be unreliable and difficult to reproduce in a standardized manner as it is affected by various factors including instrumentation and different patient types^[12]. A new reliable and reproducible method for measuring the hallux MTP ROM using dynamic X-rays has been reported by Vulcano *et al.*^[13]. There was a significant difference between clinical ROM and radiographic ROM, with clinical dorsiflexion being equal to or less than the radiographic dorsiflexion. The difference was more pronounced in patients with a clinical dorsiflexion less than 30 degrees. In addition, radiographic measurements of hallux dorsiflexion had excellent intra- and interobserver reliability^[13].

The hallux interphalangeal (IP) joint should also be carefully examined. Should the joint also be arthritic, the surgeon should avoid fusing both IP and MTP joints to prevent abnormal gait patterns.

Radiographic examination

Weight-bearing anteroposterior (AP), lateral and oblique views of the affected foot should be obtained. The degree of joint space narrowing is best observed on the oblique view. In later stages of hallux rigidus, osteophytic formation can be observed in the periarticular area of the metatarsal head and proximal phalanx. It is important to note that the dorsal osteophytes can obstruct the AP view of the joint. This can lead to false impression of more severe osteoarthritis. Deland and Williams noted that osteophytes can also mislead the actual amount of joint space narrowing as it can help maintain the joint space^[8]. The dorsal aspect of the joint is generally affected first. Other radiographic findings include joint

sclerosis and subchondral cysts. Magnetic resonance imaging (MRI) and computed tomography (CT) images should not be necessary to diagnose the condition or to plan surgery.

TREATMENT

Nonsurgical management

Non-operative treatment for hallux rigidus should be attempted prior to surgical treatments. These treatments include medical therapy, intra-articular injections, shoe modification, activity modification, and physical therapy.

Medical therapy mainly involves oral nonsteroidal anti-inflammatory drugs aimed to reduce swelling and joint pain. However it has been observed that oral medications alone are insufficient to provide pain relief^[8].

Intra-articular injections have been shown to provide good relief in some patients with hallux rigidus. Solan *et al.*^[14] conducted a study evaluating manipulation under anesthesia (MUA) and intra-articular steroid injection in patients with hallux rigidus. They found that patients with Grade 1 hallux rigidus (Karasick and Wapner classification) experienced pain relief of six months while one-third required surgery; grade 2 patients experienced pain relief of three months with two-thirds requiring surgery; grade 3 patients experience minimal benefit as all required surgery. The authors concluded that MUA and intra-articular injections should be recommended to patients with early grades of hallux rigidus^[14]. Prolotherapy, or proliferation therapy, (*i.e.*, injection of platelet rich plasma or bone marrow aspirate) has also been shown to decreased pain and stiffness while improving various quality of life parameters^[15]. However, the current scientific evidence is too scarce to draw definitive conclusions regarding its effectiveness in treating hallux rigidus.

Shoe modification and orthotics reduce pain by modifying the biomechanics of the first MTP joint. Motion extension and navicular pads have been used to immobilize and alter the loading patterns of the joint. Rocker-bottom soles can help reduce painful dorsiflexion

by allowing the patient to transition from heel strike to toe-off in the gait cycle without requiring the foot or shoe to bend. Shoes with high toe box can help prevent direct contact between the dorsal osteophytes and the shoe thereby taking pressure off the joint.

Physical therapy involves joint mobilization, manipulation and improving the ROM. Gaiting training, ice packs and rest reduce pain and inflammation. The use of extracorporeal shockwave therapy, iontophoresis and ultrasonography therapy have also been proposed^[16]. However, evidence supporting the use of these adjunct therapies are still scarce.

Surgical management

When conservative management fails, there are a variety of surgical treatment options available. These techniques can be divided into joint sparing or joint sacrificing techniques. The choice of procedure is based on the condition of the joint, patient's goals and expectations of the surgical outcome, and patient's motivation. The goal of surgery is to relieve pain, improve function, maintain stability of the first MTP joint and improve quality of life.

CHEILECTOMY

Cheilectomy is a joint-sparing technique that involve resection of < 30% of the dorsal metatarsal head. In addition, intraarticular loose bodies and osteophytes localized in the metatarsal head and proximal phalanx are removed, and the medial, lateral and plantar capsules of the metatarsal heads are released. Greater than 30% of the dorsal metatarsal head removal is not advised as the joint can become unstable and the proximal phalanx can sublux. The procedure improves dorsiflexion of the first MTP as well as gait function as it increases the peak ankle push-off power in the sagittal plane^[17].

Cheilectomy is the treatment of choice for early stages of hallux rigidus. It is a relatively simple procedure that preserves 1st MTP joint motion, allowing for faster return to daily activities. The reported complication rate for cheilectomy is low (0% to 3%)^[18]. Cheilectomy does not compromise future surgical treatments should revision become necessary. However, cheilectomy does not prevent the progression of the disease and is rarely a permanent solution to the problem. Dorsal exostosis has been observed in up to 30% of patients, with continued progression of chondrolysis and joint deterioration^[4].

Coughlin and Shumas^[19] reported the longest follow-up study to date for cheilectomy with a mean follow-up of 9.6 years. The study concluded that cheilectomy should be performed for Coughlin and Shurnas Grade I, Grade 2, and Grade 3 with less than 50% metatarsal head cartilage loss. Similarly, Bussewitz *et al.*^[18] reported an overall success rate of 98.5% in 197 cases with a mean follow-up of 3.2 years. Nicolosi *et al.*^[20] evaluated the long-term efficacy of aggressive cheilectomy by analyzing patient satisfaction using American Orthopaedic Foot and Ankle Society (AOFAS) scale in 58 patients

with mean follow-up period of 7 years. The average improvement in pain relief was 87.71%, and 94.83% of all patients stated that they would undergo the same procedure again. The authors concluded that aggressive cheilectomy should be performed over arthrodesis in patients with Grade I to Grade III hallux rigidus using the Coughlin and Shurnas classification system.

Cetinkaya *et al.*^[21] assessed the results of cheilectomy in the treatment of Grade III hallux rigidus using the Coughlin and Shurnas classification system for 21 patients (22 toes). There was no revision surgery done, and the visual analog scale (VAS) score improved from 89 preoperative to 29 postoperative. Cetinkaya *et al.*^[21] concluded that cheilectomy is the preferable method as the first line treatment option for Grade III hallux rigidus.

CHEILECTOMY WITH MOBERG OSTEOTOMY

Moberg osteotomy is a dorsal closing-wedge osteotomy of the proximal phalanx. This procedure simulates an increased dorsiflexion that facilitates the third rocker of gait. Further, the Moberg osteotomy shifts the center of pressure on the first metatarsal head in a plantar direction. As a result, less forces act on the arthritic joint surface^[22].

Moberg osteotomy is typically performed in conjunction with a cheilectomy for early stages of hallux rigidus. As noted previously, cheilectomy doesn't prevent further degeneration of the joint and therefore progressive loss of dorsiflexion can occur. Moberg osteotomy can offer decompression of the joint while preserving the movement at the first MTP joint. It has been argued that one potential drawback of the osteotomy is that it could affect dorsal plate positioning in case of arthrodesis revision surgery^[23].

In a study of 60 patients (60 toes) with an 8-year follow up, Waizy *et al.*^[24] compared the results of cheilectomy alone (27 patients) vs combined cheilectomy and Moberg osteotomy (33 patients). No revisions or further operations were done in both groups. Four patients had persistent hyperesthesia of the medial side of the great toe and 3 patients had delayed wound healing. Patients who had cheilectomy with Moberg osteotomy reported higher satisfaction than cheilectomy alone (32.6% vs 21.7%). The authors concluded that a Moberg osteotomy should be supplemented if dorsiflexion of greater than 70° could not be achieved intraoperatively with cheilectomy alone.

Moberg osteotomy alone has also demonstrated good clinical results in moderate hallux rigidus. Perez-Aznar *et al.*^[25] evaluated the results of a Moberg osteotomy alone in 40 patients (42 toes) with Coughlin and Shurnas Grade II and III hallux rigidus. Both AOFAS (51.7 to 88.8) and VAS scores (76.6 to 1.9) improved significantly from pre-op to post-op. Additionally, dorsiflexion improved from 20.3° to 55.7°.

O'Malley *et al.*^[23] investigated the use of cheilectomy and Moberg osteotomy for the treatment of advanced hallux rigidus. In a cohort of 81 grade III hallux rigidus with

a mean follow-up of 4.3 years, significant improvements in dorsiflexion and AOFAS scores were reported. Patient satisfaction was high (85.2%), with 4.9% ultimately requiring arthrodesis. The authors encouraged and recommended cheilectomy with Moberg osteotomy in patients with high grade hallux rigidus with at least 20° of preoperative dorsiflexion.

ARTHRODESIS

Arthrodesis of the 1st MTP joint has been widely accepted as the standard of care for severe, end-stage hallux rigidus due to its perceived safety and efficacy^[8,11,26-31]. The procedure is typically performed as open surgery, although few recent reports have demonstrated a percutaneous approach^[28,32]. The arthrodesis surfaces can be prepared either in a dome-cup pair configuration or flat and tapered. Dome-cup pair configuration allows for high degrees of adjustability in a three-dimensional plane, making final optimal alignment of the great toe easier.

There are multiple internal fixation techniques to achieve fusion (plates, screws, wires and staples). Ultimately, the choice depends on the surgeon's skills and experiences with a particular fixation technique. Politi *et al.*^[33] evaluated and compared the strength of fixation of five commonly utilized techniques for arthrodesis and found that the most stable technique was the combination of an oblique lag screw and a dorsal plate. The weakest technique was dorsal plate alone with Kirschner wire fixation. Dening *et al.*^[34] demonstrated that plate fixation alone has significantly fewer non-unions than a single screw fixation. Hyer *et al.*^[35] compared the cost and results of two crossed screws and dorsal plating techniques. The two crossed screws represented a simple and less costly technique, with no statistically significant differences in time to fusion, revision surgery or hardware removal rate between the two techniques.

When performing a hallux fusion it is crucial to maintain the load bearing capacity of the first ray in order to prevent lateral transfer of forces towards the lesser metatarsals. The angle of fusion should be within 15° to 40° of extension and 15° and 30° of valgus^[36].

Recent studies have reported fusion rates between 77% to 100% with dorsal plating and screw fixation^[37]. Arthrodesis has been shown to improve propulsion power, weight-bearing function of the foot, and stability during gait^[27]. However, complications such as nonunion have been reported to be as high as 20%^[29]. Further, patients may complain of joint stiffness, metatarsalgia and limited footwear options, particularly women desiring to wear high heels.

ARTHROPLASTY

Unlike arthrodesis in which the joint motion is sacrificed to improve pain, partial or total arthroplasty is a surgical option intended to relieve pain while preserving the mobility of the first MTP joint. Both total joint arthroplasty and

hemiarthroplasty of the proximal phalanx or metatarsal have been developed. Despite the potential benefit of maintaining joint motion while relieving pain, multiple complications have been documented for arthroplasty, including implant failure, soft tissue instability, aseptic loosening of components, pathological wear, limited soft tissue coverage and infection^[38,39].

Mixed results have been reported on the long-term outcomes of various types of implants^[38-41]. Good short-term and long-term functional outcome and high patient satisfaction level were reported with the use of ToFit-Plus (Plus Orthopedics AG, Switzerland) implants and silicone implant prosthesis^[40,41]. Conversely, a loss of ROM and changes in component alignment over time was demonstrated with the use of an anatomically designed 3-component MTP-I prosthesis (Metis, Newdeal SA, Integra Life Science ILS, New Jersey, United States)^[38]. Similarly, high rates of radiolucency, change in angulation, sinkage and malalignment were observed with the use of the second-generation ceramic press fit prosthesis (Press-fit Plus MTP, Moje Keramik-Implantate GmbH and Co KG, Petersberg, Germany)^[39]. Because of the poor clinical and radiological results, the authors in the study did not recommend the prosthesis.

Similar to total joint arthroplasty, hemiarthroplasty also helps maintain the motion of the first MTP joint. However, hemiarthroplasty requires less bone resection and ensures maintenance of toe length. As a result, conversion to arthrodesis would be easier if a revision becomes necessary. Like total arthroplasty, studies on hemiarthroplasty have shown mixed results. Gheorghiu *et al.*^[42] observed a marked decrease in patient satisfaction along with significant decrease in ROM in patients with hemiarthroplasty compared to arthrodesis with a mean follow-up of 3.92 years. On the other hand, Voskuijl and Onstenk^[43] found patients with hemiarthroplasty in their study reported greater satisfaction. In addition, symptom intensity and magnitude of disability were found comparable in both hemiarthroplasty and arthrodesis.

While the success and benefit of implants have been documented in the literature, the reports of higher complication rates, unpredictable results and poor survival have led orthopedic surgeons to become cautious with the use of implant arthroplasty. Part of the challenge with arthroplasty is the difficulty in mimicking the native joint and the various anatomical and mechanical stresses it endures. Failure of the arthroplasty is very difficult to manage as significant bone loss was introduced by the procedure in the first place. Additionally, the cost compared to arthrodesis is significantly higher^[38]. Therefore, larger cohorts and longer follow-up studies are necessary to draw more definitive conclusions on arthroplasty in hallux rigidus.

INTERPOSITIONAL ARTHROPLASTY

Interpositional arthroplasty is a joint sparing procedure that maintains joint motion in patients with severe hallux rigidus. Keller resection arthroplasty was one of the

pioneer procedures for the treatment of hallux rigidus that involves the resection of up to 50% of the base of the proximal phalanx. The goal of the procedure was to decompress the joint while increasing dorsiflexion. However, the procedure may destabilize the first MTP joint leading to transfer metatarsalgia, excessive shortening of the toe, cock-up deformity, clawing of the IP joint, and high rates of revision^[8,44-47]. In addition, pedobarographic evaluations of foot following Keller resection arthroplasty have demonstrated a decrease in the maximum pressure, force and contact area under the operated great toe^[45].

Schneider *et al.*^[45] reported a 90% stable first MTP joint in 78 patients (87 toes) who underwent Keller resection arthroplasty with 23 years of follow-up. The revision rate was reported at 5%. However, it is important to note that even though only one patient required revision with a cock-up deformity, 23% (19 toes) of patients presented with a cock-up deformity. It has been proposed to reserve the Keller resection arthroplasty in patients with advanced hallux rigidus, over the age of 70, and with less physical demand^[8,46].

In light of the potential complications, multiple modifications of the Keller resection arthroplasty have been developed. These include a much more limited resection of the proximal phalanx, addition of a cheilectomy, and a placement of a spacer (joint capsule, extensor hallucis brevis, tendon autograft, tendon allograft, synthetic matrix, etc.). The aim of the modifications is to preserve the bone stock, maintain or increase joint motion, stability and length^[48].

Aynardi *et al.*^[49] retrospectively reviewed 133 patients who underwent interpositional arthroplasty with either autograft or synthetic soft tissue. Ninety percent of patients reported good to excellent outcomes at a mean follow-up of 62.2 mo. Overall failure rate was 3.8%, and a 1.5% infection rate. Six patients reported cock-up deformity of the 1st MTP joint and 23 patients reported metatarsalgia of the 2nd or 3rd MTP joint.

Schenk *et al.*^[50] compared the outcomes of Keller resection arthroplasty and interpositional arthroplasty and found no significant difference between the clinical and radiological outcomes of the two procedures. However, these were short term-results with a mean follow-up of 1.26 years. Mackey *et al.*^[47] compared interpositional arthroplasty with arthrodesis and reported that interpositional arthroplasty had equivalent clinical outcomes to arthrodesis. However, it presented the additional benefit of motion preservation and resulted in a more physiologic pattern of plantar pressure during gait.

Berlet *et al.*^[48] described the use of a regenerative tissue matrix (RTM) (Wright Medical Technology, Inc., Memphis, TN, United States) as an allograft interpositional spacer for the treatment of advanced hallux rigidus. RTM is a biologically engineered allograft consisting of collagen and extracellular protein matrices. In their preliminary report, 9 patients underwent the procedure and no failures were reported at 10.1 mo follow-up. At 5-year follow-up, none of the patients had subsequent fusion or

additional procedures performed on the first MTP joint and all were satisfied with the procedure^[51].

Baumhauer *et al.*^[5] described the use of a synthetic cartilage implant as an allograft interpositional spacer. This synthetic cartilage implant (Cartiva, Inc., Alpharetta, GA, United States) is 8 or 10 mm in diameter and requires minimal bone and joint resection for implantation. The authors compared synthetic cartilage implant and arthrodesis in patients with advanced stage hallux rigidus and concluded that both procedures had equivalent decrease in pain and improvement function at 2-year, with an overall failure rate of 10%.

ARTHODIASTASIS

Arthodiastasis involves extra-articular distraction of a joint. This is based on the principle that offloading the articular surfaces of a joint can provide an environment that stimulates bone healing and fibrocartilage generation^[4]. Pain can potentially be reduced, and arthrodesis or arthroplasty is still possible if distraction fails. Distraction of other joints in the body has been well reported, including the hip and ankle^[52-54]. Abraham *et al.*^[55] reported a statistically significant reduction of pain in 9 hallux rigidus patients (10 distractions) using joint distraction with a mean follow up of 2.2 years. All patients were stage II or III hallux rigidus on the Regnaud classification system, and none of the patients had subsequent procedures on the first MTP joint. The downside of the procedure, however, is the need to carry an external fixator for about 3 mo.

ARTHROSCOPY

The use of arthroscopy in the treatment of hallux rigidus is an emerging technique that has recently been described^[56,57]. It is mainly used for grade I and II hallux rigidus where joint motion still remains. For patients that have failed conservative treatments, arthroscopic debridement and dorsal cheilectomy can be performed as an alternative to an open cheilectomy. Advantages include smaller incisions, reduced operative morbidity and more rapid rehabilitation. In addition, access to the entire joint is easier, which allows for identification of concomitant pathologies in the joint. If visualization of the joint is limited, the dorsomedial portal can be extended and convert the procedure to an open cheilectomy^[56]. Arthroscopy of the 1st MTP joint is technically challenging and requires additional surgical training. Complications that have been described include iatrogenic articular cartilage injury, superficial or deep infection, wound dehiscence and sinus tract formation^[56].

CONCLUSION

An array of techniques has been developed to address the arthritic changes in hallux rigidus. Surgical treatments can be considered only after failure with non-operative management. Surgical options can be divided into joint sparing and joint sacrificing. Determining the extent of

the degenerative changes in the first MTP joint is critical in selecting which surgical technique to perform. Cheilectomy has demonstrated excellent outcomes for early stages of hallux rigidus, while arthrodesis is the gold standard for end-stage hallux rigidus. Other procedures, such as interpositional arthroplasty, seem to provide promising patient outcomes, but long-term follow-up studies are needed to validate the available results.

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Basic Study

Light and electron microscopic study of the medial collateral ligament epiligament tissue in human knees

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Abstract**AIM**

To examine the normal morphology of the epiligament tissue of the knee medial collateral ligament (MCL) in humans.

METHODS

Several samples of the mid-substance of the MCL of the knee joint from 7 fresh human cadavers (3 females and 4 males) were taken. Examination of the epiligament tissue was conducted by light microscopy and photomicrography on semi-thin sections of formalin fixed paraffin-embedded blocks that were routinely stained with haematoxylin and eosin, Mallory stain and Van Gieson's stain. Electron microscopy of the epiligament tissue was performed on ultra-thin sections incubated in 1% osmium tetroxide and contrasted with 2.5% uranyl acetate, lead nitrate, and sodium citrate.

RESULTS

The current light microscopic study demonstrated that the epiligament of the MCL consisted of fibroblasts, fibrocytes, adipocytes, neuro-vascular bundles and numerous multidirectional collagen fibers. In contrast, the ligament body was poorly vascularised, composed

of hypo-cellular fascicles which were formed of longitudinal groups of collagen fibers. Moreover, most of the vessels of the epiligament-ligament complex were situated in the epiligament tissue. The electron microscopic study revealed fibroblasts with various shapes in the epiligament substance. All of them had the ultrastructural characteristics of active cells with large nuclei, well developed rough endoplasmic reticulum, multiple ribosomes, poorly developed Golgi apparatus, elliptical mitochondria and oval lysosomes. The electron microscopy also confirmed the presence of adipocytes, mast cells, myelinated and unmyelinated nerve fibers and chaotically oriented collagen fibers.

CONCLUSION

Significant differences exist between the normal structure of the ligament and the epiligament whose morphology and function is to be studied further.

Key words: Knee; Epiligament; Knee medial collateral ligament; Electron Microscopy; Humans; Microscopy; Photomicrography

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Core tip: The epiligament of the medial collateral ligament of the human knee is an important enveloping supporting structure of the ligament proper containing fibroblasts, fibrocytes, adipocytes, mast cells, and neurovascular bundles in a network of collagen fibres that is not limited to the surface of the ligament but also pervades it, as the endoligament, thus providing the cellular elements and blood vessels that participate in the ligament's nutrition and during the process of healing.

Georgiev GP, Iliev A, Kotov G, Kinov P, Slavchev S, Landzhov B. Light and electron microscopic study of the medial collateral ligament epiligament tissue in human knees. *World J Orthop* 2017; 8(5): 372-378 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/372.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.372>

INTRODUCTION

The medial collateral ligament (MCL) of the knee joint, also known as tibial collateral ligament (TCL), is an often injured ligamentous structure of the knee joint^[1-3]. Ninety percent of knee ligament injuries involve the MCL or the anterior cruciate ligament (ACL)^[4]. The incidence of this injury has increased in recent years and presents a commonly encountered problem in modern sports medicine^[5,6]. Most injuries result from a valgus force on the knee from direct contact or with cutting manoeuvres, namely when athletes place a foot in a stable position and then rapidly change the direction of movement^[7]. The popularity of sports such as football, skiing and ice

hockey has also contributed to the increased incidence of MCL injuries^[8]. According to the model of Warren and Marshall, the medial knee is divided into the following three layers: Superficial (I), intermediate (II), and deep (III)^[9]. The superficial layer (I) consists of the deep crural fascia which invests the sartorius and quadriceps and continues into the deep fascia of the lower extremity, where it covers the gastrocnemius and the popliteal fossa. Layer II , or the intermediate layer, includes the superficial MCL (sMCL) and medial patellofemoral ligament (MPFL). Layer III is the deep layer and comprises the joint capsule and the deep MCL (dMCL). The superficial and dMCL have similar functions and act as the primary supporting structures of the medial side of the knee^[5,10], therefore injuries to these structures merit due attention and adequate treatment^[1]. The healing of ligaments after injury is associated with scar tissue formation rather than regeneration^[11-14].

The structure of the MCL has been studied extensively, however, very little is known about the thin layer of connective tissue adherent to this ligament, termed the epiligament (EL) [epi-(Greek-on or upon); ligament (Latin-ligare, to bind)]. In 1990, Bray *et al*^[15] described the epiligament as a "surrounding adherent connective tissue removed simultaneously with the ligament but which was grossly distinguishable from ligament tissue proper". Our previous studies on the MCL in rat knee models led to the conclusion that the EL tissue plays a key role in the healing of the ligament tissue after injury^[13,16,17]. According to Georgiev and Vidinov^[18-20] and Georgiev *et al*^[12,13,16,21,22] the EL is a donor of fibroblasts, progenitor cells and blood vessels, which proliferate and migrate towards the body of the ligament through the endoligament during the process of ligament recovery. Fibroblasts in the EL tissue normally produce collagen types I , III , V , fibronectin (FN) and matrix metalloproteinases-2 and -9 (MMP-2, -9) which are essential for the normal functioning of the ligament and their synthesis is increased in order to promote adequate repair after injury^[13,16,17,21,23]. Therefore, detailed knowledge of the morphology and function of the EL during physiological conditions and post injury is important in deepening our knowledge with regard to ligament healing and may thus lead to proposal of better treatment options in the future. There is plentiful literature data concerning the role of the EL during MCL healing in rats, however its normal anatomy in humans has not been studied yet. In line with this, the aim of this study is to investigate the normal morphology of the MCL EL in humans for the first time in the literature, through light and electron microscopy and to compare it to the ligament substance.

MATERIALS AND METHODS

Several samples of the mid-substance of the MCL of the knee joint of 7 cadavers (3 females and 4 males) were taken from the fresh human cadavers available at the Department of Anatomy, Histology and Embryology at

the Medical University of Sofia. The study was approved by the Medical Legal Office, the Local Ethics Committee and the Institutional Review Board.

After skin incision, the overlying connective tissue was dissected to expose the knee's MCL. The MCL and the external surface of the surrounding EL were precisely dissected and then the pieces were immediately fixed in formalin (Merck Catalogue No. 1040031000) for light microscopy or in 3% glutaraldehyde (Merck Catalogue No. 354400) for 2 h for electron microscopy.

Light microscopic study protocol

After fixation, the samples were embedded in paraffin and cut into semi-thin sections that were stained routinely with HE (Haematoxylin Merck Catalogue No. 105 1741000; Eosin Merck Catalogue No. 1170811000), Mallory stain and Van Gieson's stain. Photomicrographs of representative fields of the light microscopy staining were obtained using Olympus CX 21 microscope fitted with an Olympus C5050Z digital camera (Olympus Optical Co, Ltd).

Electron microscopic study protocol

After fixation, the tissues were rinsed several times with 0.1% phosphate buffer (Merck Catalogue No. 146 5920006) to remove the fixative solution and were incubated in 1% osmium tetroxide (Merck Catalogue No. 1245050500) for 2 h. Then the pieces were dehydrated in EtOH (50%, 70%, 95%, 100%) (Merck Catalogue No. 1009835000) and treated for 30 min with a 2:1 mixture of propylene oxide (Merck Catalogue No. 807027) and epon. The pieces were embedded in Durcupan (Fluka, Buchs, Switzerland). Afterwards, all slices were processed with a dissection microscope and cut by an ultramicrotome (LKB, Stockholm-Bromma, Sweden). The EL regions were identified on semi-thin sections. Ultrathin sections (60 nm thick) were taken only from the MCL EL and then both were contrasted with 2.5% uranyl acetate, lead nitrate, and sodium citrate. We used a Hitachi 500 electron microscope.

RESULTS

Normal morphology of the MCL EL: Light microscopy

The light microscopic study revealed that human MCL EL is markedly distinctive from the ligament substance and confirmed our previous observations in rats. The external surface of the MCL EL was comprised of fibroblasts, fibrocytes, adipocytes, mast cells and neuro-vascular bundles as well as numerous multidirectional collagen fibres (Figure 1). The EL was relatively rich in blood vessels (Figure 1A). In contrast to the EL, the ligament tissue was poorly vascularised and composed of uniform fascicles that were formed of longitudinally aligned groups of collagen fibres. Each fascicle appeared hypocellular and the scarce cells were interspersed between bundles of collagen fibres. Unlike in the ligament, the collagen fibres in the EL of the midportion of the MCL

were quite similar in diameter and were positioned in bundles with various orientation.

Normal morphology of the MCL EL: Electron microscopy

The electron microscopy revealed the presence of various types of fibroblasts in the EL: Spindle-shaped, spinous-shaped, elongated and fibroblasts with irregular shape. They had large nuclei, well developed rough endoplasmic reticulum, multiple ribosomes, poorly developed Golgi complex, individual elliptical mitochondria and oval, individually located lysosomes (Figure 2A-C). The electron microscopy also manifested the presence of adipocytes and mast cells (Figure 1F). The mast cells had well-presented nuclei with peripheral heterochromatin. The cytoplasm contained the specific round or oval granules. The granules were always enclosed by a membrane and separated from other granules by cytoplasmic septa. The matrix of each granule was homogeneous and electron-dense. The electron microscopy revealed that the adipocytes had large lipid droplets which pushed the rest of cytoplasm at the periphery of the cell. The nuclei of the adipocytes were eccentrically located.

Collagen fibres in the EL of the midportion of the MCL were quite similar in diameter and were organized in bundles with various orientation, unlike the parallel pattern of distribution of collagen fibres in the ligament (Figure 2D and E). Again, chaotically oriented small groups of collagen fibres were observed. Both myelinated and unmyelinated nerve fibres were detected.

DISCUSSION

The ligament is built of connective tissue, which comprises two main elements-connective tissue cells and extracellular matrix^[11,24]. Collagen fibres in the ligaments are organized in longitudinal groups and form fascicles^[11,24,25]. The thin layer of connective tissue separating these fascicles is known as endoligament and is related to another connective tissue structure, containing more blood vessels, which envelops the entire ligament and is known as epiligament^[12,13,16-18]. In rabbits, Chowdhury *et al*^[26] (1991) examined the external surface of the MCL EL and described two types of cells - spinous-shaped adipocytes and fibroblasts. It is fibroblasts that produce collagen fibers and thus are responsible for the formation of scar tissue^[26]. In rats, Georgiev *et al*^[12,13,16,17] showed the external portion of the MCL EL to consist of fibroblasts, fibrocytes, adipocytes, neurovascular bundles, and a number of collagen fibres, oriented in varying directions. These cells are located among bundles of collagen fibres. Georgiev *et al*^[22] also described the ultrastructural characteristics of the different types of fibroblasts in the EL of the lateral collateral ligament (LCL) in rat knees. In terms of shape, they described spindle-shaped fibroblasts, small elongated fibroblasts and fibroblasts with irregular shape. All of these cells were characterized by the presence of a large nucleus with prominent nucleoli, well-developed rough endoplasmic

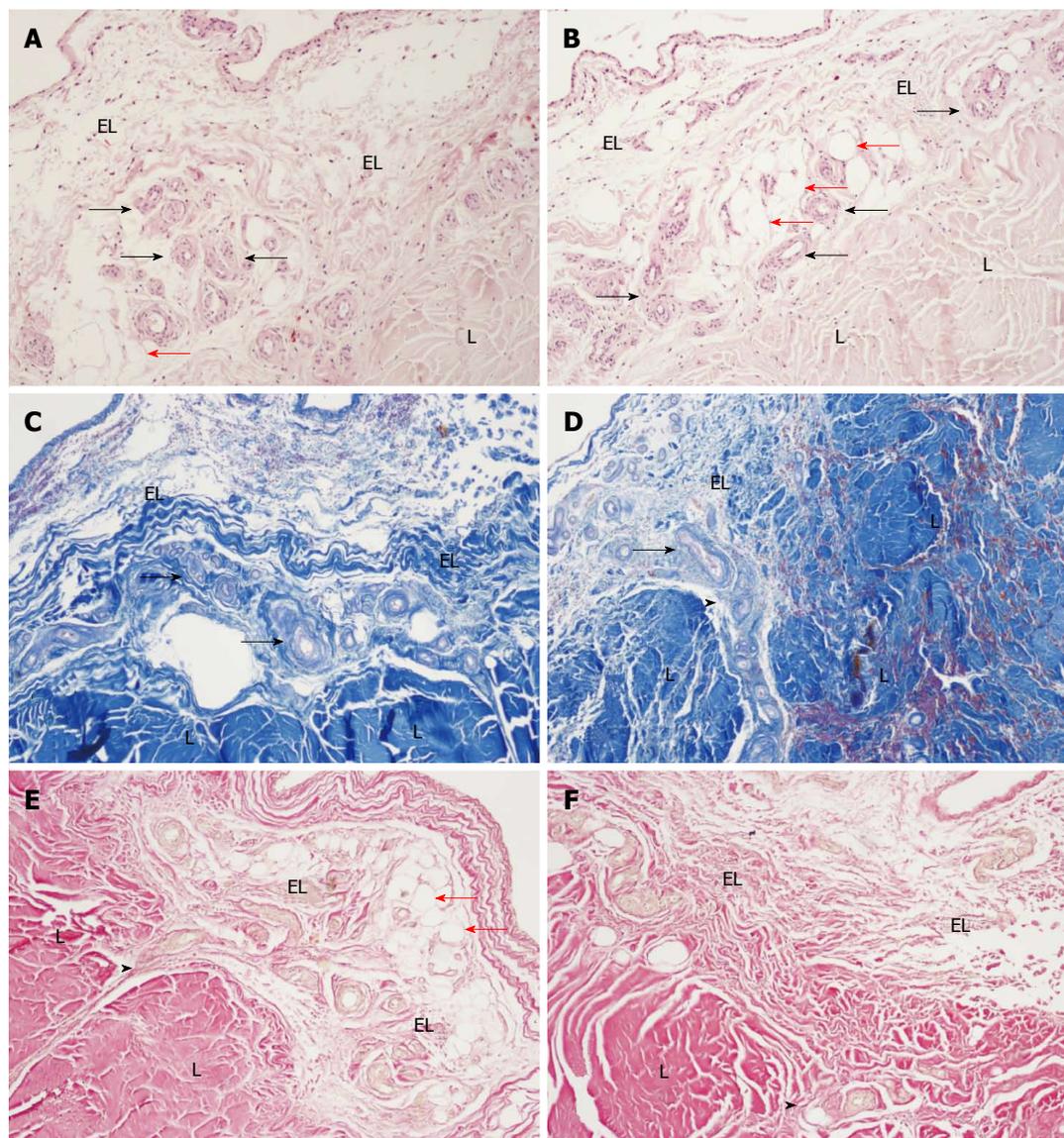


Figure 1 Normal morphology of the medial collateral ligament epiligament tissue in humans. A and B: Normal morphology of the MCL EL tissue. Haematoxylin and eosin stain, $\times 200$. E: Epiligament; L: Ligament; red arrows: Adipocytes; arrows: Vessels in the EL tissue; C and D: Normal morphology of the MCL EL tissue. Mallory stain, $\times 200$. E: Epiligament; L: Ligament; arrows: Vessels in the EL tissue; arrow head: The EL extending into the endoligament; E and F: Normal morphology of the MCL EL tissue. Van Gieson's stain, $\times 200$. EL: Epiligament; L: Ligament; red arrows: Adipocytes; arrow head: The EL extending into the endoligament; MCL: Medial collateral ligament.

reticulum and numerous ribosomes. These ultrastructural characteristics led Georgiev *et al.*^[22] to conclude that fibroblasts in the EL might take part in the differentiation, phagocytosis and collagen synthesis, possibly thus playing a role in the regeneration of the ligament after injury, which has also been proposed by other authors^[11]. Moreover, fibroblasts in the EL may proliferate and migrate through the endoligament into the ligament proper^[18,27].

Other rarely observed types of cells are mast cells which have an oval shape and numerous granules with homogeneous density^[22]. Adipocytes are organized in cellular lobuli, enveloped by thin connective tissue fibres and represent the building blocks of white adipose tissue^[24]. According to Chowdhury *et al.*^[26] adipocytes synthesize, process and store lipids and thus participate in nutrition and confine specific storage and protective

functions to the EL.

In humans, our light microscopic and ultrastructural study confirmed the aforementioned characteristics of the EL tissue and its constituent cells. On light microscopy, we noted the existence of fibroblasts, fibrocytes, adipocytes, neuro-muscular bundles and numerous multidirectional collagen fibres. This greatly resembled the structure of the EL observed in rats^[22]. Also, we observed that the main cytological features of the EL were closely related to those in the synovium. This provides further support to the theory that the EL is a specialised form of synovium^[11,28]. Electron microscopy revealed a great variety of fibroblasts in terms of shape - spindle-shaped, spinous-shaped, elongated and irregularly-shaped, which confirmed earlier results in rats^[22]. We found an abundance of structures in their cytoplasm, namely a well-developed rough

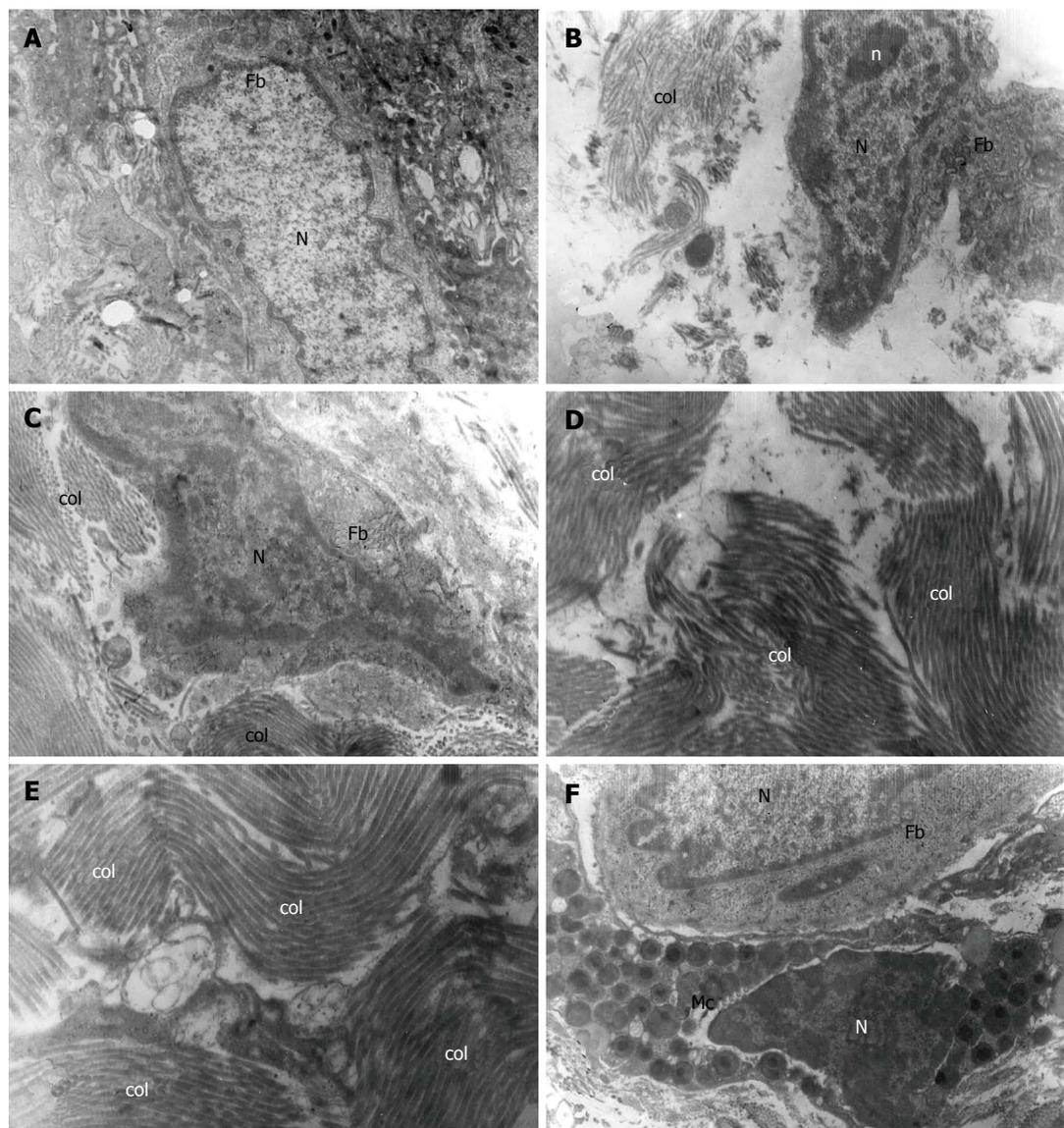


Figure 2 Normal morphology of the medial collateral ligament epiligament tissue in human. A-C: Electron micrograph of a fibroblast (Fb) and its nucleus (N). Mitochondria, lysosomes and rough endoplasmic reticulum are visible in the cytoplasm of the Fb; in the extracellular matrix numerous collagen fibers (col) are presented $\times 7000$; D and E: Electron micrograph of EL collagen fibers (col) in the extracellular matrix oriented in different directions $\times 7000$, $\times 9000$; F: Electron micrograph of a fibroblast (Fb) and its nucleus (N) and a mast cell (Mc) with numerous granules and its nucleus (N), $\times 9000$.

endoplasmic reticulum and multiple ribosomes, which supports the hypothesis that fibroblasts play a key role in the ligament nutrition and healing after injury^[11,22].

As in the rat and the rabbit, the EL tissue in humans appears to contain a relative abundance of blood vessels^[12,24,26,29,30]. Blood vessels in the EL are randomly dispersed in an amorphous structure, built of loose connective tissue^[26,30]. They branch extensively, forming anastomotic networks of interconnected vessels^[29,30]. Blood vessels in the EL are often accompanied by nerve bundles, but apparently not all blood vessels are organized in a neurovascular bundle^[15,26,30].

The healing of ligaments after injury is associated with scar tissue formation rather than regeneration, which shows common mechanisms to the healing processes in other soft tissue structures^[31-34]. According to Frank *et al.*^[32] injury location has an impact on ligament healing.

The MCL heals much better and faster than the ACL of the knee joint. This is most likely due to the specific characteristics of the EL, located above the MCL. Georgiev and Vidinov^[18-20], Georgiev *et al.*^[13,16,17,21,22] and Lo *et al.*^[29], claim that the EL may be the primary donor of connective tissue cells participating in the scar formation as part of the process of ligament healing. Fibroblasts are not static cells and as such can migrate from the EL to the healing ligament^[12,13,21,22,26]. According to Chamberlain *et al.*^[27], ligament injuries stimulate the migration of various cell types from the EL, including neutrophils and cells in the process of mitosis up to the fifth day after injury, which proves that there is a bilateral cooperation between the EL and the ligament with regard to adequate healing of the ligament.

In conclusion, this study illustrates in detail the normal morphology of the MCL EL in humans and demonstrates

its difference from the structure of the ligament tissue for the first time. The electron microscopic study reveals the specific characteristics of the various types of cells in the EL and supports the hypothesis that fibroblasts in particular, together with the abundant blood vessels are essential for the nutrition and healing of the MCL.

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COMMENTS

Background

The epiligament has relatively recently been shown to be a distinct structure enveloping ligaments in mammals and to be the main donor of cells and blood vessels for ligament nutrition and healing not only at its periphery but also within its substance where it penetrates as a ramified network - the endoligament.

Research frontiers

Previous research was performed on rat and rabbit models yielding consistent results.

Innovations and breakthroughs

This is the first light microscopic and ultrastructural study of the epiligament in humans showing it to be structurally, and possibly functionally, similar to that of other mammals.

Applications

Improving the understanding of the biology of the epiligament tissue might further the development and fine-tuning of treatment modalities after ligament injuries.

Terminology

Epiligament: A connective tissue structure enveloping the ligaments and containing cells and blood vessels necessary for the nutrition and healing of the ligament; Endoligament: The ramifications of the epiligament within the ligament substance.

Peer-review

The content is clear and definite, level of structure is logical and accurate. The research method is scientific and reasonable. The article is well-written.

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Observational Study

Technical note: Anterior cruciate ligament reconstruction in the presence of an intramedullary femoral nail using anteromedial drilling

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Abstract**AIM**

To describe an approach to anterior cruciate ligament (ACL) reconstruction using autologous hamstring by drilling *via* the anteromedial portal in the presence of an intramedullary (IM) femoral nail.

METHODS

Once preoperative imaging has characterized the proposed location of the femoral tunnel preparations are made to remove all of the hardware (locking bolts and IM nail). A diagnostic arthroscopy is performed in the usual fashion addressing all intra-articular pathology. The ACL remnant and lateral wall soft tissues are removed from the intercondylar, to provide adequate visualization of the ACL footprint. Femoral tunnel placement is performed using a transportal ACL guide with desired offset and the knee flexed to 2.09 rad. The Beath pin is placed through the guide starting at the ACL's anatomic footprint using arthroscopic visualization and/or fluoroscopic guidance. If resistance is met while placing the Beath pin, the arthroscopy should be discontinued and the obstructing hardware should be removed under fluoroscopic guidance. When the Beath pin is successfully placed through the lateral femur, it is overdrilled with a 4.5 mm Endobutton

drill. If the Endobutton drill is obstructed, the obstructing hardware should be removed under fluoroscopic guidance. In this case, the obstruction is more likely during Endobutton drilling due to its larger diameter and increased rigidity compared to the Beath pin. The femoral tunnel is then drilled using a best approximation of the graft's outer diameter. We recommend at least 7 mm diameter to minimize the risk of graft failure. Autologous hamstring grafts are generally between 6.8 and 8.6 mm in diameter. After reaming, the knee is flexed to 1.57 rad, the arthroscope placed through the anteromedial portal to confirm the femoral tunnel position, referencing the posterior wall and lateral cortex. For a quadrupled hamstring graft, the gracilis and semitendinosus tendons are then harvested in the standard fashion. The tendons are whip stitched, quadrupled and shaped to match the diameter of the prepared femoral tunnel. If the diameter of the patient's autologous hamstring graft is insufficient to fill the prepared femoral tunnel, the autograft may be supplemented with an allograft. The remainder of the reconstruction is performed according to surgeon preference.

RESULTS

The presence of retained hardware presents a challenge for surgeons treating patients with knee instability. In cruciate ligament reconstruction, distal femoral and proximal tibial implants hardware may confound tunnel placement, making removal of hardware necessary, unless techniques are adopted to allow for anatomic placement of the graft.

CONCLUSION

This report demonstrates how the femoral tunnel can be created using the anteromedial portal instead of a transtibial approach for reconstruction of the ACL.

Key words: Anteromedial drilling; Intramedullary femoral nail; Anterior cruciate ligament reconstruction; Retained hardware

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Core tip: The presence of retained hardware presents a challenge for surgeons treating patients with knee instability. In anterior cruciate ligament (ACL) reconstruction, intramedullary (IM) nails may confound tunnel placement, making removal of hardware necessary, unless techniques are adopted to allow for anatomic placement of the graft. We strongly recommend delaying the ACL graft harvest until creation of the femoral tunnel has been successful in these settings. Although unlikely when using anteromedial portal drilling, if the IM rod needs to be removed for anatomic graft placement but cannot be removed, the ACL reconstruction may have to be delayed until this issue is addressed.

Lacey M, Lamplot J, Walley KC, DeAngelis JP, Ramappa AJ. Technical note: Anterior cruciate ligament reconstruction in the

presence of an intramedullary femoral nail using anteromedial drilling. *World J Orthop* 2017; 8(5): 379-384 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/379.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.379>

INTRODUCTION

Anterior cruciate ligament (ACL) reconstruction offers patients with knee instability an excellent result following an isolated ACL rupture. However, because this injury often occurs in conjunction with lower extremity trauma, ACL reconstruction may follow surgical fixation of femur and/or tibia fractures^[1-5]. When the hardware is located in the distal femur or proximal tibia, it may obstruct the normal placement of the tibial or femoral tunnels. Preoperative planning and intraoperative fluoroscopy can facilitate anatomic placement of the femoral tunnel using the anteromedial portal (AMP) rather than a transtibial (TT) approach in order to avoid removal of retained hardware. It has been shown that the use of AMP may be superior to the TT drilling technique in the setting of acute ACL reconstruction based on physical examination and patient reported outcomes; however these reported improvements have neither reached a minimally clinically important difference nor have been reported in the setting of a femoral fixation hardware^[6]. In this technical note, we describe an approach to ACL reconstruction using autologous hamstring by drilling *via* the AMP in the presence of an intramedullary (IM) femoral nail.

MATERIALS AND METHODS

Surgical technique

Preoperative planning: Preoperative imaging including a computed tomography (CT) scan of the distal femur is reviewed to assess the proposed location of the femoral tunnel (Figure 1A and B). Preparations are made to remove all of the hardware (locking bolts and IM nail) by requesting proper instrumentation, personnel and imaging support. While this process confirms that drilling *via* the AMP should avoid the IM nail, we recommend preparing the femoral tunnel before harvesting the hamstring tendons and preparing the graft after femoral drilling has been successfully completed in cases where the size of the femoral tunnel is a concern. Finally, since the femoral tunnel is drilled before harvesting autologous hamstring graft, a cadaveric graft should be available in case the diameter of the harvested hamstrings is insufficient to fill the femoral tunnel.

Operative technique

A diagnostic arthroscopy is performed in the usual fashion. All intra-articular pathology, including meniscal tears and loose bodies, is addressed. The ACL remnant and lateral wall soft tissues are removed from the

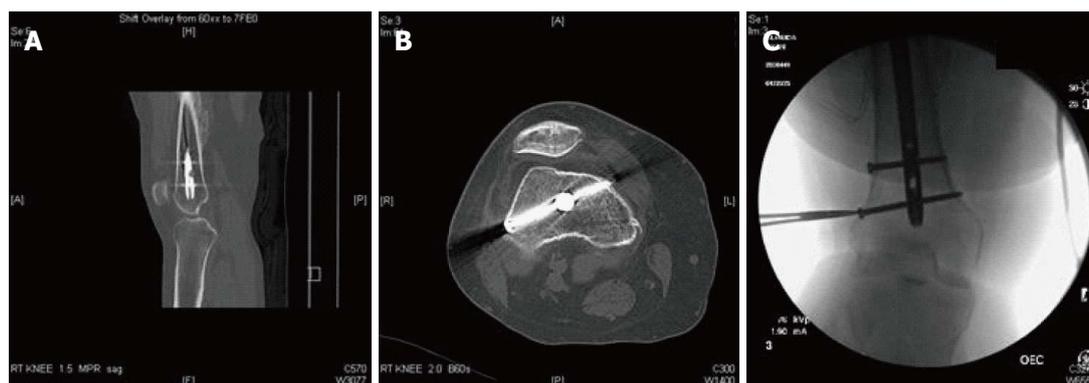


Figure 1 Preoperative imaging of femoral nail. A 380 mm × 11 mm Synthes trochanteric femoral nail was in place from prior and now well-healed femoral neck fracture. Two 5 mm diameter distal locking screws were used. The distal-most locking screw was placed in the distal femur approximately 20 mm superior to the trochlear notch and oriented from posterolateral to anteromedial, in close proximity to the posterolateral femoral cortex and planned femoral tunnel. A: Sagittal; B: Axial CT images; C: Intraoperative fluoroscopic radiograph. CT: Computed tomography.

intercondylar, to provide adequate visualization of the ACL footprint. Femoral tunnel placement is performed using a transportal ACL guide with desired offset (Arthrex, Naples, FL) and the knee flexed to 2.09 rad. The Beath pin is placed through the guide starting at the ACL's anatomic footprint using arthroscopic visualization and/or fluoroscopic guidance. If resistance is met while placing the Beath pin, the arthroscopy should be discontinued and the obstructing hardware should be removed under fluoroscopic guidance. When the Beath pin is successfully placed through the lateral femur, it is overdrilled with a 4.5 mm Endobutton drill (Smith and Nephew, Andover, MA). If the Endobutton drill is obstructed, the obstructing hardware should be removed under fluoroscopic guidance (Figure 1C). In this case, the obstruction is more likely during Endobutton drilling due to its larger diameter and increased rigidity compared to the Beath pin. The femoral tunnel is then drilled using a best approximation of the graft's outer diameter. We recommend at least 7 mm diameter to minimize the risk of graft failure^[7]. Autologous hamstring grafts are generally between 6.8 and 8.6 mm in diameter^[8]. After reaming, the knee is flexed to 1.57 rad, the arthroscope placed through the anteromedial portal to confirm the femoral tunnel position, referencing the posterior wall and lateral cortex.

For a quadrupled hamstring graft, the gracilis and semitendinosus tendons are then harvested in the standard fashion. The tendons are whip stitched, quadrupled and shaped to match the diameter of the prepared femoral tunnel. If the diameter of the patient's autologous hamstring graft is insufficient to fill the prepared femoral tunnel, the autograft may be supplemented with an allograft. The remainder of the reconstruction is performed according to surgeon preference (Figure 2).

RESULTS

We present a systematic approach to ACL reconstruction in the presence of distal femoral hardware using anteromedial portal femoral drilling followed by autologous

hamstring harvest. Like several techniques of femoral tunneling, AMP drilling may provide improved rotation stability, decreased anterior translation and greater coverage of ACL's anatomic footprint compared to TT techniques, but there is little evidence to support a clinical difference^[6,9-12]. To this end, clinical outcomes of TT and AMP drilling techniques for ACL reconstruction were directly appraised in a 2016 systematic literature review, however all outcomes suggesting superior result of AMP drilling technique failed to surpass a minimal clinically important difference despite notable improvements based on the physical exam and scoring system results^[6].

DISCUSSION

In a biomechanical setting, Steiner *et al.*^[13] argued that single-bundle ACL reconstructions may be improved if grafts are centered in their anatomical insertions by an independent drilling method vs grafts placed by a conventional TT drilling method. The proposed advantage of AMP femoral drilling is the creation of an independent tunnel, which may be oriented to avoid existing hardware. This benefit, depending on the location of the hardware as obstruction, may be unattainable. Ideally, this difficulty would be determined during preoperative planning, as outlined in (Table 1), using CT imaging.

In this case, one distal locking screw was located approximately 2 cm superior to the intercondylar notch, adjacent to posterior femoral cortex and oriented from posterolateral to anteromedial (Figure 1). This screw had to be removed after an unsuccessful attempt at overdrilling the Beath pin (Figure 3). AMP drilling may allow the surgeon to minimize the amount of hardware removed. Because TT femoral drilling techniques result in a more vertically-oriented femoral tunnel that is closer to the midline in the coronal plane. Removal of multiple screws or the entire IM nail may have been necessary.

We strongly recommend delaying the hamstring harvest until creation of the femoral tunnel has been

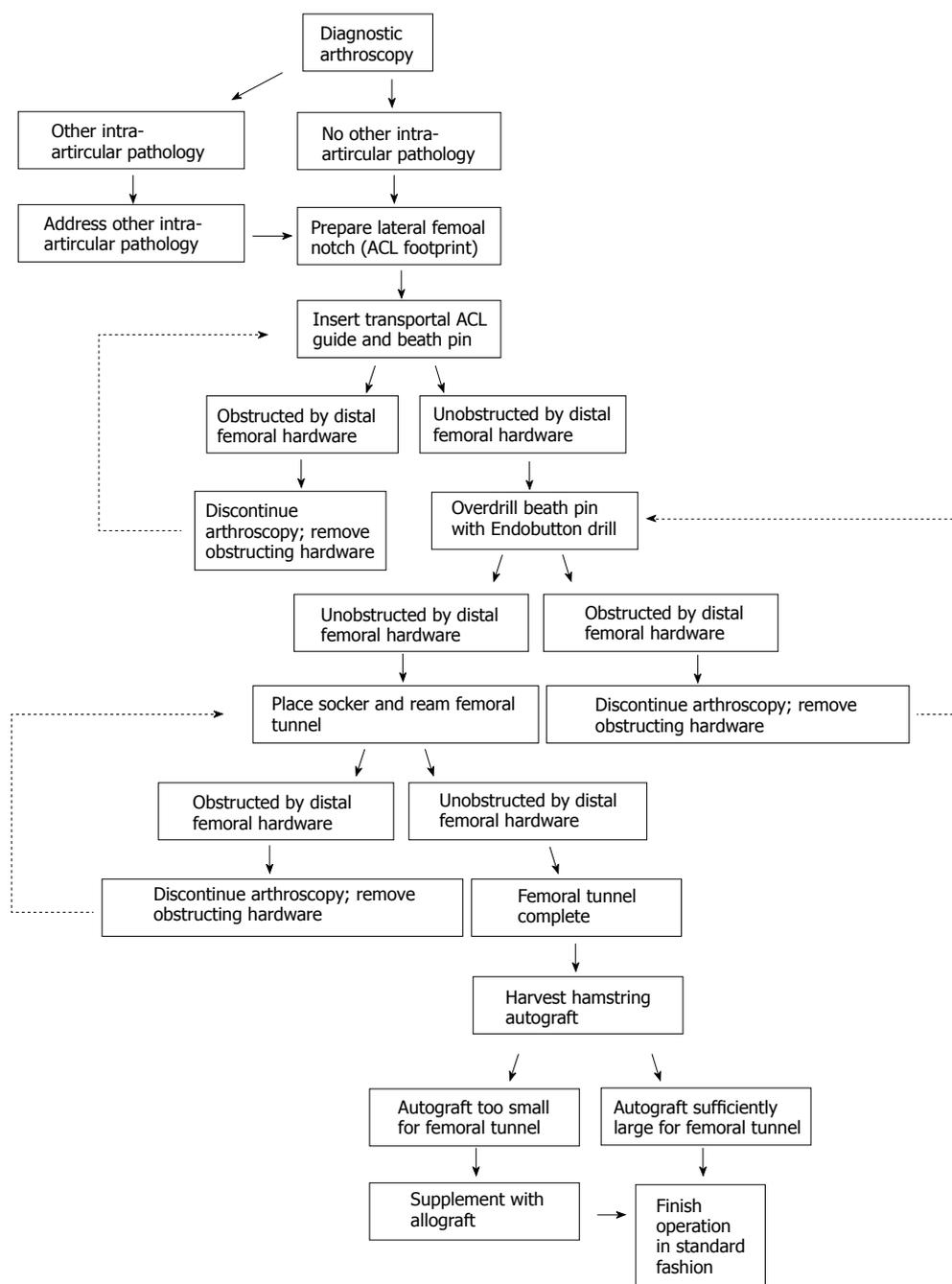


Figure 2 Algorithm for anterior cruciate ligament reconstruction with anteromedial portal femoral drilling and distal femoral hardware. Preoperative planning should guide femoral tunnel trajectory and size. Each step of femoral tunnel preparation may be performed under fluoroscopic guidance to avoid contact with existing hardware. Hardware obstruction is most likely to occur during Endobutton drilling. ACL: Anterior cruciate ligament.

Table 1 Preoperative planning for anterior cruciate ligament reconstruction with distal femoral hardware

Obtain and review radiographic studies including computed tomography scan of distal femur to determine location of hardware which may interfere with femoral tunnel placement Discuss feasibility and necessity of hardware removal, considering location of individual components and entire construct relative to planned femoral tunnel site, with primary surgeon or consulting trauma surgeon Arrange for proper instrumentation, fluoroscopy and personnel for removal of hardware Arrange for access to allograft in case hamstring autograft is insufficient in diameter

successful. Although unlikely when using AMP drilling, if the retained hardware needs to be removed but this

process is unsuccessful, the ACL reconstruction may have to be delayed until this issue is addressed.

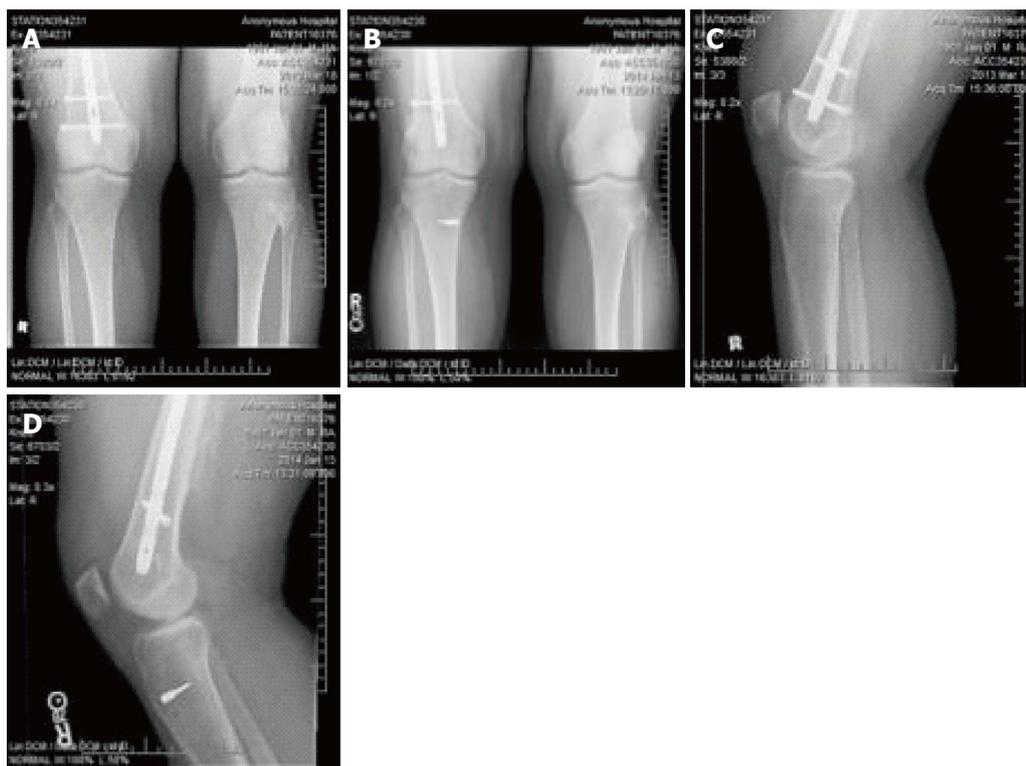


Figure 3 Preoperative and postoperative imaging of distal femoral hardware. Anterior cruciate ligament (ACL) reconstruction required removal of existing distal femoral locking screw located approximately 2 cm superior to the intercondylar notch adjacent to posterior femoral cortex and oriented from posterolateral to anteromedial. A: Preoperative Coronal X-ray; B: Postoperative Coronal X-ray; C: Preoperative Sagittal X-ray; D: Postoperative Sagittal X-ray.

COMMENTS

Background

Anterior cruciate ligament (ACL) reconstruction offers patients with knee instability an excellent result following an isolated ACL rupture. However, because this injury often occurs in conjunction with lower extremity trauma, ACL reconstruction may follow surgical fixation of femur and/or tibia fractures.

Research frontiers

When the hardware is located in the distal femur or proximal tibia, it may obstruct the normal placement of the tibial or femoral tunnels. Preoperative planning and intraoperative fluoroscopy can facilitate anatomic placement of the femoral tunnel using the anteromedial portal (AMP) rather than a transtibial (TT) approach in order to avoid removal of retained hardware.

Innovations and breakthroughs

It has been shown that the use of AMP was superior to the TT drilling technique in the setting of acute ACL reconstruction based on physical examination and patient reported outcomes, however this has not been reported in the setting of a femoral nail.

Applications

The authors strongly recommend delaying the hamstring harvest until creation of the femoral tunnel has been successful. Although unlikely when using AMP drilling, if the retained hardware needs to be removed but this process is unsuccessful, the ACL reconstruction may have to be delayed until this issue is addressed.

Peer-review

This is a short communication with a clear and useful message to other clinicians regarding the best approach to repair ACL injury whilst allowing correct positioning of other implant materials to repair local bone areas.

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Prospective Study

Functional outcome of tibial fracture with acute compartment syndrome and correlation to deep posterior compartment pressure

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Abstract**AIM**

To measure single baseline deep posterior compartment pressure in tibial fracture complicated by acute compartment syndrome (ACS) and to correlate it with functional outcome.

METHODS

Thirty-two tibial fractures with ACS were evaluated clinically and the deep posterior compartment pressure was measured. Urgent fasciotomy was needed in 30 patients. Definite surgical fixation was performed either primarily or once fasciotomy wound was healthy. The patients were followed up at 3 mo, 6 mo and one year. At one year, the functional outcome [lower extremity functional scale (LEFS)] and complications were assessed.

RESULTS

Three limbs were amputated. In remaining 29 patients, the average times for clinical and radiological union were 25.2 ± 10.9 wk (10 to 54 wk) and 23.8 ± 9.2 wk (12 to 52 wk) respectively. Nine patients had delayed union and 2 had nonunion who needed bone grafting to augment healing. Most common complaint at follow up was ankle stiffness (76%) that caused difficulty in walking,

running and squatting. Of 21 patients who had paralysis at diagnosis, 13 (62%) did not recover and additional five patients developed paralysis at follow-up. On LEFS evaluation, there were 14 patients (48.3%) with severe disability, 10 patients (34.5%) with moderate disability and 5 patients (17.2%) with minimal disability. The mean pressures in patients with minimal disability, moderate disability and severe disability were 37.8, 48.4 and 58.79 mmHg respectively ($P < 0.001$).

CONCLUSION

ACS in tibial fractures causes severe functional disability in majority of patients. These patients are prone for delayed union and nonunion; however, long term disability is mainly because of severe soft tissue contracture. Intra-compartmental pressure (ICP) correlates with functional disability; patients with relatively high ICP are prone for poor functional outcome.

Key words: Compartment syndrome; Leg; Tibial fracture; Deep posterior compartment; Intracompartmental pressure; Functional outcome

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Core tip: Anterior and deep posterior compartments are commonly involved in acute compartment syndrome (ACS) of leg after tibial fracture. Assessment of functional outcome in these patients and correlation with deep posterior compartment pressure has never been reported. This study revealed that ACS in tibial fractures causes severe functional disability and about 48% patients were severely disabled at one year. But this study did not find statistically significant relation between fracture union rate and deep compartment pressure value. The intra-compartmental pressure correlates with functional disability. Patients with relatively high pressure are prone for severe residual pain and poor functional outcome.

Goyal S, Naik MA, Tripathy SK, Rao SK. Functional outcome of tibial fracture with acute compartment syndrome and correlation to deep posterior compartment pressure. *World J Orthop* 2017; 8(5): 385-393 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/385.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.385>

INTRODUCTION

Acute compartment syndrome (ACS) is an orthopedic emergency which is commonly noticed in leg bones and forearm bones fracture^[1-7]. The reported incidence of ACS is around 3% to 10% following tibial fracture. Prompt diagnosis with early fasciotomy to decompress the tense compartment is crucial in preserving the life and limb of the patient in this grave situation^[1-7].

Although a constellation of clinical signs and sym-

ptoms are taken into consideration for diagnosis of ACS, these are poorly predictive of compartment syndrome and are often difficult to assess in obtunded patients^[2,5,6,8-11]. Measurement of the intra-compartmental pressure (ICP) offers an objective method to confirm the clinical suspicion of compartment syndrome. Various techniques for measurement of compartment syndrome are available in the literature and the most widely accepted threshold for surgical intervention is ICP within 30 mmHg of patient's diastolic blood pressure^[12-20]. Adequate and timely fasciotomy is expected to provide good functional and cosmetic results. Delay in decompression of ACS can result in permanent neurological impairment, disabling muscle contractures and delay in fracture union causing severe functional disability^[6,8,21-23]. The severity of disability and morbidity, even after fasciotomy in ACS, is dependent on several factors including ICP, time of fasciotomy, adequacy of fasciotomy and demographic profile of the patients^[21-23]. Although it is established that anterior and deep posterior compartments are commonly involved in ACS of leg, researchers have used only anterior compartment pressure for diagnosis. Considering the superficial location of anterior compartment, a raised pressure within this compartment may be revealed clinically easily. This may not be true for deep posterior compartment and hence, Matsen *et al*^[24] have warned the orthopaedic surgeons that isolated raised deep posterior compartment pressure may be missed in few patients.

This prospective study was designed to measure at least a single baseline deep posterior compartment pressure in patients of tibial fracture complicated by ACS and to correlate the raised pressures to the functional outcome.

MATERIALS AND METHODS

Patient recruitment

Between May 2010 and October 2012, a prospective study was conducted to evaluate the functional outcome of tibial fractures complicated with ACS. The study also aimed at correlating the outcome with initial deep posterior compartment pressure. Patients of > 18 years old with tibial fracture and clinical suspicion of ACS were recruited in this study after getting their written informed consent. Patients with associated ipsilateral limb injury, vascular injury (Doppler confirmed absent blood flow), poor general status (GCS \leq 13, patients in shock (SBP < 90 mmHg or MAP < 70 mmHg), pathological fractures or pre-existing disease in the limb (prior surgery, neuromuscular disorders; polio, *etc.*) were excluded. Institutional ethical committee permission was obtained before recruiting patient in this study.

Patient evaluation

All patients were evaluated initially by an orthopedic surgeon. Demographic profiles and injury mechanisms were mentioned in a predesigned proforma. Appropriate



Figure 1 Clinical photograph and radiograph of a patient with right proximal tibial fracture and compartment syndrome.

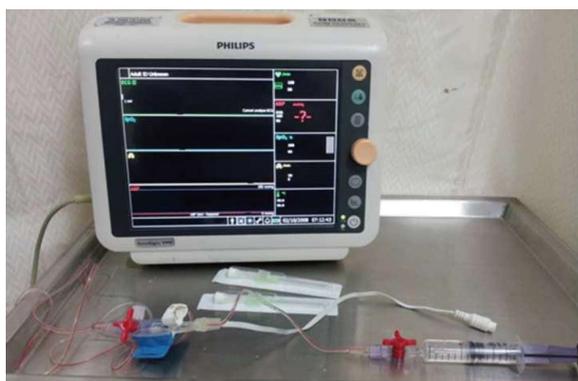


Figure 2 Equipment used for compartment pressure measurement; 18G iv cannula, saline filled line with electronic transducer and Philips VM8 monitor.

radiographs were taken to assess the fracture pattern and classified as per OTA classification and Schatzker classification for proximal tibial fractures. Doppler was done to confirm that there was no vascular injury in these patients.

The patients were evaluated clinically for signs and symptoms of ACS by two attending orthopaedic surgeons. If there were any signs or symptoms of ACS, then the deep posterior compartment pressure of the injured leg was measured and documented. The diagnosis of ACS was established if there were at least 3 clinical signs/symptoms (Figure 1), a differential pressure (ΔP) of less than 30 mmHg between the diastolic and compartment pressures (McQueen and Court-Brown 1996) or a combination of both clinical and pressure indications. Fasciotomy was performed in patients diagnosed with ACS.

Technique for measuring the compartment pressure

The pressure in the limb was measured in the deep posterior compartment of leg using modified Whiteside's technique. The patient was positioned supine and limbs flat at rest on the bed. All measurements were made within 5 cm of the level of the fracture^[25]. Under strict aseptic conditions a straight cannulated 18-gauge intravenous needle was inserted at an angle of approximately 45° relative to the skin surface skirting the posterior border of tibia to reach the posterior compartment. An arterial-

line transducer (PHILIPS V-08) connected to a monitor was placed at the same level as the needle, saline flushed through the system to remove air, and the monitor was kept at zero. Half milliliter of normal saline was injected to allow the compartment to equilibrate with interstitial fluids. Measurement was recorded from the monitor after values were stabilized, usually within 20 to 30 s (Figure 2).

Clinical and functional outcome evaluation

The patients were followed up regularly at an interval of two weeks till the fasciotomy wound was healed. After that they were followed up at 3 mo, 6 mo and one year. Time of clinical (no pain at fracture site with full weight bearing) union and radiological union (bridging trabeculae at the fracture site) and complications encountered during post-operative period were recorded in the predesigned proforma. Fractures which did not unite till 6 mo' time were considered as delayed union and, if there was no progressive radiological evidence of union for further three consecutive months, it was considered as nonunion (> 9 mo since the time of injury). At the end of one year, the patients were examined particularly for any pain, toe deformity, ankle stiffness, residual paralysis of leg muscles, paraesthesia and limb contracture. Functional limitation of the patient to sit with 90° knee flexion, sitting cross-leg, squatting, walking, running and climbing stairs was evaluated on a Likert-Scale. Overall functional assessment of the limb was done using lower extremity functional scale (LEFS). LEFS score was calculated for each patient using questionnaire and percentage of disability calculated. The mean score was 51.03 (out of 80) corresponding to 63.78% of maximal function. The patients were categorized into five groups of disability based on their percentage of maximal function ($LEFS/80 \times 100$): Bedbound - 0% to 20% score, crippled - 20% to 40% score, severe disability - 40% to 60% score, moderate disability - 60% to 80% score, minimal disability - 80% to 100% score).

Statistical analysis

Data was analyzed using commercial statistical package SPSS (Version 16, SPSS Inc, Chicago, IL) for MS-Windows. The data summary was presented in a descriptive fashion as mean, standard deviation, skewness and Kurtosis, etc. to describe the clinical characteristics and functional and



Figure 3 Deep posterior compartment pressure of 67 mmHg in the same patient (clinical photograph in Figure 1).

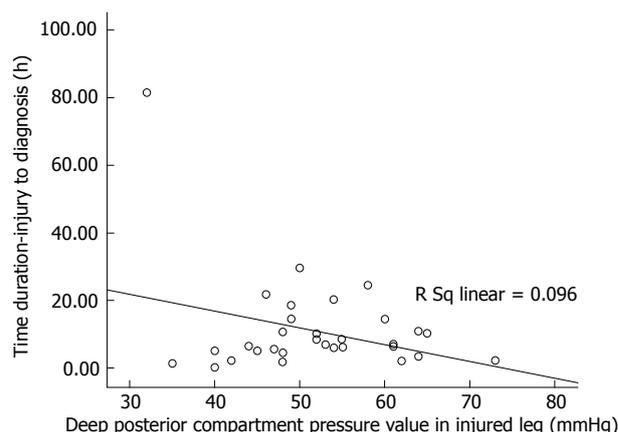


Figure 4 Correlation of time since injury to pressure values.

radiological outcome. The relationship of the radiological union and functional outcome were analyzed and related to the fracture pattern, delay in fasciotomy, pressure threshold and clinical diagnosis of ACS.

Differences between variables were analysed using Pearson's χ^2 test. The strength of association was carried out using Karl Pearson's or Spearman's rank correlation coefficient. Various comparisons were made either using independent *t*-test or analysis of variance (ANOVA). Difference was considered significant with a *P* value of < 0.05. The statistical review of this study was performed by a biomedical statistician before submission.

RESULTS

Six hundred and three patients with tibial fractures were treated during this period. Of which, 48 patients with ACS met the inclusion criteria; 6 did not consent to participate in the study and data of 10 patients were incomplete. Remaining 32 patients were evaluated to assess functional outcome of ACS of leg. The mean age of the patients was 40.3 years (range, 25 to 64 years). There were 30 males and 2 females. Only one patient presented to us after 72 h of injury and remaining patients presented to our service after an average delay of 9.0 h (median 6.75 h, range 0.25 to 29.5 h). There were 16 diaphyseal and 16 proximal tibial fractures in this study. Among proximal tibial fracture patients, 15 had tibial plateau fracture (10 Schatzker type VI, 3 Schatzker type V, One type IV and one type I) and only one had extra-articular fracture. There were six open fractures and all were Gustilo Anderson type I injury.

Twenty-four patients (75%) had tense palpable swelling and 30 (93.75%) had pain on passive stretch. Paraesthesia and paralysis in the affected limb was noticed in 20 (62.5%) and 21 (65.63%) patients respectively. Three patients (9.38%) had pulselessness and only one patient (3.13%) had pallor in the leg. Clinical diagnosis (3 signs/symptoms) of ACS was established in 20 patients.

The mean ICP of deep posterior compartment of leg

was 51.84 mmHg (range 32 to 73 mmHg). All patients had absolute ICP above 30 mmHg, and 26 (81%) patients had ICP above 45 mmHg (Figure 3). Mean differential pressure was (ΔP) 23.97 + 13.389; 25 patients (78.1%) had ΔP above 20 mmHg and 15 patients (46.9%) had ΔP above 30 mmHg. Twenty patients had at least 3 clinical signs/symptoms and diagnosed clinically. They all underwent fasciotomy. Twelve patients who did not fit the clinical criteria for ACS had ΔP within 30 mmHg of diastolic pressure, but only 10 patients underwent fasciotomy; among the other two patients, one patient had > 48 h delay and the other showed clinical improvement; hence fasciotomy was avoided in both patients. Both single and double incision fasciotomy was used in equal frequency (15 each).

In our set of patients, there was an asymmetrical distribution for the time delay; therefore we considered median value (5.00 h, mean 7.91 h) for analysis. Seven (21.86%) fractures were definitely fixed at the time of fasciotomy and remaining patients were temporarily stabilized using external fixator (12, 37.5%) or POP (13, 40.6%). Ultimately, three patients had to undergo amputation as a result of complication of ACS and remaining patients were treated with IM nailing (14, 48.3%), plate osteo-synthesis (13, 44.8%) or external fixator (2, 6.9%) as a method of fracture fixation.

Analysis of variables affecting pressure values

The effect of age on compartment pressure was analyzed by dividing the patients into two groups (≥ 35 years and < 35 years). Patients < 35 years old had mean pressure of 52.33 mmHg compared to 51.25 mmHg in older age group (*P* = 0.777, independent sample *t*-test). The pressure values were also compared between the two age groups and it was found that older age patients were more within the diagnostic threshold for ACS, though again no statistical difference was seen. Gender, mechanism of injury, open/closed fracture and the site (diaphyseal or proximal tibia) of injury had no effect on pressure values (*P* > 0.05). We found that ICP was decreasing with the progression of time (Figure 4),



Figure 5 Residual right side toe deformity and ankle stiffness in a patient (shown in Figure 1) at follow up, X-ray of fracture union of this patient.

Table 1 Complications in tibial fracture patients with acute compartment syndrome (*n* = 29)

Complication	No. of patients (%)
Amputation (<i>n</i> = 32)	3 (9.4)
Infection (fasciotomy wound)	5 (17.2)
Toe deformities (e.g., clawing)	8 (27.6)
Ankle stiffness (affecting function)	19 (76.0)
Residual paralysis (EHL/FHL/ankle DF/ankle PF)	18 (62.1)
Paraesthesia or nerve dysfunction	3 (10.3)
Limb contracture	5 (17.2)
Muscle herniation (fasciotomy site)	2 (6.9)
Pain (apart from fracture site)	15 (51.7)
Others (DVT, limb edema)	9 (31.0)

DVT: Deep vein thrombosis.

contrary to the expectation, with pearson co-efficient -0.310; but it was not statistically significant ($P = 0.084$).

Functional outcome and complications

For follow up and outcome assessment, 3 patients who had to undergo amputation were not considered. Average follow up period was 93.1 wk (range 54 to 123 wk). Average time for clinical union was 25.2 ± 10.9 wk (ranging from 10 to 54 wk) and radiological union was 23.8 ± 9.2 wk (ranging 12 to 52 wk) (Figure 5). Nine patients had delayed union and 2 had nonunion who needed bone grafting to augment healing. Most common complaint at follow up was ankle stiffness (76%), which caused difficulty in walking, running and/or squatting (Tables 1 and 2, Figure 5). Out of 21 patients who had paralysis at diagnosis, 13 (62%) did not recover. Additional 5 patients developed paralysis at follow up even after fasciotomy (Table 1).

On LEFS evaluation, there were 14 patients (48.3%) with severe disability, 10 patients (34.5%) with moderate disability and 5 patients (17.2%) with minimal disability (Table 2).

Analysis of variables affecting functional outcome

Six out of 13 (46.2%) proximal tibial fractured patients and 5 out of 16 (31.2%) diaphyseal fractured patients had delayed union or nonunion, statistically no significant

Table 2 Disability in tibial fracture patients with acute compartment syndrome (*n* = 29)

Function (<i>n</i> = 29)	No. of patients (%)	
	(None/mild)	(Moderate/severe)
Sitting 90°	27 (93.1)	2 (6.9)
Cross legged sitting	22 (75.9)	7 (24.1)
Squatting	17 (58.6)	12 (41.4)
Walking	24 (84.8)	5 (17.2)
Running	13 (48.8)	16 (55.2)
Stair climbing	19 (65.5)	10 (34.5)

difference was observed between the type of fracture ($P = 0.706$). Eight patients with clinical ACS (3 signs/symptoms) and 3 patients without clinical ACS had delayed union or nonunion. Although it appears that patients diagnosed with clinical ACS had propensity to undergo delayed union or nonunion, there was no statistical difference ($P = 0.332$). The mean ICP in patients with normal union was 54.36 mmHg and it was 49.48 mmHg in patients with delayed union or nonunion ($P = 0.214$). So there was no effect of ICP on fracture union. Relatively high ICP was also noted in patients with residual disability and complications, but apart from persistent pain ($P = 0.019$), none of other group had statistically significant difference in pressures (Table 3).

Functional scores were expected to be poor in patients with higher pressure values. The mean LEFS score in our patients was 51 (63.75%) which corresponded to moderate disability. We found pressure values to be higher in patients with lower LEFS score, also there was a negative correlation between the same. Significant difference in pressure was found in LEFS groups (Figure 6). The mean pressures in patients with minimal disability ($n = 5$), moderate disability ($n = 10$) and severe disability ($n = 13$) were 37.8, 48.4 and 58.79 mmHg respectively (one way ANOVA, $P < 0.001$).

Thirty patients (30/32) had fasciotomy to decompress the compartment and 3 of these eventually ended up with amputation. We considered delay of more than 6 h to be significant and evaluated the outcome of patients. The average delay in fasciotomy was 9.8 h in patients who underwent amputation and 7.7 h in

Table 3 Mean pressure values (mmHg) in patients with complications (n = 29)

	Pain	Ankle/toe deformity	Residual paralysis	Running difficulty	Squatting difficulty
Yes	55.4 (15)	51.9 (18)	53.7 (18)	52.2 (16)	52.2 (12)
No	47.5 (14)	51.1 (11)	48.2 (11)	50.8 (13)	51.1 (17)
P value	0.019	0.827	0.125	0.753	0.702

Deep posterior compartment pressure value in injured leg (mmHg)

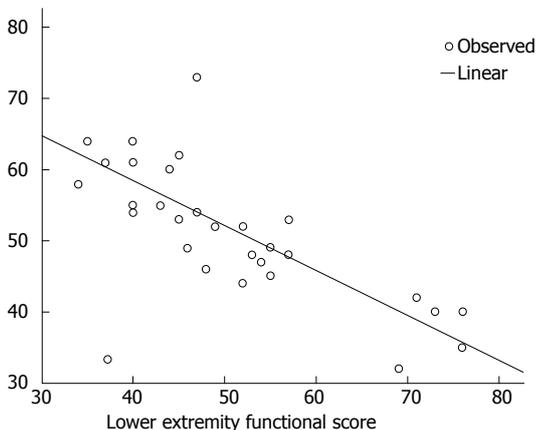


Figure 6 Negative correlation plot of lower extremity functional scale with rising pressure (Pearson's R = -0.814, P < 0.001).

patients who didn't end up with amputation; but, there was no statistically significant difference in these two groups (independent *t*-test, *P* = 0.564). There were 14 patients who were late for > 6 h in fasciotomy; 4 had good functional outcome (LEFS score > 60%) and 10 had poor outcome (LEFS score < 60% or amputation). Among remaining 16 patients who had fasciotomy done within 6 h, 9 patients had good functional outcome and 7 had poor outcome. Although it appears that delay in fasciotomy for more than 6 h effects the eventual functional outcome, it was not statistically significant in this study (Pearson's $\chi^2 = 2.330$, *P* = 0.159). Both delay in fasciotomy and total time since injury showed negative relationship with LEFS with a slightly better correlation of time from injury to fasciotomy, but it was not statistically significant (Figure 7). No difference was found in single incision and double incision fasciotomy on LEFS outcome (*P* = 0.856).

DISCUSSION

ACS in tibial fracture is a serious complication and absence of prompt intervention can cause considerable morbidity or, even mortality^[1-7]. Clinical judgment is based on subjective appraisal of the limb condition and there is a risk of missing the diagnosis or getting late. ICP of the anterior compartment has helped the surgeon in establishing the diagnosis. However, some reports have stressed on measurement of deep posterior compartment pressure as this compartment get involve equally or may involve in isolation^[25]. In this study, we have evaluated the functional disability of the patient objectively and correlated it with

deep posterior compartment pressure.

There are few limitations in this study. The number of patients was small and there was no control group. The technique of compartment measurement was not validated with a standard technique. Only single baseline deep compartment pressure was measured and it was correlated with functional outcome. Despite these limitations, this study has strength as it was based on prospective evaluation of patient and the measuring technique was reliable^[26,27]. Several authors have reported that continuous pressure monitoring does not influence outcome in tibial fracture complicated with ACS^[8,28-30]. Therefore, single deep posterior compartment pressure measurement was used as an adjunct to diagnosis and the effects of elevated pressure was evaluated. For clinical union, an ability to bear full weight without any pain at the fracture site was considered, however the residual effect of ACS may have some influence on the decision. Because of contracture some patients may have pain on weight bearing and that might have caused a longer clinical union (25 wk) time than the radiological union (24 wk).

Young males with high energy injuries of tibial shaft are prone for development of ACS^[1,2,5]. But, we did not observe any statistically significant difference between proximal tibia and tibial shaft fractures. Also, patients < 35 years and older did not have any effect on ACS occurrence, this was because the mean age of our patients was 40 years and there was equal incidence of diaphyseal and proximal tibial fractures; majority (41%) of proximal tibial fractures were high impact injuries with severe comminution (OTA 41C1-3) and open fractures.

Systemic hypotension, vascular injuries and patients with decreased alertness pose difficulty in diagnosing compartment syndrome and interpretation of elevated pressure^[6,31], therefore these patients were excluded. Diagnosis of ACS and the decision for fasciotomy was based on clinical judgement without any objective criteria. Ulmer proposed presence of 3 or more clinical symptoms to diagnose ACS^[9]. Applying only these criteria, we would have diagnosed only 20 patients with diagnosis of compartment syndrome and missing the remaining patients. The patients usually have different threshold of pain, and clinical symptoms are also variable, thus we used pressure measurement to assess their risk of compartment syndrome. However, absolute ICP was not found to be diagnostic of ACS when considered alone. We found that applying the threshold of pressure difference from diastolic blood pressure (DBP) within 30 mmHg identified ACS in more than 75% cases. Using absolute ICP of 30 mmHg may result in overtreatment. Delta P within 20 mmHg of DBP would have resulted in

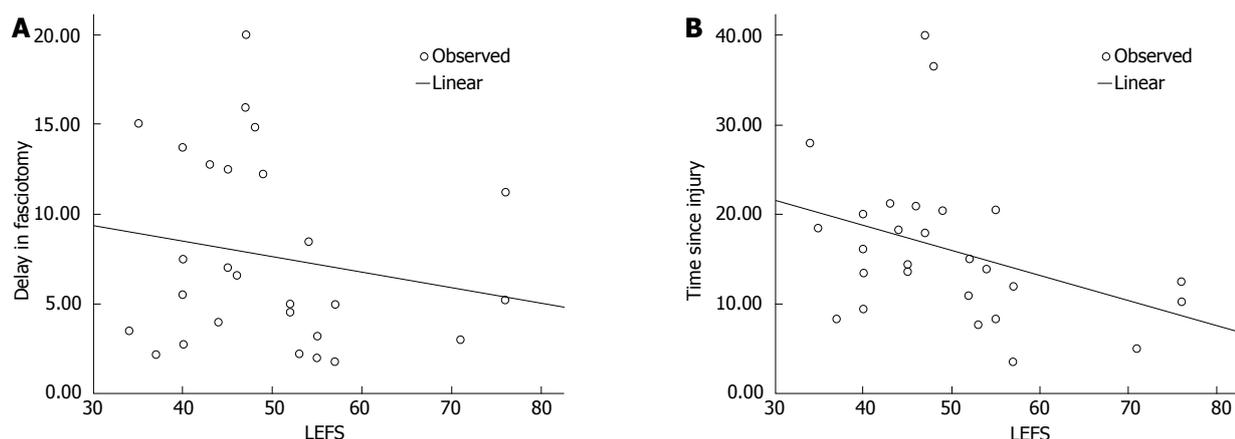


Figure 7 Correlation of (A) fasciotomy delay (Pearson's $R = -0.182$, $P = 0.928$) and (B) time since injury (Pearson's $R = -0.369$, $P = 1.984$) with lower extremity functional scale. LEFS: Lower extremity functional score.

missing 25%-70% patients of ACS. The duration of onset of compartment syndrome was not possible to predict from the time since injury in this study and we found decrease in compartmental pressure with progression of time. However, decreased LEFS score was found with the progression of time.

The long term functional outcome of ACS in tibial fractures can be evaluated on two broad aspects; first, the impact on fracture-healing and second about the impact on soft tissue leading to contracture. Increase in ICP compromises the perfusion of neuro-muscular tissues causing ischemia and cell death. Initial traumatic micro and macro muscle fibre damage, loss of haematoma from the fracture site because of fasciotomy, secondary neutrophilic microvascular dysfunction and reperfusion injury also contributes to the poor fracture healing, muscular contracture and persistent neuralgic pain^[23,31,32]. We noticed 38% delayed or non-unions with a mean union time of 24 wk. A recent systematic review by Reverte *et al.*^[23], reported the mean time of tibial fracture union in ACS to be 31.7 wk and the incidence of delayed union and nonunion was 25% (in patients > 18 years). Other available literature reported the incidence of delayed union and nonunion to be 55%^[22,23]. Our finding on fracture union is almost comparable to the available literature. Three factors such as fracture site, mode of diagnosis and ICP value were analysed to evaluate their effects on fracture healing. Although it seemed that proximal tibial fracture and clinically diagnosed ACS patients were at risk of delayed union and nonunion, it was statistically insignificant.

We found that the major long term functional disability of compartment syndrome is mainly because of soft tissue contracture. Ankle stiffness (76%) and toe deformities (62%) because of soft tissue contractures were the most common complications. Residual persistent pain was also seen in 55% of pain. The cause of pain in these patients may be multifactorial. Soft tissue contracture causes restriction of knee, ankle and toes movement and elicits pain on stretching or weight bearing. Ischemic damage of

nerve fibre inducing neuralgic pain may also be contributory. Although a majority of patients were able to sit (with knee bending 90 degree and cross leg), climb stair and walk, there was difficulty in running and squatting. About 55% of patients were unable to run and 42% patients were unable to squat. A statistically significant correlation between persistent pain and raised ICP was noted, however none of the other sequelae/complications of ACS showed significant association.

The functional disability in ACS of leg has never been evaluated objectively. We found a severe functional disability in majority of patients because of residual disability as evaluated on LEFS. Fifty percent of patients had severe disability and 30% had moderate disability. More than 55% patients had LEFS score of less than 60% maximal functional capacity. We found lower LEFS scores had significant correlation with higher ICP ($R = 0.814$, $P < 0.001$). Outcome of ACS is most importantly determined by timing and adequate decompression of all the compartments. Both single and double incision fasciotomy have been proved to be effective. In our study also we did not find any difference in outcome of either surgical technique ($P > 0.05$). The average delay in fasciotomy in our study was 7.91 h which is higher than critical delay of 6 h and, this delay correlated with poor outcome scores; although not significantly ($P > 0.05$). We also noted that despite fasciotomy more than 50% patients still had poor outcome. This could be because of several reasons like, 40% of these had delay of more than 6 h, 3 patients ended up with amputation after fasciotomy. We also noted that the average time to diagnosis of ACS from the time of injury was about 9 h which could have contributed to significant tissue damage by the time ACS was diagnosed.

To conclude, ACS in tibial fractures leads to severe functional disability in majority of patients. These patients are prone for delayed union and nonunion; however, long term disability is mainly because of severe soft tissue contracture. ICP correlates with functional disability; patients with relatively high ICP are prone for poor functional outcome.

COMMENTS

Background

The intracompartmental pressure affects the union and functional capability of patients in tibial fracture complicated with acute compartment syndrome (ACS).

Research frontiers

Tibial fractures with compartment syndrome are prone for delayed union and nonunion. These patients usually suffer from functional disabilities because of soft tissue contracture, neuralgic pain and residual paralysis. There is no literature about correlation of deep posterior compartment pressure of leg and functional outcome in tibial fracture with ACS. An objective assessment of the disabilities in such patients is lacking.

Innovations and breakthroughs

The deep posterior compartment pressure of the leg was measured in patients with clinically diagnosed compartment syndrome after a tibial fracture using modified Whiteside's technique. The union rate, union time and functional disabilities in these patients were correlated to the pressure value. The average times for clinical and radiological union were 25 wk (10 to 54 wk) and 24 wk (12 to 52 wk) respectively. Thirty-eight percent patients had delayed union or nonunion. Most common complaint at follow up was ankle stiffness (76%) that caused difficulty in walking, running and squatting. On lower extremity functional scale evaluation, there were 48% patients with severe disability, 35% with moderate disability and 17% with minimal disability. The mean pressures in patients with minimal disability, moderate disability and severe disability were 37.8, 48.4 and 58.79 mmHg respectively.

Applications

Compartment syndrome in tibial fractures leads to severe functional disability in majority of patients. These patients are prone for delayed union and nonunion; however, long term disability is mainly because of severe soft tissue contracture. The deep posterior compartment pressure correlates with functional disability; patients with relatively high pressure are prone for poor functional outcome.

Peer-review

The authors evaluated patients with tibia fracture and compartment syndrome. The authors found the correlation between compartment pressure and the functional disability. The article is well-written.

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Randomized Clinical Trial

Frozen shoulder - A prospective randomized clinical trial

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Institutional review board statement: The ethics committee of All India Institute of Medical Sciences, New Delhi, approved the study.

Informed consent statement: All the patients were informed about the study before including them in the study. The informed consent was explained to them in their native language and a written consent was obtained as advised by the ethic committee of our institute. The identity of any of the patients was not disclosed.

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Abstract

AIM

To compare the results of arthroscopic capsular release with intra-articular steroid injections in patients of frozen shoulder.

METHODS

Fifty-six patients with frozen shoulder were randomised to one of two treatment groups: Group 1, complete 360 degree arthroscopic capsular release and group 2, intra-articular corticosteroid injection (40 mg methyl prednisolone acetate). Both groups were put on active and passive range of motion exercises following the intervention. The outcome parameters were visual analogue scale (VAS) score for pain, range of motion and Constant score which were measured at baseline, 4, 8, 12, 16 and 20 wk after intervention.

RESULTS

All the parameters improved in both the groups. The mean VAS score improved significantly more in the group 1 as compared to group 2 at 8 wk. This greater improvement was maintained at 20 wk with *P* value of 0.007 at 8 wk, 0.006 at 12 wk, 0.006 at 16 wk and 0.019 at 20 wk. The Constant score showed a more significant improvement in group 1 compared to group 2 at 4 wk, which was again maintained at 20 wk with *P* value of 0.01 at 4, 8, 12 and 16 wk. The gain in abduction movement was statistically significantly more in arthroscopy group with *P* value of 0.001 at 4, 8, 12, 16 wk and 0.005 at 20 wk. The gain in external rotation was statistically significantly more in arthroscopy group with *P* value of 0.007 at 4 wk, 0.001 at 8, 12, and 16 wk and 0.003 at 20 wk. There was no statistically significant difference in

extension and internal rotation between the two groups at any time.

CONCLUSION

Arthroscopic capsular release provides subjective and objective improvement earlier than intra-articular steroid injection.

Key words: Adhesive capsulitis; Frozen shoulder; Capsular release; Corticosteroid; Idiopathic stiff shoulder; Intra articular injection; Steroid injection; Arthroscopic arthrolysis; Constant score

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Core tip: The treatment of frozen shoulder is selected depending on the preference of the treating physician, since there are no guidelines or protocols. The physicians, physiotherapists, occupational therapists and orthopedicians who are not trained in shoulder arthroscopy often select non-surgical methods. On the other hand, shoulder arthroscopists prefer arthroscopic arthrolysis. We conducted a randomised clinical trial to compare the results of arthroscopic arthrolysis and intra-articular steroid injection in frozen shoulder. Both modalities resulted in significant improvement in pain, range of motion and Constant score. However the improvement in surgery group preceded those in injection group by 4-8 wk.

Mukherjee RN, Pandey RM, Nag HL, Mittal R. Frozen shoulder - A prospective randomized clinical trial. *World J Orthop* 2017; 8(5): 394-399 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/394.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.394>

INTRODUCTION

Frozen shoulder also termed as adhesive capsulitis of shoulder, is a common cause of shoulder pain and global stiffness of the glenohumeral joint. It is estimated to affect 2%-5% of the population^[1]. Frozen shoulder has been described as a self-limiting condition, lasting on average 2-3 years^[2-4]. Some studies, however, have reported that 20%-50% of the sufferers continue to have pain and restricted movement beyond 3 years^[5,6]. Though it is a self-limiting condition, patients find it impractical and difficult to wait for such a long period as it interferes with the activities of daily life.

A variety of treatment strategies for adhesive capsulitis have been developed to alleviate pain and enhance range of motion (ROM) of the shoulder. The commonest modalities to achieve this are physiotherapy^[7] and corticosteroid injections^[8] either through local injection or systemically. Other options include manipulation under general anaesthesia^[9-11], scalene block, arthrographic capsular distension^[12-14] and surgical intervention (arthroscopic and open arthrolysis).

Arthroscopic capsular release for the treatment of

adhesive capsulitis has gained popularity for its high safety and efficacy reported in literature^[15-18]. Our study aims to compare the results of arthroscopic capsular release with those of intra-articular corticosteroid injection^[19-21] which seems to be the most commonly prescribed treatment for adhesive capsulitis of shoulder at present, and ascertain whether arthroscopic capsular release can provide a speedier recovery compared to the more commonly prescribed intra-articular steroid injections. Our null hypothesis was that the two modalities would provide equal outcomes.

MATERIALS AND METHODS

Patient selection

The criteria to include patients in this study were idiopathic stiffness of the shoulder with global restriction of shoulder movements for at least six months and normal findings on plain radiograph. Global restrictions would imply decrease in active and passive movements in all directions. Patients with prior history of trauma, surgery or injections to the shoulder were excluded from the study. Patients who had received any form of treatment to the affected shoulder other than physiotherapy were also excluded.

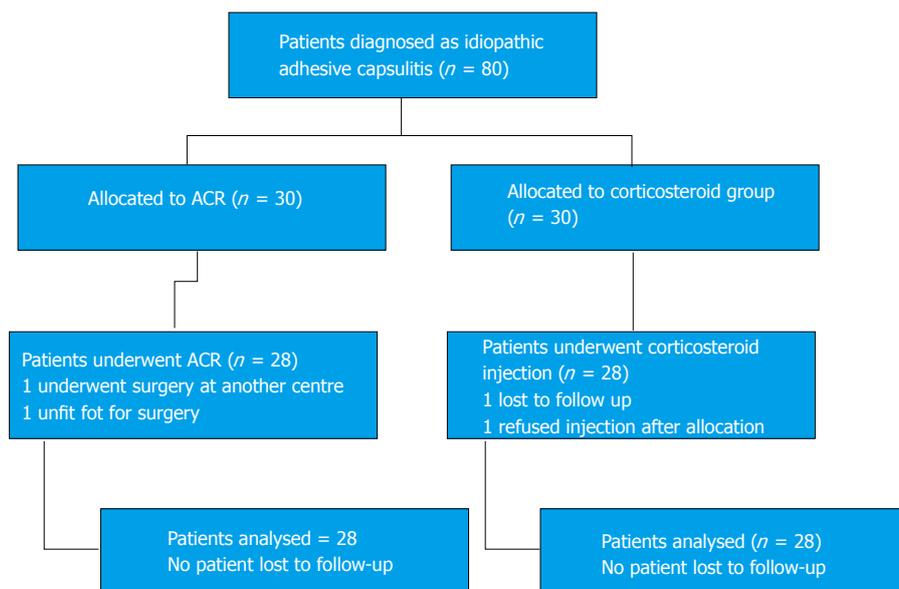
Patients

Sample size was calculated using Master 2.0 software. All the patients were explained about the study in their native language and a written consent was obtained before enrolment in the study. Sixty such patients were randomly allocated to one of the two study groups using computer tables. The patient inclusion and dropouts from the study groups is described in the consort diagram (Figure 1). In group 1, complete 360-degree arthroscopic capsular release of the affected shoulder was performed under general anaesthesia in lateral position in 28 patients. These patients underwent pre-operative magnetic resonance imaging (MRI) examination to rule out any intra-articular pathology. Arthroscopic capsular release involved excising the tissues in the rotator interval up to the coracoids process, division of the superior, middle and inferior glenohumeral ligaments and release of the anterior, posterior, superior and inferior capsule of the shoulder joint. Subacromial bursa was not viewed. In group 2, single dose of 40 mg methylprednisolone acetate along with 3 mL of 2% lignocaine was injected into the affected shoulder without image guidance through the posterior approach in 28 patients. The intervention in the both study groups was followed by active and passive range of motion exercises. Both groups of patients were given a combination of a NSAID with tramadol as analgesics for pain control.

Outcome measures

The clinical outcome measures used in the study were: Visual analogue scale (VAS) score for pain (0-10), range of motion and Constant score (0-100). The parameters were initially recorded before the intervention (baseline) and then after the intervention at 4, 8, 12, 16 and 20

Figure 1 Consort diagram.



wk. The outcome parameters in both the study groups were compared with each other. Any complications encountered in the study were also noted.

Arthroscopic findings

Twenty-seven out of the 28 patients who underwent arthroscopic capsular release showed fibrous contracture of the rotator interval, suggesting that it is the most important pathology associated with the development of adhesive capsulitis. Synovitis was present in all the patients. Twenty-four patients had global synovitis involving the rotator interval, the joint capsule, subscapularis tendon and the rotator cuff and 4 patients had synovitis limited only to the rotator interval. Apart from the above findings, which are suggestive of adhesive capsulitis, 4 patients had partial tear of the rotator cuff on the articular side and 1 patient had a type 2 superior labrum anterior to posterior (SLAP) lesion, which were not diagnosed preoperatively. These lesions were not detected on pre-operative MRI also. The partial cuff tears were debrided and SLAP was left as such. These 4 patients were not excluded from the study because the intra-articular lesions were not symptomatic, but were incidental findings. The arthroscopic group did not experience any post-operative infection or neurovascular damage. There was one case of articular cartilage scuffing of glenoid and one case of the humeral head.

Statistical analysis

Statistical analysis was carried out using SPSS software version 20. Data was presented as number (%) or mean ± SD as appropriate. The baseline characteristics were compared using χ^2 test (categorical variables) and Student’s *t* test (continuous variables). The outcome parameters such as VAS, range of motion and Constant score measures at baseline, 4, 8, 12, 16 and 20 wk were compared between the two groups using Student’s *t* test. The change in outcome parameters within each group was detected using a general linear model. *P* value of <

Table 1 Changes in visual analogue scale scores in both groups

Duration	VAS score in group (mean ± SD)		P value
	ACR	Corticosteroid	
Baseline	7.1 ± 1.8	7.1 ± 1.8	1
4 wk	4.4 ± 1.6	5.1 ± 1.7	0.101
8 wk	3.6 ± 1.7	4.8 ± 1.7	0.007
12 wk	3.0 ± 1.6	4.2 ± 1.6	0.006
16 wk	2.5 ± 1.8	3.7 ± 1.5	0.006
20 wk	2.0 ± 1.7	3.2 ± 1.5	0.019

VAS: Visual analogue scale.

0.05 was considered statistically significant.

RESULTS

Demography

The mean age of the patients included in the study was 50.4 ± 9.0 years (capsular release group, 48.1 ± 9.6 years, and corticosteroid group, 52.6 ± 7.9 years). Out of the 56 patients in the study, 23 patients were male and 33 patients were female with 18 male patients in the capsular release group and 15 male patients in the corticosteroid group. Twenty-four patients had involvement of the dominant side and 32 patients had involvement of the non-dominant (17 patients in the capsular release group involving the non-dominant and 15 patients in the corticosteroid group involving the non-dominant side). The condition most commonly associated with adhesive capsulitis in the study was diabetes mellitus. Sixteen patients out of the 56 patients recruited in the study had diabetes mellitus. The age, sex, shoulder affected and the patients with diabetes mellitus were similarly distributed in the two groups. The average duration of symptoms was 6.3 mo (6.5-9.5 mo).

Clinical parameters

VAS score: The mean VAS score showed significant

Table 2 Change in range motion in both groups

Movement type	Study group	Movement in degrees (mean \pm SD)					
		Baseline	4 wk	8 wk	12 wk	16 wk	20 wk
Forward flexion	ACR	99.8 \pm 13.4	133.3 \pm 19.1	140.1 \pm 18.6	145.5 \pm 17.4	151.2 \pm 16.4	152.9 \pm 14.6
	Corticosteroid	100.8 \pm 16.7	118.9 \pm 17.4	126.4 \pm 16.9	132.5 \pm 17.3	138.9 \pm 17.6	143.9 \pm 16.6
	<i>P</i> value	0.79	0.005	0.006	0.007	0.009	0.05
Extension	ACR	34.1 \pm 7.5	42.6 \pm 8.1	45.0 \pm 7.6	48.0 \pm 6.8	49.8 \pm 7.0	50.6 \pm 7.2
	Corticosteroid	34.4 \pm 7.4	41.6 \pm 6.3	43.7 \pm 5.3	46.7 \pm 6.1	49.2 \pm 5.5	50.0 \pm 5.4
	<i>P</i> value	0.86	0.58	0.48	0.47	0.53	0.68
Abduction	ACR	78.3 \pm 13.2	113.2 \pm 20.4	121.6 \pm 21.8	127.6 \pm 21.3	131.9 \pm 19.8	135.6 \pm 18.5
	Corticosteroid	78.0 \pm 18.8	94.6 \pm 20.2	100.0 \pm 22.4	107.5 \pm 21.2	109.2 \pm 26.9	118.3 \pm 22.0
	<i>P</i> value	0.93	0.001	0.001	0.001	0.001	0.005
Adduction	ACR	28.0 \pm 5.6	37.3 \pm 6.1	39.1 \pm 5.9	41.7 \pm 5.1	43.9 \pm 5.5	45.9 \pm 5.0
	Corticosteroid	28.7 \pm 6.3	33.2 \pm 5.4	35.8 \pm 5.9	38.2 \pm 6.6	41.2 \pm 5.5	43.0 \pm 5.8
	<i>P</i> value	0.65	0.01	0.04	0.02	0.07	0.07
Internal rotation	ACR	28.9 \pm 6.4	39.8 \pm 8.4	42.5 \pm 8.9	44.8 \pm 9.1	48.3 \pm 9.0	50.4 \pm 7.5
	Corticosteroid	32.6 \pm 8.3	38.7 \pm 6.7	41.0 \pm 5.6	44.2 \pm 6.1	46.4 \pm 4.6	47.8 \pm 5.5
	<i>P</i> value	0.06	0.6	0.47	0.79	0.31	0.16
External rotation	ACR	39.1 \pm 6.2	56.4 \pm 11.4	61.4 \pm 12.9	65.7 \pm 13.2	69.8 \pm 12.7	73.4 \pm 14.2
	Corticosteroid	42.6 \pm 8.2	49.1 \pm 7.7	51.4 \pm 8.9	54.8 \pm 8.2	59.2 \pm 8.8	62.6 \pm 9.9
	<i>P</i> value	0.07	0.007	0.001	0.001	0.001	0.003

Table 3 Changes in Constant score in both groups

Duration	Constant score in group (mean \pm SD)		<i>P</i> value
	ACR	Corticosteroid	
Baseline	29.5 \pm 6.2	30.4 \pm 8.3	0.64
4 wk	50.3 \pm 10.7	43.4 \pm 9.5	0.01
8 wk	56.0 \pm 11.9	47.6 \pm 10.3	0.01
12 wk	61.0 \pm 12.3	53.0 \pm 9.9	0.01
16 wk	66.5 \pm 13.0	58.4 \pm 11.2	0.01
20 wk	70.2 \pm 12.1	62.6 \pm 11.6	0.03

improvement at baseline, and at 4, 8, 12, 16 and 20 wk in both groups. The improvement in VAS was statistically significant in the capsular release group at 8, 12, 16 and 20 wk as compared to injection group (Table 1).

Range of motion: All the movement measured in the study, *i.e.*, forward flexion, extension, abduction, adduction, external rotation and internal rotation, showed significant improvement in both groups during the follow-up at 4, 8, 12, 16 and 20 wk (Table 2). Forward flexion, abduction and external rotation showed a statistically significant improvement in the capsular release group as compared to that in the injection group and the improvement was maintained till the end of 20 wk.

Constant score: The Constant score showed significant improvement at each follow-up in both groups. However, improvement was more significant in the surgical release group than in the injection group. No difference was found in the change of clinical parameters between the patients with and without diabetes mellitus in either groups (Table 3).

DISCUSSION

Despite the wide variety of treatment options available

and the amount of research done, the results still appear to be inconclusive about the effectiveness of different interventions for adhesive capsulitis. There is no definitive guideline as to when to change from one treatment modality to another. But it is generally acceptable to wait for 3 mo before declaring any conservative treatment ineffective. Physiotherapy and intra-articular injections of corticosteroids continue to be the commonest mode of treatment for this condition. Injections into shoulder joint is most frequently administered without any image guidance in general practice even though multiple studies have shown that even in expert hands, a large number of injections may be out of the joint. In order to replicate the general practice, no image guidance was performed during the injections in this study. Arthroscopic capsular release has shown to provide early relief of symptoms^[22] and is increasingly being performed for the treatment of adhesive capsulitis of shoulder.

Baums *et al*^[17], Smith *et al*^[18] and Le Lievre *et al*^[23] have demonstrated a significant early improvement in pain, range of motion and overall shoulder function following arthroscopic capsular release. In the Indian population, similar results have been shown by Sabat and Kumar^[22]. Jerosch *et al*^[24], Warner *et al*^[25], Ogilvie-Harris *et al*^[26] have shown the safety and effectiveness of arthroscopic capsular release for the treatment of adhesive capsulitis of shoulder. However, we could only find one study by De Carli *et al*^[27] which compared arthroscopic capsular release with intra articular corticosteroid injections. The results of our study are in agreement with those by De Carli *et al*^[27] in which arthroscopic capsular release resulted in an early relief of pain and increased shoulder range of motion.

Our study showed continuous improvement in all parameters in both the groups and it started as early as 4 wk after the intervention. The scores of different parameters in the injection group at 20 wk were achi-

eved 4-8 wk earlier in the surgery group. In contrast to the Constant score which showed significant difference between the two groups as early as 4 wk, the VAS score for pain showed significant difference between the two groups in the 8th week. The initial period of pain following surgery could be the possible reason for this slightly delayed significant improvement in VAS score in the arthroscopic group. Extension and internal rotation of the shoulder were the only two parameters where there was no significant difference between the two groups.

Our study had some notable strengths. These include a strict inclusion and exclusion criteria, random allocation of the patients to both study groups and a frequent follow-up at a 4-wk interval. The limitations of our study included the lack of a control group, a relatively small sample size, short-term follow-up of only 20 wk and lack of blinding in the study.

In conclusion, our null hypothesis was proved wrong as both the modalities of treatment give good clinical improvement both subjectively and objectively but arthroscopic capsular release can give improvement earlier as compared to intra-articular steroid injections. However, intra-articular corticosteroids injection is a much less invasive and cheaper option and continues to be an effective modality to alleviate the symptoms in patients with adhesive capsulitis of shoulder. Hence we conclude that intra-articular steroids should be more routinely recommended as the first-line therapy for treatment of idiopathic adhesive capsulitis of shoulder. Arthroscopic capsular release may be recommended as a first-line treatment to patients who do not wish to wait for the results of intra-articular steroid injections. It may also be used for the failures of conservative treatment.

COMMENTS

Background

Frozen shoulder is a common condition and many treatment options are available, but with no clear guidelines. This study compares the outcomes of the two very common methods of treatment - injection steroid (non-surgical method) and arthroscopic arthrolysis (surgical method).

Research frontiers

Researchers are trying to make an animal model mimicking frozen shoulder. Many recent studies have evaluated non-operative methods of treatment and quality of life in patients with frozen shoulder.

Innovations and breakthroughs

The study emphasizes that injection of a steroid in the shoulder without any image guidance gives significant relief in frozen shoulder. This is the situation in most of the actual clinical settings. It improves pain and range of motion, which are the main problems in frozen shoulder. It dispels the belief that image guidance is a must for the intra-articular injection. It also re-establishes the findings of De Carli *et al* that arthroscopic arthrolysis yields outcomes similar to steroid injection but they occur 2 wk earlier.

Application

The fact that the benefits of arthroscopic arthrolysis precede those of injection of steroid by 4 to 8 wk, may help in selection of treatment modalities depending on the patient profile. This may also be the baseline for future researches.

Peer-review

It is an interesting research.

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Predicting lower limb periprosthetic joint infections: A review of risk factors and their classification

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Abstract

AIM

To undertake a systematic review to determine factors that increase a patient's risk of developing lower limb periprosthetic joint infections (PJI).

METHODS

This systematic review included full-text studies that reviewed risk factors of developing either a hip or knee PJI following a primary arthroplasty published from January 1998 to November 2016. A variety of keywords were used to identify studies through international databases referencing hip arthroplasty, knee arthroplasty, infection, and risk factors. Studies were only included if they included greater than 20 patients in their study cohort, and there was clear documentation of the statistical parameter used; specifically *P*-value, hazard ratio, relative risk, or/and odds ratio (OR). Furthermore a quality assessment criteria for the individual studies was undertaken to evaluate the presence of record and reporting bias.

RESULTS

Twenty-seven original studies reviewing risk factors relating to primary total hip and knee arthroplasty infections were included. Four studies (14.8%) reviewed PJI of the hip, 3 (11.21%) of the knee, and 20 (74.1%) reviewed both joints. Nineteen studies (70.4%) were retrospective and 8 (29.6%) prospective. Record bias was identified in the majority of studies (66.7%). The definition of PJI varied amongst the studies but there was a general consensus to define infection by previously validated methods. The most significant risks were the use of preoperative high dose steroids (OR = 21.0, 95%CI: 3.5-127.2, *P* < 0.001), a BMI above 50 (OR = 18.3, *P* < 0.001), tobacco use (OR = 12.76, 95%CI: 2.47-66.16, *P*

= 0.017), body mass index below 20 (OR = 6.00, 95%CI: 1.2-30.9, $P = 0.033$), diabetes (OR = 5.47, 95%CI: 1.77-16.97, $P = 0.003$), and coronary artery disease (OR = 5.10, 95%CI: 1.3-19.8, $P = 0.017$).

CONCLUSION

We have highlighted the need for the provider to optimise modifiable risk factors, and develop strategies to limit the impact of non-modifiable factors.

Key words: Periprosthetic joint infection; Risk factor; Predictive; Hip arthroplasty; Knee arthroplasty

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Core tip: This systematic review determines the most statistically significant factors that increase a patient's risk of developing lower limb periprosthetic joint infections. Reviewing all relevant papers until November 2016 through international databases, we have included 27 original studies. The results include multiple factors relating to the patient and the Institute, as well as post-operative predictors and causes of infection. This ultimately reiterates the importance of optimising the patients pre-operatively by addressing modifiable risk factors (such as their immunosuppression, nutrition, diabetes, and smoking), and develops strategies to limit the impact of non-modifiable factors.

George DA, Drago L, Scarponi S, Gallazzi E, Haddad FS, Romano CL. Predicting lower limb periprosthetic joint infections: A review of risk factors and their classification. *World J Orthop* 2017; 8(5): 400-411 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/400.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.400>

INTRODUCTION

Chronic periprosthetic joint infections (PJI) have received increasing interest in the medical literature as the profession has acknowledged the real-life implications to the patient and the health service^[1,2]. The treatment of PJI is costly to the health service with strain upon limited resources as multiple operations and trials of antibiotic therapy may be attempted. But the cost to the patient is greatest, with loss or reduced joint function, deterioration in their physical and psychological health, and loss in trust with the profession.

Prevention is key. Despite improved outcomes following the various treatment modalities for treating established infections today, the patient has to endure the consequences of the infection^[3]. Prior to the initial surgery it is imperative the patient is medically optimised and any reversible risk factors be corrected. Such risk factors are well known such as diabetes^[4], systemic infections^[5], and immunocompromise^[6].

However, risk factors vary and are dependent upon

the patient cohort, and often findings from isolated studies are not transferable. Therefore, we undertook a systematic review of the literature to determine overall predictive factors that increase a patient's risk of developing a lower limb PJI, and determine which risk factors are most predictive of infection.

In this review, we categorised risk factors in order to better understand the relative role of the host, of the healthcare provider, and of post-surgical conditions, the latter acting more as prognostic factors since the surgical procedure has already taken place. To this aim, we have subdivided known risk factors for PJI in three groups: (1) those relating to the host (host-related risk factors); (2) those that are related to the treatment provider and to the surgical environment (provider-related risk factors); and (3) those that arise from clinical interventions, increasing the patient's inherent risk (post-surgical risk factors). We have then compared the absolute number of risk factors in each main category, scored them according to their relative weight and divided in "modifiable" and "non-modifiable" risk factors.

MATERIALS AND METHODS

This systematic review included full-text studies that reviewed risk factors of developing either a hip or knee PJI following a primary arthroplasty published from January 1998 to November 2016. These were identified through international databases, such as EMBASE, PubMed/MEDLINE, MEDLINE Daily Update, MEDLINE In-Process, Google Scholar, SCOPUS, CINAHL, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.

A variety of keywords were used either alone or in combinations to identify the studies. This included references to hip infections (total hip replacement; THR; periprosthetic hip infection, hip arthroplasty infection), knee infections (total knee replacement; TKR; periprosthetic knee infection, knee arthroplasty infection), general joint infections (PJI, PPI), and "risk factors". We did not use specific keywords to search for individual risk factors, such as diabetes, *etc.*

Studies were only included if the risk factors were calculated by involving greater than 20 patients in their study cohort, and there was clear documentation of the statistical parameter used, and were only included if the P -value was quoted and one or more of the following; hazard ratio (HR), relative risk (RR), or/and odds ratio. Studies were excluded if they referred to recurrent infection following a revision procedure, hip or knee fracture, and a risk factor was excluded if the P -value was greater than 0.05. Results from combined studies, as seen in meta-analysis, were also excluded.

Two investigators, DAG and CLR, independently searched and reviewed the literature and determined if the study should be included based on their title and abstract. Once the two lists were compared, if the same material was presented in more than one study, only the most recent one was included.

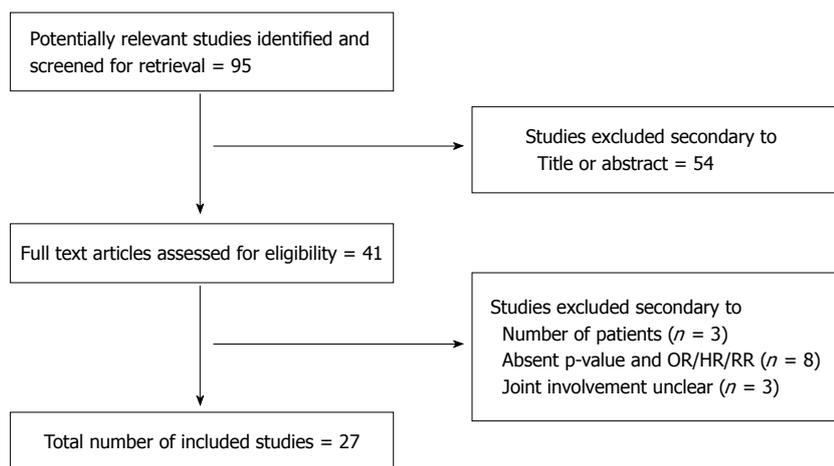


Figure 1 Flowchart summarizing the results of the literature search. RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 1 Study characteristics including number of patients, statistical method used, site (hip, knee or both), and duration of patient follow-up

Ref.	Year	Patients (n)			Statistical method used	Site	Follow-up (mo)		
		Infected (cases)	Non-infected (controls)	Total			Min	Max	Mean
Berberi <i>et al</i> ^[9]	1998	462	462	924	OR, CI, P	Both	-	-	-
Lai <i>et al</i> ^[10]	2007	51	-	-	OR, CI, P	Both	-	84	-
Parvizi <i>et al</i> ^[11]	2007	78	156	234	OR, CI, P	Both	-	-	-
Pulido <i>et al</i> ^[12]	2008	63	9182	9245	HR, CI, P	Both	12	72	43
Malinzak <i>et al</i> ^[13]	2009	43	8451	8494	OR, P	Both	24	192	74.4
Ong <i>et al</i> ^[14]	2009	887	39042	39929	OR, P	Hip	-	108	-
Berberi <i>et al</i> ^[5]	2010	339	339	678	OR, CI, P	Both	-	-	-
Peel <i>et al</i> ^[15]	2011	63	126	189	OR, CI, P	Both	-	-	-
Bozic <i>et al</i> ^[16]	2012	-	-	40919	HR, CI, P	Hip	12	-	-
Jämsen <i>et al</i> ^[17]	2012	52	7129	7181	HR, CI, P	Both	0	12	12
Bozic <i>et al</i> ^[4]	2012	-	-	83011	OR, CI, P	Knee	12	-	-
Dale <i>et al</i> ^[18]	2012	2778	429390	432168	RR, CI, P	Hip	0	60	60
Greenky <i>et al</i> ^[19]	2012	389	15333	15722	OR, CI, P	Both	36	108	62.4
Namba <i>et al</i> ^[20]	2013	404	55812	56216	HR, CI, P	Knee	-	-	-
Somayaji <i>et al</i> ^[21]	2013	5	254	259	OR, CI, P	Both	12	124	24
Coelho-Prabhu <i>et al</i> ^[22]	2013	339	339	678	OR, CI, P	Both	2	24	-
Maoz <i>et al</i> ^[23]	2014	47	3625	3672	OR, CI, P	Hip	12	48	24
Gómez-Lesmes <i>et al</i> ^[24]	2014	32	1299	1331	OR, CI, P	Knee	-	3	-
Yi <i>et al</i> ^[25]	2014	126	375	501	OR, CI, P	Both	3	-	-
Wu <i>et al</i> ^[26]	2014	45	252	297	OR, CI, P	Both	12	144	28
Sousa <i>et al</i> ^[27]	2014	43	2454	2497	OR, CI, P	Both	1	12	12
Jiang <i>et al</i> ^[28]	2014	-	-	306946	HR, P	Hip	6	-	-
	2014	-	-	573840	HR, P	Knee	6	-	-
Duchman <i>et al</i> ^[29]	2015	8062+	70129+	78191	OR, CI, P	Both	-	-	-
Chrastil <i>et al</i> ^[30]	2015	-	-	13272	HR, CI, P	Both	24	120	-
Crowe <i>et al</i> ^[31]	2015	26	3393	3419	OR, CI, P	Both	-	12	-
Debreuve-Theresette <i>et al</i> ^[32]	2015	45	90		OR, CI, P	Both	-	-	-
Bohl <i>et al</i> ^[33]	2015	-	-	49603	RR, CI, P	Both	-	1	-

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

The quality assessment criteria for the inclusion of the individual studies was adapted from George *et al*^[7]. to reflect the information we expect to be present in each study. Therefore we evaluated the presence of (1) record bias reflecting the source of data, and whether the analysis was retrospective or prospective; and (2) reporting bias; each study's definition of PJI (the measured outcome).

Figure 1 demonstrates the overall selection process according to the Prisma model^[8]. DAG, CLR, SS and EG compared the overall findings and any discrepancies were solved by reclassification as mutually agreed.

RESULTS

Included studies

In all, 27 original studies reviewing risk factors relating to primary total hip and knee arthroplasty infections were included. The number of risk factors identified ranged from 1 to 18. Four studies (14.8%) reviewed PJI on the hip, 3 (11.21%) on the knee, and 20 (74.1%) reviewed both joints. The statistical methods used to determine significance are also shown in Table 1^[4,5,9-33].

The quality of the included studies is demonstrated in Table 2. Nineteen studies (70.4%) were retrospective

Table 2 Paper quality, defined by presence of record and reporting bias

Ref.	Design	Record bias	Reporting bias (outcome measure); definition of infection
Berbari <i>et al</i> ^[9]	Retrospective	No	2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint
Lai <i>et al</i> ^[10]	Retrospective	No	2 or more cultural examination positive for the same microorganism; clinical diagnosis
Parvizi <i>et al</i> ^[11]	Prospective	No	Criteria based upon 3 of 5 features ¹
Pulido <i>et al</i> ^[12]	Retrospective	Yes	Criteria based upon 3 of 5 features ¹
Malinzak <i>et al</i> ^[13]	Retrospective	No	Unknown
Ong <i>et al</i> ^[14]	Retrospective	Yes	Diagnostic code in Medicare database
Berbari <i>et al</i> ^[5]	Prospective	Yes	2 or more cultural examination positive for the same microorganism; acute inflammation on histopathological examination; sinus tract; purulence around the prosthesis/joint
Peel <i>et al</i> ^[15]	Prospective	Yes	Criteria based upon 3 of 5 features ¹
Bozic <i>et al</i> ^[16]	Retrospective	Yes	Diagnostic code in Medicare database
Jämsen <i>et al</i> ^[17]	Prospective	Yes	CDC definition of surgical site infection ³
¹ Bozic <i>et al</i> ^[4]	Retrospective	Yes	Diagnostic code in Medicare database
Dale <i>et al</i> ^[18]	Retrospective	Yes	Clinical as reported by the surgeon after surgery
Greenky <i>et al</i> ^[19]	Retrospective	No	Criteria based upon 3 of 5 features ¹
Namba <i>et al</i> ^[20]	Retrospective	Yes	CDC definition of surgical site infection ³
Somayaji <i>et al</i> ^[21]	Retrospective	No	Criteria based upon 3 of 5 features ¹
Coelho-Prabhu <i>et al</i> ^[22]	Retrospective	Yes	2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint
Maoz <i>et al</i> ^[23]	Retrospective	Yes	CDC definition of surgical site infection ³
Gómez-Lesmes <i>et al</i> ^[24]	Prospective	Yes	Criteria based upon 3 of 5 features ¹
Yi <i>et al</i> ^[25]	Retrospective	No	Criteria based upon 3 of 5 features ¹
Wu <i>et al</i> ^[26]	Retrospective	Yes	MSIS definition ²
Sousa <i>et al</i> ^[27]	Retrospective	No	Criteria based upon 3 of 5 features ¹
Jiang <i>et al</i> ^[28]	Prospective	Yes	Diagnostic code in Medicare database
Duchman <i>et al</i> ^[29]	Prospective	Yes	Criteria based upon 3 of 5 features ¹
Chrastil <i>et al</i> ^[30]	Retrospective	Yes	Diagnostic code in Medicare database
Crowe <i>et al</i> ^[31]	Retrospective	Yes	CDC definition of surgical site infection ³
Debreuve-Theresette <i>et al</i> ^[32]	Retrospective	No	CDC definition of surgical site infection ³
Bohl <i>et al</i> ^[33]	Prospective	Yes	American College of Surgeons National Surgical Quality Improvement Program definition

¹Refers to 3 of 5 of the following criteria: (1) abnormal serology (ESR > 30 mm/h; CRP > 1 mg/dL); (2) strong clinical and radiographic suspicion for infection; (3) positive joint aspiration culture for infection; (4) evidence of purulence during the subsequent surgical intervention; and (5) positive intraoperative culture; ²Musculoskeletal Infection Society (MSIS) definition; ³Defined as (1) deep infection; (2) purulent drainage; (3) dehiscence; (4) fever; and (5) localized pain. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

and 8 (29.6%) prospective. Record bias was identified in the majority of studies (66.7%). The definition of PJI varied amongst the studies but there was a general consensus to define infection by previously validated methods.

This included the presence of 2 or more cultural positive results for the same microorganism (plus other features on infection) in 4 studies (14.8%), the CDC definition in 5 studies (18.5%), the Medicare code for infection in 5 studies (18.5%), and 9 studies (33.3%) based their definition on patients meeting 3 of the following 5 features; (1) abnormal serology (ESR > 30 mm/h; CRP > 1 mg/dL); (2) strong clinical and radiographic suspicion for infection; (3) positive joint aspiration culture for infection; (4) evidence of purulence during the subsequent surgical intervention; and (5) positive intraoperative culture.

One study used the MSIS criteria, which includes: (1) a sinus tract; (2) positive culture results from 2 or more tissue or fluid samples; and (3) 4 of the following 6 criteria are present: (I) elevated CRP/ESR; (II) elevated synovial WCC; (III) high synovial PMN leukocyte percentage; (IV) presence of purulence in the joint; (V)

positive culture result from one sample from the affected joint; and (VI) PMN leukocyte count of more than 5 per high-powered field in 5 high-powered fields on histologic analysis at 400 × magnification^[34].

Host-related risk factors

Risk factors relating to the host have been shown in Table 3, and are the most abundant group of risk factors identified. The majority of the risk factors are systemic referring to patient co-morbidities that are negatively associated with patient outcome following a primary THR or TKR, such as presence of diabetes mellitus^[4,9,17,20,26], immunocompromised^[5,15,21], concomittent systemic infection^[5,10,27,31], cardiology^[4,16,21] and gastroenterology disorders^[22,28], high ASA (American Society of Anesthesiologists) grade^[12,15,20] and malnutrition^[13,17,21,23,25,26,33].

Patient demographics also have been shown to have an impact upon risk of PJI, including age^[16], rural residence^[16], race^[20], male gender^[14,18,20,31], and alcohol^[26] or tobacco use^[23,29,31,32]. Previous operations to the joint (excluding revisions arthroplasty as this was excluded from analysis) increased the risk of PJI^[5,32].

Table 3 Host-related risk factors

	Ref.	Statistical parameter				Site	
		HR	OR	RR	95%CI		P value
General							
Age: 65-75 yr (compared to 45-65)	[26]		3.36		1.30-8.69	0.013	Hip/knee
Comorbidities (total number)	[10]		1.35		1.10-1.66	0.005	Hip/knee
Charlson index + 5 (compared to 0)	[14]		2.57		1.96-3.37	< 0.001	Hip
Place of residence (rural)	[26]		2.63		1.13-6.10	0.025	Hip/knee
Hispanic race (compared to White)	[20]	0.69			0.49-0.98	0.038	Knee
Alcohol abuse	[26]		2.95		1.06-8.23	0.039	Hip/knee
Tobacco use	[29]		1.47		1.21-1.78	0.001	Hip/knee
	[31]		3.4		1.23-9.44	0.029	Hip/knee
	[32]	3.91			1.19-12.84	0.032	Hip/knee
Tobacco use (S aureus colonization)	[23]		12.76		2.47-66.16	0.017	Hip
Gender							
Female	[14]		0.83			0.009	Hip
Male	[18]			1.9	1.80-2.10	< 0.001	Hip
	[20]	1.89			1.54-2.32	< 0.001	Knee
	[31]		3.55		1.60-7.84	0.002	
Endocrine disorders							
Diabetes mellitus							
	[4]		1.19		1.06-1.34	0.0025	Knee
	[26]		5.47		1.77-16.97	0.003	Hip/knee
	[22]	1.46			1.27-1.68	0.0007	Hip
	[9]		4		1.13-14.18	0.032	Hip/knee
	[20]	1.28			1.03-1.60	0.025	Knee
	[17]	2.31			1.12-4.72	< 0.001	Hip/knee
	[15]		1.4		0.90-2.10	0.06	Hip/knee
	[5]		1.8		1.20-2.80	0.006	Hip/knee
	[13]		3.1			0.02	Hip/knee
	[44]		2.21		1.34-3.64	0.001	Knee
Pre-op BM > 6.9 mmol/L	[17]	2.25			0.60-8.50	0.073	Hip/knee
Pre-operative hyperglycemia	[30]	1.44			1.09-1.89	0.008	Hip/knee
Psychiatric disorders							
Depression							
	[4]		1.28		1.08-1.51	0.0035	Knee
	[16]	1.6			1.32-1.93	0.0039	Hip
Psychosis							
	[16]	1.74			1.38-2.20	0.0044	Hip
	[4]		1.26		1.02-1.57	0.0331	Knee
Haematological disorders							
Preoperative anaemia							
	[16]	1.36			1.15-1.62	0.0005	Hip
	[19]		1.95		1.41-2.69	< 0.001	Hip/knee
	[4]		1.26		1.09-1.45	0.0014	Knee
Coagulopathy	[16]	1.58			1.24-2.01	0.0002	Hip
Malignancy							
Metastatic malignancy							
	[4]		1.59		1.03-2.47	0.0369	Knee
Tumour 5 yr before implant	[5]		3.1		1.30-7.20	< 0.01	Hip/knee
Cardiovascular disorders							
Congestive heart failure							
	[4]		1.28		1.13-1.46	< 0.0001	Knee
	[16]	1.57			1.33-1.84	0.0409	Hip
Cardiac arrhythmia	[16]	1.48			1.30-1.70	0.0012	Hip
Coronary artery disease	[21]		5.10		1.30-19.8	0.017	Hip/knee
Valvular disease	[4]		1.15		1.01-1.31	0.039	Knee
Peripheral vascular disease	[4]		1.13		1.01-1.27	0.0381	Knee
	[16]	1.44			1.24-1.68	0.0032	Hip
Gastroenterology disorders							
Liver cirrhosis							
	[28]	5.4				< 0.001	Hip
	[28]	3.4				< 0.001	Knee
Hepatitis B virus (amongst males)	[44]		4.32		1.85-10.09	< 0.001	Knee
OGD with biopsy	[22]		2.8		1.10-7.10	0.03	Hip/knee
Respiratory disorders							
Chronic pulmonary disease							
	[4]		1.22		1.10-1.36	< 0.0001	Knee
	[31]		4.34		1.28-14.70	0.041	Both
Pulmonary circulation disorders	[4]		1.42		1.06-1.91	0.0205	Knee
Renal disorders							
Renal disease							
	[4]		1.38		1.11-1.71	0.0038	Knee
Renal function (mL/min)	[15]		1		0.90-1.00	0.05	Hip
Rheumatoid arthritis							
Rheumatoid arthritis	[15]		3.3		0.80-13.90	0.09	Hip/knee
	[4]		1.18		1.02-1.37	0.0277	Knee
	[16]	1.71			1.42-2.06	< 0.0001	Hip

ASA grade						
ASA score	[15]		2.2	1.30-4.00	0.006	Hip/knee
Mean score	[11]		2.07	1.08-1.97	0.03	Hip/knee
3 (compared to 1 or 2)	[20]	1.65		1.33-2.00	< 0.001	Knee
> 4	[12]	1.95		1.00-3.70	0.04	Hip/knee
Body mass index						
Obesity	[4]		1.22	1.03-1.44	0.0219	Knee
	[16]	1.73		1.35-2.22	< 0.0001	Hip
BMI (kg/m ²)	[15]		1.1	1.00-1.10	0.05	Hip
	[12]	3.23		1.60-6.50	0.001	Hip/knee
< 20	[21]		6	1.20-30.9	0.033	Hip/knee
25-30	[5]		0.4	0.30-0.70	< 0.001	Hip/knee
≥ 28 (compared to 18.5-28)	[26]		2.77	1.20-6.40	0.017	Hip/knee
31-39	[5]		0.5	0.30-0.70	< 0.001	Hip/knee
35 (compared to < 35)	[20]	1.47		1.17-1.85	0.001	Knee
	[32]	1.84		1.11-3.05	0.007	Both
> 40	[23]		4.13	1.30-12.88	0.01	Hip
	[13]		3.3		0.045	Knee
	[17]	6.41		1.67-24.59	< 0.001	Hip/knee
> 50	[13]		18.3		< 0.001	Hip/knee
Malnutrition	[25]		2.3	1.50-3.50	< 0.001	Hip/knee
Serum albumin < 3.5 g/dL	[33]		2	1.50-2.80	< 0.001	Hip/knee
Immunocompromise						
Immunocompromise	[5]		2.2	1.60-3.00	< 0.001	Hip/knee
Inflammatory disease	[18]		1.4	1.10-1.70	0.001	Hip
Prednisone dose exceeds 15 mg/d	[21]		21	3.50-127.2	< 0.001	Hip/knee
Systemic steroid therapy	[15]		3.3	0.80-13.90	0.09	Hip/knee
Infection						
Distant organ infection	[5]		2.2	1.50-3.25	< 0.001	Hip/knee
Nasal <i>S. Aureus</i> Infection	[31]		3.95	1.80-8.71	< 0.001	Hip/knee
Nasal MRSA Infection	[31]		8.24	3.23-21.02	< 0.001	Hip/knee
Asymptomatic bacteriuria	[27]		3.23	1.67-6.27	0.001	Hip/knee
Genitourinary infection	[10]		2.8	1.01-7.77	0.048	Hip/knee
Operative indication						
Hip fracture	[18]		2.1	1.90-2.40	< 0.001	Hip
Post-traumatic osteoarthritis	[20]	3.23		1.68-6.23	< 0.001	Knee
Prior operation on the index joint	[5]		1.9	1.30-2.60	< 0.001	Hip/knee
Per additional surgery	[32]		2.88	1.45-5.80	0.018	Hip/knee
Avascular necrosis	[18]		1.7	1.40-2.10	< 0.001	Hip

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Provider-related risk factors

Risk factors relating to the provider are shown in Table 4. Prolonged operative duration of greater than 115 minutes in hip arthroplasty is a strong predictor of infection^[5,14,23], as is non-same day surgery^[23]. During knee arthroplasty, exposure to the joint requiring quadriceps release significantly increases the risks of infection^[20].

Protective measures include the use of antibiotic surgical prophylaxis systemically^[5] and locally as irrigation^[20], but antibiotic impregnated cement may or may not be protective^[18,20]. In addition, bilateral procedures during the same operation have been shown by some studies to increase the risk^[12], whilst in others decrease it^[20].

Post-surgical risk factors

Post-operatively patients may present with a superficial infection to the joint with a warm, cellulitic, and sometimes discharging wound, which is a high predictor of an underlying PJI^[5,11,9,15]. Table 5 demonstrates other factors that have a high correlation with a PJI, including receiving a blood transfusion^[11,12,15] (especially if the blood has been stored for greater than 14 d^[24]), post-operative urinary tract infection (UTI)^[5,12], and onset of cardiac arrhythmias^[12].

Risk factor impact

Several risk factors were shown to have greater significance than others, and a vast majority of the risk factors were directly related to the patient (host-factors). The most significant risks were the use of preoperative high dose steroids (OR = 21.0, 95%CI: 3.5-127.2, $P < 0.001$)^[21], a BMI above 50 (OR = 18.3, $P < 0.001$)^[13], tobacco use (OR = 12.76, 95%CI: 2.47-66.16, $P = 0.017$)^[23], BMI below 20 (OR = 6.00, 95%CI: 1.2-30.9, $P = 0.033$)^[21], diabetes (OR = 5.47, 95%CI: 1.77-16.97, $P = 0.003$)^[26], and coronary artery disease (OR = 5.10, 95%CI: 1.3-19.8, $P = 0.017$)^[21].

Modifiable risk factors

We further categorised the resultant risk factors into whether or not they were modifiable, reflecting the opportunity of the surgeon to optimise their patient pre-operatively and to reduce the risk of developing a PJI (Table 6).

DISCUSSION

It is extremely difficult to predict if a patient will develop a

Table 4 Provider-related risk factors

	Ref.	Statistical parameter				Site	
		HR	OR	RR	95%CI		P value
Antibiotic use							
Antibiotic surgical prophylaxis	[5]		0.5		0.30-0.80	0.003	Hip/knee
Antibiotic irrigation	[20]	0.67			0.48-0.92	0.014	Knee
Surgical technique							
Exposure requiring quadriceps release	[20]	4.76			1.18-19.21	0.029	Knee
Use of wound drain tube	[15]		0.09		0.01-0.80	0.03	Knee
Side of surgery							
Simultaneous bilateral surgery	[12]	5.85			2.50-13.90	< 0.0001	Hip/knee
	[20]	0.51			0.31-0.83	0.007	Knee
Single side (compared to bilateral)	[13]		3.1			0.0024	Hip/knee
	[13]		4			0.009	Knee
Cement							
Antibiotic-laden cement	[20]	1.53			1.18-1.98	< 0.001	Knee
Non-antibiotic cement	[8]			1.5	1.30-1.80	< 0.001	Hip
Hybrid (compared to uncemented)	[8]			1.6	1.40-1.80	< 0.001	Hip
Operative duration							
Length of operation (> 115 min)	[23]		3.38		1.23-9.28	0.018	Hip
(> 210 min)	[14]		1.78		1.40-2.26	< 0.0001	Hip
(≥ 240 min)	[5]		2.7		1.50- 5.00	0.002	Hip/knee
Hospital factors							
Hospital volume < 100 (<i>vs</i> > 200/yr)	[20]	0.33			0.12-0.90	0.03	Knee
Medicare buy-in	[14]		1.34			0.005	Hip

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 5 Post-surgical risk factors

	Ref.	Statistical parameter				Site	
		HR	OR	RR	95%CI		P value
Anaesthetic factors							
Intensive care length of stay (d)	[15]		0.5		0.20-1.00	0.06	Knee
Haematological							
Blood transfusion	[12]	2.11			1.10-3.90	0.02	Hip/knee
	[15]		2.1		1.00-4.20	0.04	Hip/knee
	[11]		1.63		1.14-2.33	0.007	Hip/knee
Transfusion if RBCs stored > 14 d	[24]		5.9		2.60-13.20	< 0.001	Knee
Perioperative blood loss (<i>via</i> drain tube)	[15]		1		1.00-1.01	0.008	Hip
Cardiac							
Postoperative atrial fibrillation	[12]	6.22			1.40-28.5	0.02	Hip/knee
Postoperative myocardial infarction	[12]	20.4			2.10-199.9	0.009	Hip/knee
Hospital factors							
Longer hospital stay	[12]	1.09			1.00-1.10	0.0003	Hip/knee
Non same-day surgery	[23]		4.16		1.44-12.02	0.008	Hip
Wound complications							
All wound complications	[11]		27		11.00-91.6	0.0002	Hip/knee
Wound discharge	[5]		18.7		7.40-47.2	< 0.001	Hip/knee
	[15]		6.3		1.30-30.7	0.02	Knee
	[15]		5.4		2.00-15.0	0.001	Hip
	[15]		5.7		2.40-13.3	<0.001	Hip/knee
	[11]		32.2		8.7-119.17	< 0.0001	Hip/knee
Haematoma	[5]		3.5		1.30-9.50	0.01	Hip/knee
Surgical site infection	[1]		35.9		8.30-154.6	< 0.01	Hip/knee
Superficial incisional SSI	[15]		3.7		1.10-11.9	0.03	Knee
	[15]		5		1.60-15.9	0.007	Hip
	[15]		4.3		1.90 - 9.90	0.001	Hip/knee
NNIS risk index 2	[9]		3.9		2.00-7.50	< 0.01	Hip/knee
Urinary							
Postoperative urinary infection	[12]	5.45			1.00-8.70	0.04	Hip/Knee
	[5]		2.7		1.04-7.10	0.04	Hip/Knee

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 6 Classification of risk factors and probability of infection (main factors)

	Risk factor	Minimum increase	Maximum increase	Statistical parameter	Ref.
Host-related risk factors					
Modifiable					
	Systemic steroids	3.3	21	OR	[15,21]
	Tobacco use	3.4	12.76	OR	[23,32]
	Nasal MRSA infection	-	8.24	OR	[31]
	BMI < 20	-	6	OR	[21]
	Coronary artery disease	-	5.1	OR	[21]
	COPD	1.22	4.34	OR	[4,31]
	BMI > 40	-	4.13	OR	[23]
	Pre-operative BM	-	2.25	OR	[17]
Non-modifiable					
	Diabetes	1.4	5.47	OR	[15,26]
	Liver cirrhosis	-	5.4	HR	[28]
	Male	1.89	3.55	HR,OR	[20,31]
	Age	-	3.36	OR	[26]
	Rheumatoid arthritis	1.18	3.3	OR	[4,15]
	Malignancy	-	3.1	OR	[5]
Provider-related risk factors					
Modifiable					
	Quadriceps release (TKR)	-	4.76	HR	[20]
	Non-same day procedure	-	4.16	OR	[23]
	Prolonged operation	1.78	3.38	HR	[14,23]
Non-modifiable					
	Prolonged storage of blood	2.6	13.2	OR	[24]

BMI: Body mass index; RR: Relative risk; HR: Hazard ratio; OR: Odds ratio; COPD: Chronic obstructive pulmonary disease; TKR: Total knee replacement.

post-operative infection following lower limb arthroplasty. Multiple prospective and retrospective studies have reviewed the risks associated with their patient cohort developing such infections. This paper was undertaken to combine these risks and determine if there was a consensus to which factors puts a patient at highest risk, and categorise them if they related directly to the host (patient), provider (the surgical team and their Institute), or occurred during the post-operative period.

Little is known about the interaction between, or synergistic effect, of specific patient risk factors^[35], as it is likely they have a multiplicity effect, rather than additive risk, as shown by Tomás^[6]. In their cohort if a patient had two (or more) significant factors the probability of infection development was 14-times higher, whereas having three (or more) factors the probability was increased 16-times.

Several themes have emerged following this systematic review of the literature, specifically the patient's immunological and systematic responses to infection, other sources of infection, antibiotic use, and provider factors.

Immunological response

The most frequently quoted risk factor was diabetes mellitus^[4,9,17,20,22,26], which had one of the highest odds ratios^[26]. Almost all the other highest odds ratio, or hazard ratio, also belonged to medical conditions ultimately impairing a patient's immunity, as demonstrated from high dose pre-operative steroids^[21], malnutrition (reflective of high alcohol intake^[26], BMI below 20^[21] and above 50^[13]), and tobacco use^[23]. Malignancy^[4,5], rheumatoid arthritis^[4,15,16], and liver cirrhosis^[28] can also impair a patient's immunity.

Immunosuppression has long been known to increase a patient's risk of systemic infection, and has widely

been documented in arthroplasty patients. Ragni *et al.*^[36] demonstrated this in human immunodeficiency virus-positive hemophiliacs with CD4 counts of 200 mm³ or less undergoing orthopaedic surgery. Post-operative infection occurred in 10 (15.1%) of 66 patients^[36]. Local steroid injection causing focal immunosuppression about the joint has also been shown to increase the risk, compared to those that have not received any joint injections in hip arthroplasty cases^[37].

In rheumatoid patients treated with immunosuppressive drugs (including biologic agents) undergoing all orthopaedic procedures, a statistically significant higher risk of infection was seen in this patient cohort compared to a degenerative/post-traumatic group (OR = 2.58, 95%CI: 1.91-3.48, $P < 0.001$)^[38]. Furthermore this risk was significantly increased in patients taking multiple disease-modifying antirheumatic drugs (DMARDs) ($P = 0.036$) or tumor necrosis factor α (TNF α) inhibitors ($P = 0.032$), especially if the last dose of TNF α inhibitor was given < 1 administration interval before surgery^[38].

Infection response

While not directed specifically to immunosuppression, other co-morbidities have a role in reducing the patient's systemic response to infection. Cardiac dysfunction^[4,16,21], renal failure^[4,15], anaemia^[4,9,16] and coagulopathy^[16] have all been shown to increase the risk of infection. This may be directed through specific cellular pathways^[39], but may demonstrate the insult the surgical procedures has in causing a secondary inflammatory insult, worsening multiple organ dysfunction^[40,41].

Derangements in renal function, with progressively higher poor glomerular filtration rate (GFR) in either the acute or chronic stages, reduces the ability to remove unwanted and hazardous chemicals from the blood, and places the patient at a higher risk. Lieberman *et al.*^[42] demonstrated

a high rates of infection in patients on chronic renal dialysis (19%), however in a separate patient series no significant increase in infection risk was seen^[43].

Infection source

We believe that if a patient is known to have systemic infection, or a localised infection but distant to the operative joint, the risk of haematological spread of infection to the implant is highly likely. We have demonstrated a statistically significant increased risk of PJI in patients with a pre-operative confirmation of a genitourinary infection^[10,27], nasal *S. Aureus* and *MRSA* infections^[31], or other distant organ infections^[6], such as hepatitis B^[44].

Conditions that further increase this risk are those that may make the patient more susceptible for the introduction of a new pathogen, such as chronic pulmonary disease^[4,31] with known high rates of pneumonia, peripheral vascular disease^[4,16] with high risk of skin ulceration and introduction of skin contaminants, and recent oesophagogastroduodenoscopy (EGD) with biopsy^[22], risking the introduction of gut flora to the blood system.

Furthermore, perioperative blood transfusion increases the risk of PJI in both hip and knee arthroplasty^[11,12,15], and allogeneic blood transfusion has been shown to instigate a detrimental immunomodulation reaction, and decreases T-cell-mediated immunity, and may enhance the acute inflammatory response^[45,46]. Stored blood can cause a significant increase in inflammatory cytokine release from the stored neutrophils, and superoxide release results in delayed neutrophil apoptosis and risks cytotoxicity^[47,48].

This has been confirmed in a recent systematic meta-analysis of 6 studies demonstrating the association between allogeneic blood transfusion and an increased risk for a SSI after total hip and knee arthroplasty. Data was included from over 20000 patients, and the blood transfusion group had a significantly higher frequency of infection (pooled OR = 1.71, 95%CI: 1.23-2.40, $P = 0.002$) compared to the non-exposed group^[49].

Antibiotic use

The use of antibiotic-impregnated cement was shown by Dale *et al*^[18] to protect against revisions due to infection, whereas Namba *et al*^[20] identified an increased risk. Such conflicting outcomes are common in the literature regarding the use of antibiotic-impregnated cement in primary procedures. A prospective randomized study with 2948 cemented total knee arthroplasties failed to see an improvement of PJI rates by using bone cement loaded with erythromycin and colistin compared to controls^[50], whereas the Norwegian Arthroplasty Register has demonstrated a synergistic effect of systemic and cement antibiotics^[51]. However there is a general consensus that antibiotic-impregnated cement has a greater role in revision cases^[52], and is recommended as standard practice in these high-risk cases^[53].

Systemic antibiotics given at anaesthetic induction are generally the standard of care, and continued post-operatively for a further two doses in the United

Kingdom, and for two days in Italy (authors experience). The choice of antibiotic varies in each Institute to reflect the prominent pathogen and patient cohort. Multiple studies have demonstrated the benefits of antibiotics given during the procedure to reduce the risk of post-operative infection^[51,54].

Provider factors

Concerning the relative impact of the hospitals yearly volume of procedures, we found only one retrospective review of joint registry data, that suggests that the fewer total knee arthroplasties undertaken per year will result in a lower rate of infection^[20]. This particular finding needs, in our opinion, further validation, since it contradicts other reports demonstrating better outcomes from greater volumes of surgery and greater experience of the surgeons, as exemplified by the Hospital for Special Surgery, New York^[55], while other studies have shown no difference between the two^[56].

Furthermore, the use of a drain post-operatively has been shown by Peel *et al*^[15] to reduce the risk of PJI following knee arthroplasty, however multiple meta-analyses and prospective, randomised, controlled trials have demonstrated no significant difference in post-operative infections between the wounds treated with a drain and those without^[57,58].

Modifiable risk factors

When the risk factors were further categorised into modifiable or not, the vast majority of factors were non-modifiable. Many risk factors increased a patient's risk by less than 5 times (OR < 5), and very few increased the risk by more than 10 times.

However, the presence of non-modifiable risk factors still requires attention, and may be more important than modifiable ones. Alternate methods should be adopted to reduce the patient's burden and may include a combination of implant modifications (such as silver or disposable microbiological coatings)^[59,60], antibiotic impregnated cement or bone graft^[61,62], or other novel therapies^[63] to provide a personalized and more effective prophylaxis.

It is the responsibility of the operating team to act upon these, and modify or optimise the patient prior to surgery. For example, intensive insulin therapy, maintaining tight blood glucose concentrations between 80 and 110 mg/dL, has been shown to decrease infection-related complications and mortality^[64]. Normal renal function should be sought, nutrition improved, cardiac investigations and interventions should be offered, local and systemic infections appropriately treated, as should chronic anaemia, and patients should be informed to withhold DMARDs and stop tobacco smoking and alcohol use preoperatively.

Risk-analysis tools

Indeed, determining individual patients risks is an important step in personalized informed consent. Surgeons may quote published rates or their own, but the risk

is individual and should reflect all the aforementioned factors, which may have consequences in the medico-legal evaluation in case of damage evaluation after PJI.

Previous attempts to combine such measures in a scoring system have been attempted by The Mayo Clinic^[65] who based the data on their cohort of patients at baseline and at one month. Bozic *et al.*^[35] developed a risk calculator using data from 11 years worth of Medicare claims. A similar tool has been developed in the Chinese population^[26].

The main disadvantage of such tools is the calculations relate to a specific set of patients, and may not reflect the general public risks, as they have not been externally validated. In addition the data is unlikely to appreciate advances in perioperative care over the time period, and may not capture patients with late onset PJI if follow-up is short.

Limitations

A wide variety of studies were included in this systematic review, which gives an overview of risk factors for hip and knee PJI but the quality of each study is generally poor. As previously discussed, only 8 studies (29.6%) were prospective, and one third of studies demonstrated record bias. Reporting bias was also seen amongst the studies, as a variety of diagnostic criteria were used. This is common amongst studies reviewing PJI as there is no gold standard measure to determine presence of infection, nor an agreement to the medical, or surgical management, for these patients^[53].

Our search criteria only highlighted studies with "risk factor" in the title, and therefore we did not search for studies looking at individual risk factors. Therefore studies, some of high quality, may not have met our inclusion criteria. Furthermore, we were unable to undertake a meta-analysis due to the heterogeneity of the data.

In conclusion, as demonstrated, current data is conflicting as the influence of the risk factors vary widely, and we believe more emphasis is required regarding the multiplicity effects of risk factors. We need larger studies and novel tools to investigate single and combined risk factors, and to identify key areas of improvement and modification for these patients.

The literature has demonstrated significant variation in the number and type of risk factors that places a patient at higher risk of developing a PJI, which is heavily weighted towards the patient. However the provider has a role in addressing the modifiable risk factors pre-operatively to optimise their patient, and develop new strategies to limit the impact of non-modifiable factors.

COMMENTS

Background

Several studies have previously shown the impact of various risk factors on the probability of developing an infection after joint replacement. The heterogeneity of the available data notwithstanding, in this systematic review a detailed analysis of the respective weight of known risk factors, classified as host-, provider- or post-surgical-related, is performed; moreover, a further distinction in modifiable or not-

modifiable risk factors is proposed.

Research frontiers

A classification and ranking of known risk factors may open new frontiers in prevention and control of peri-prosthetic infections. Furthermore, it can be helpful to improve the information to the patient prior to surgery, to drive personalised prophylaxis and to better evaluate the cost-to-benefit ratio of new technologies, like antibacterial coatings, designed to reduce bacterial adhesion on implanted biomaterials.

Innovations and breakthrough

This systematic review sheds new lights on the relative impact of various risk factors that increase a patient's risk of developing lower limb periprosthetic joint infections (PJI). This ultimately reiterates the importance of optimising the patients pre-operatively by addressing modifiable risk factors (such as their immunosuppression, nutrition, diabetes, and smoking), and develops strategies to limit the impact of non-modifiable factors.

Applications

The data obtained in this systematic review may form the basis for the development of specific software, like the "PJI Risk App", an application for smartphones, specifically designed to calculate the risk of developing a peri-prosthetic infection in a given patient. This in turn may be useful for surgeons and their patients to understand the specific risk of undergoing joint replacement and eventually to better tailor antibiotic prophylaxis.

Peer-review

In this manuscript authors reviewed provider risk factors of chronic PJI. This study is interesting and the objective very clear.

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Dementia and osteoporosis in a geriatric population: Is there a common link?

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Abstract

AIM

To determine the existence of a common pathological link between dementia and osteoporosis through reviewing the current evidence base.

METHODS

This paper reviews the current literature on osteoporosis and dementia in order to ascertain evidence of a common predisposing aetiology. A literature search of Ovid MEDLINE (1950 to June 2016) was conducted. The keywords "osteoporosis", "osteoporotic fracture", "dementia" and "Alzheimer's disease" (AD) were used to determine the theoretical links with the most significant evidence base behind them. The key links were found to be vitamins D and K, calcium, thyroid disease, statins, alcohol and sex steroids. These subjects were then searched in combination with the previous terms and the resulting papers manually examined. Theoretical, *in vitro* and *in vivo* research were all used to inform this review which focuses on the most well developed theoretical common causes for dementia (predominantly Alzheimer's type) and osteoporosis.

RESULTS

Dementia and osteoporosis are multifaceted disease processes with similar epidemiology and a marked increase in prevalence in elderly populations. The existence of

a common link between the two has been suggested despite a lack of clear pathological overlap in our current understanding. Research to date has tended to be fragmented and relatively weak in nature with multiple confounding factors reflecting the difficulties of *in vivo* experimentation in the population of interest. Despite exploration of various possible mechanisms in search for a link between the two pathologies, this paper found that it is possible that these associations are coincidental due to the nature of the evidence available. One finding in this review is that prior investigation into common aetiologies has found raised amyloid beta peptide levels in osteoporotic bone tissue, with a hypothesis that amyloid beta disorders are systemic disorders resulting in differing tissue manifestations. However, our findings were that the most compelling evidence of a common yet independent aetiology lies in the APOE4 allele, which is a well-established risk for AD but also carries an independent association with fracture risk. The mechanism behind this is thought to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele which may be amplified by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies.

CONCLUSION

Robust evidence remains to be produced regarding potential links and regarding the exact aetiology of these diseases and remains relevant given the burden of dementia and osteoporosis in our ageing population. Future research into amyloid beta, APOE4 and vitamins K and D as the most promising aetiological links should be welcomed.

Key words: Osteoporosis; Fracture; Dementia; Thyroid disease; Alzheimer's disease; Elderly; Vitamin D; Vitamin K; Calcium; Statins; Alcohol; Sex steroids

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Core tip: A potential pathological link between osteoporosis and dementia has been explored in observational studies, but there exists a lack of large scale randomised controlled trials. We hypothesise that dementia and osteoporosis have common yet independent aetiologies. The most compelling evidence lies in the APOE4 allele, a well-established risk factor for Alzheimer's disease. APOE4 is associated with fracture, independent of dementia and falling. The mechanism behind this is postulated to be reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele. This may be augmented by the nutritional deficiencies associated with dementia, known to include vitamins K and D.

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INTRODUCTION

Dementia and osteoporosis are complex disease processes with similar epidemiology. Alzheimer's disease (AD) is the most common form of dementia and increases from 16% in 75-year-old to 84-year-old to 48% in over-85s^[1]. Osteoporosis affects 25% of women and 10% of men over 60^[2]. The two diseases co-exist in a subsection of the population, especially amongst females^[3]. Indeed, an odds ratio of 6.9 for fracture prevalence between people with and without AD has been reported^[4]. Thus a common link has been suggested despite no apparent pathological overlap.

The pathogenesis of AD lies in three complex mechanisms^[5]. The development of amyloid senile plaques causes neuronal death and phosphorylation of Tau proteins. Tau disassembles the microtubules resulting in neurofibrillary tangles and ultimately neuronal degeneration. Amyloid and Tau localise in the synapses, causing excessive calcium entry into post-synaptic neurons, necrosis and apoptosis. Despite extensive research into the disease, current treatment options are limited by their cost and efficacy. Their action lies in palliation of symptoms and most are only effective in a subsection of AD sufferers.

Osteoporosis is a progressive skeletal disease characterised by reduced bone density and micro-architectural bone destruction. This leads to increased bone fragility and susceptibility to fracture. Like dementia, the pathophysiology of osteoporosis is multifactorial and extends far past the traditional theory of nutritional calcium depletion. Indeed, both diseases have been associated with a number of other metabolic disturbances such as decreased vitamin D concentration and elevated serum parathyroid hormone, in addition to postulated common genetic variations such as the APOE4 allele^[2].

The burden of elderly care is a significant challenge to healthcare systems throughout the world and will only continue to grow in the coming decades. AD is the leading cause of loss of autonomy and independency in the elderly, and is associated with a number of comorbidities^[6]. Osteoporotic fractures have huge impact in terms of morbidity and mortality. Both diseases form part of the frailty syndrome, a collection of signs and symptoms associated with significant disability and public expenditure^[7]. Here we hypothesize that osteoporosis and dementia share a common predisposing aetiology. We propose that this is multifactorial, involving genetic, metabolic, endocrine and environmental factors. Elucidation of a common link between the two diseases could prove vital in the development of novel treatments for these complex medical and social problems.

MATERIALS AND METHODS

A comprehensive literature search of Ovid MEDLINE (1950

to June 2016) was conducted. The keywords "osteoporosis", "osteoporotic fracture", "dementia" and "Alzheimer's disease" were used initially to determine the theoretical links with the most significant evidence base behind them. From manual study of key papers the lead investigators selected these to be vitamins D and K, calcium, thyroid disease, statins, alcohol and sex steroids. These subjects were searched in combination with the previous terms. Manual examination of titles and abstracts was used to exclude irrelevant articles. Theoretical, *in vitro* and *in vivo* research were all used to inform this review which focuses on the most well developed theoretical common causes for dementia (predominantly Alzheimer's type) and osteoporosis.

RESULTS

Vitamin D

Approximately 1 billion adults are vitamin D deficient worldwide, and the prevalence is especially marked in older people, ranging from 50%-80%^[5]. Vitamin D has long been known for its effects on phosphocalcic metabolisms and bone^[5], thus vitamin D deficiency is well established as a risk factor for the development of osteoporosis^[8]. In contrast, the association between vitamin D and dementia requires clarification.

In 1995, Kipen *et al.*^[8] found significantly lower vitamin D in women with dementia compared to cognitively-intact controls. A subsequent cross-sectional study found a vitamin D deficiency of < 10 ng/mL doubled the risk of cognitive impairment^[9]. A similar association between severe vitamin D deficiency (here defined as < 25 nmol/L at baseline) and mild cognitive impairment has been seen in elderly subjects over 65 years of age^[10].

A recent large Danish prospective study looked at participants who were free of cognitive impairment at enrolment and found that a decline in serum levels of vitamin D were associated with increased risk of participants developing AD^[11]. A more diverse American prospective study with a shorter length of follow up also found an association between baseline vitamin D deficiency (defined by the authors as serum levels < 50 nmol/L) and likelihood of participants developing AD and other all-cause dementias, an association that remained despite adjustment for mediators such as diabetes and hypertension^[12]. Both these studies looked at healthy participants who were ambulatory at enrolment^[11,12]. However reduced exposure to sunlight in patients with AD has been implicated as the main cause of vitamin D deficiency in patients with dementia^[13]. Patients with dementia are often immobile or housebound, and may be unable to gain sufficient sunlight exposure. Furthermore, generalised malnutrition either due to changes in functional ability, appetite disturbance, or disease may compound this problem.

In addition to environmental and functional changes, a decline in renal function accompanies the process of aging with the incidence of chronic kidney disease quoted as up to 35.8% in the geriatric population^[14].

Chronic renal disease results in impaired 1,25 dihydroxycholecalciferol production, the physiologically active metabolite within the body. Patients with suboptimal production of 1,25 dihydroxycholecalciferol may have this confirmed by low serum levels, and evidence of a secondary hyperparathyroidism^[15].

Aside from well-established physiological effects on bone metabolism, vitamin D has been found to play a pivotal role in both the normal function and protection of the central nervous system (CNS). As a neurosteroid hormone, vitamin D receptors are found in the neurons and glial cells of the CNS^[5]. The binding of 1,25 dihydroxycholecalciferol to these receptors results in a number of neuroprotective mechanisms. These can be categorised as direct, immune and homeostatic.

Directly, vitamin D inhibits the synthesis of nitric oxide synthase, an enzyme which promotes neuron alterations, and increases the synthesis of neurotrophic agents such as nerve growth factor^[5]. In addition, neuronal-glia cell cultures treated with vitamin D show increased expression of genes known to limit the progression of AD^[16]. Vitamin D is also known to increase the number of macrophages and leukocytes in the brain. *In vitro* studies of macrophages from AD patients showed that stimulation with vitamin D increased phagocytosis and clearance of amyloid^[17]. Vitamin D plays an important role in the homeostasis of calcium and the avoidance of hyperparathyroidism by upregulating calcium channels and the synthesis of calcium-binding proteins^[5]. The importance of calcium and parathyroid status is discussed later.

Despite evidence *in vitro*, conclusive evidence of a link between vitamin D and dementia in patients is lacking (Table 1). In cross-sectional studies, vitamin D deficiency has been shown to double the risk of presenting with cognitive impairment^[9]. However, the nature of cross-sectional studies means that no cause and effect link can be made. Clearly, dementia may be the cause of reduced mobility and therefore reduced exposure to sunlight. A recent BMJ editorial criticised the perceived reliance on cross-sectional studies in relation to vitamin D as an aetiological factor in AD. It cited "a range of interpretational difficulties" such as reverse causality, confounding, classification bias and differences in assay methods^[18].

Nevertheless, in longitudinal studies, low baseline vitamin D levels have been found to predict incident cognitive decline in the elderly. A study of 858 Italians over the age of 65 showed that those who were "severely deficient" in vitamin D had a 1.6-fold increased risk of a substantial cognitive decline over 6 years, thus providing a temporal association^[19]. Another longitudinal study looking at time to progression to AD along with vitamin D treatment status, found that time to progression was longer in those treated with vitamin D (5.4 ± 0.4 years, $P = 0.003$) than in those who were not supplemented (4.4 ± 0.16 years, $P = 0.003$) but only in those who went on to develop severer manifestations of the disease^[20]. This study however was limited again by an observational

Table 1 Studies investigating the association between vitamin D and cognition

Study design	Ref.	Population	Results
Cross-sectional study	[88]	80 community-dwelling women 40 with mild AD 40 cognitively-intact	Vitamin D deficiency was associated with impairment on two of four measures of cognitive performance
	[89]	32 community-dwelling patients	Significant positive correlation between vitamin D concentrations and MMSE scores
	[90]	9556 community-dwelling patients	Lower 25(OH)D levels were not associated with impaired performance on various psychometric measures
	[91]	225 older outpatients diagnosed as having probable AD	Significant positive association between MMSE test scores and serum 25-hydroxyvitamin D(3) levels
Case-control study	[92]	5596 community-dwelling women	Significant positive association between vitamin D intakes and cognitive performance
	[93]	69 community-dwelling patients	A significant negative correlation between dietary intake of vitamin D and poor performance on cognitive tests
	[94]	148 community-dwelling patients	No significant positive association between cognitive performance and serum 25-hydroxyvitamin D(3) levels
Longitudinal study	[95]	1138 community-dwelling men	Independent association between lower vitamin D levels and odds of cognitive decline
	[19]	175 community-dwelling patients	1.60-fold risk of losing at least 3 points on MMSE in 6 yr with low baseline vitamin D
Pre-post study	[96]	63 frail nursing home residents 25 in intervention group 38 in control group	No treatment-induced improvement in ambulation, cognition or behaviour was observed
	[21]	13 community-dwelling patients with mild to moderate AD	Significant improvement in ADAs-cog score
Randomised controlled trial	[21]	32 community-dwelling patients with mild to moderate AD 16 in intervention group 16 in control group	Neither cognition nor disability changed significantly after high-dose D

AD: Alzheimer's disease.

study design and exclusion of some confounders from analysis, for example treatment with psychotropic medication^[20]. Pre-post studies, where cognitive function was measured before and after supplementation of vitamin D, found an improvement in cognition concomitant with the increase in vitamin D concentrations^[5]. There is only one, small randomised controlled trial on this topic, where 32 individuals with mild to moderate AD received low-dose vitamin D supplementation for 8 wk, before being randomised to either continue with the low dose (plus placebo) or to receive an additional high-dose supplement for a further 8 wk. Cognition was tested using a number of validated scales. Despite promising results from a smaller pilot study, the authors found that supraphysiological doses of vitamin D were no better than physiological doses at improving cognition or disability in this group, but acknowledge the limitations of such a small sample size^[21].

Vitamin K

Vitamin K is the collective term for a group of fat-soluble vitamins responsible for gamma-carboxylation of glutamate at various sites in the body. In the liver, vitamin K plays a vital role in the modification of prothrombin and other proteins responsible for haemostasis^[1]. In addition, vitamin K promotes bone health by means of site-specific carboxylation of osteocalcin (a marker of bone formation) and other bone matrix proteins such as matrix Gla-protein and protein S^[22]. In vitamin K deficiency,

undercarboxylated osteocalcin is associated with osteoporosis and increased risk of fracture^[1]. A meta-analysis of 3 trials involving patients with neurological disease (AD, stroke and Parkinson's Disease) showed that when vitamin K is replaced, there is a decreased risk of fractures compared to non-treatment^[23].

As with vitamin D, the link between vitamin K and osteoporosis is well-established, whilst any connection to dementia remains both multifactorial and largely theoretical. Numerous observational studies from Japan have indicated that vitamin K deficiencies contribute to reduced bone mineral density in patients with AD^[22]. A number of reasons have been postulated for the association between vitamin K deficiency and dementia including that of reverse causality.

It is plausible that, rather than vitamin K deficiency causing dementia, it is the dementia which affects vitamin K levels through malnutrition. Suboptimal dietary intake is evident even in the early stages of AD compared to cognitively intact age-matched controls^[24]. In humans, vitamin K₁ is dietary, whilst K₂ is synthesised by gut bacteria^[3]. In a cross-sectional study of 100 women with varying degrees of AD, BMI, bone mineral density and vitamin K₁ levels were significantly lower in severe AD compared to mild AD^[3]. However, vitamin K₂ levels were not significantly decreased, indicating a nutritional cause. Another study analysed the dietary vitamin K intakes of 31 patients with mild AD, compared to 31 controls.

Vitamin K intakes were significantly less in patients with AD, even after adjusting for energy intake^[25].

Nevertheless, vitamin K does also appear to have a direct effect on the brain. Vitamin K-dependent gamma-carboxylation of glutamate in the liver and bone has already been discussed. This process is also apparent in the brain, by which growth-arrest-specific gene (*Gas6*) is biologically activated. Yagami *et al.*^[26] investigated the effect of *Gas6* in primary cultures of rat cortical neurons. *Gas6* was shown to protect against AD by the rescue of cortical neurons from amyloid-induced apoptosis^[26]. In addition, vitamin K is involved in sphingolipid synthesis. Sphingolipids are an important constituent of the myelin sheath and the neuron cell membrane, and alterations in sphingolipid metabolism have been identified in the brains of patients with mild AD^[25].

Alternatively, dementia and vitamin K deficiency may share a common cause. As previously discussed, apolipoprotein E4 (APOE4) is an allele that has been well-established as a risk factor for AD^[3]. APOE is found in chylomicrons which bind to vitamin K in plasma^[1]. APOE binds to a hepatic LDL receptor and LDL receptor-related protein (LRP); the variant APOE4 binds particularly quickly, thus reducing plasma vitamin K levels^[1]. The concentration of vitamin K is therefore lower in the circulating blood of APOE4 carriers^[1] and women expressing the APOE4 allele have been shown to have a significantly increased risk of osteoporotic hip fractures compared with those with other APOE genotypes^[27]. Another genotype, consisting of two copies of the apolipoprotein allele E2, has also been associated with increased frequency of vertebral fractures, suggesting further that apolipoprotein polymorphisms may play a role in bone mineral density and fracture risk^[28].

Although the association between vitamin K and dementia appears strong, there is little outside of cell work to prove a causal relationship. The evidence thus far lies in observational studies^[22] and a small number of randomised controlled trials in which vitamin K supplementation has been proven to reduce the risk of fractures in patients with neurological disease^[23]. This effect is assumed to be bone-mediated, and the possibility of improved cognitive function is not explored.

Calcium and hyperparathyroidism

Calcium has long been known to contribute to bone health. In combination with vitamin D, calcium promotes osteoblast differentiation and formation of mineralised bone, thus impairment in calcium signalling can contribute to the pathophysiology of osteoporosis^[29]. Likewise, the role of calcium homeostasis in the pathophysiology of dementia has been extensively investigated for almost three decades. The "calcium hypothesis" of the late 1980s^[30] postulates that "in the aging brain, transient or sustained increases in the average concentration of intracellular free calcium contribute to impaired function, eventually leading to cell death". This hypothesis was supported by a range of animal and human studies, the earliest of which have been well-described by Disterhoft *et al.*^[30]. For example, administration of magnesium, a

calcium channel antagonist, to aging rats was shown to reduce calcium influx in hippocampal neurons and reverse functional and learning difficulties. Similarly, nimodipine, an isopropyl calcium channel antagonist that readily crosses the blood-brain barrier, was found by a recent Cochrane review to be of "some benefit in the treatment of patients with features of dementia due to unclassified disease or to AD, cerebrovascular disease, or mixed Alzheimer's and cerebrovascular disease" although the authors stressed this benefit could only be applied to short-term outcomes^[31].

The role of calcium in the pathophysiology of impaired cognition is complex. Calcium is required for the function of all cells in the body, including neurons. The neurons of aged animals have been found to exhibit enhanced calcium activity compared to their younger counterparts^[32]. This has been attributed to an excess of calcium influx *via* voltage-gated calcium channels. Indeed, an increased density of these channels has been positively correlated with cognitive decline in animals. Further, in humans, enhanced intracellular calcium release from the endoplasmic reticulum has been found in the ageing brain, and research into this phenomenon continues^[32].

To propose that changes in calcium transport and metabolism forms the basis of link between osteoporosis and dementia seems counterintuitive, as the former may result from falling calcium levels, whilst the latter has been attributed to high intracellular calcium. One possible mechanism is that calcium deficiency and the resultant secondary hyperparathyroidism results in bone loss whilst shifting calcium from the skeleton to the soft tissue, and from the extracellular to the intracellular compartments^[33]. Indeed a recent cross-sectional study has found association between high levels of PTH with low bone mineral density, which persisted even in participants where serum calcium levels were not overtly deficient^[34].

Increased parathyroid activity is well known to be associated with impaired cognitive function. Moreover, a recent 10-year longitudinal prospective study found that elevated PTH concentrations are associated with a five-year cognitive decline in a general aged population, although this was found to be independent of calcium concentrations^[35]. Further investigation would be required to establish a common role for calcium as a contributing factor to both osteoporosis and cognitive decline.

Thyroid disease

Overt thyroid disease is well known to be a reversible cause of cognitive impairment and altered bone metabolism^[36]. Subclinical thyroid disease - whereby normal levels of thyroxine (T4) and tri-iodothyronine (T3) are coupled with a deranged level of thyroid stimulating hormone (TSH) - is being increasingly recognised as a cause of significant morbidity and mortality within the elderly population^[37].

Subclinical hyperthyroidism: Subclinical hyper-

thyroidism (levels of T3 and T4 that are towards the top of the reference range coupled with reduced TSH, without symptoms of thyrotoxicosis) has been associated with various pathologies, and affects both bone mineral density and cognition^[38]. This may be due to exogenous causes, *i.e.*, excessive replacement with levothyroxine in hypothyroid patients; or endogenous causes such as Grave's disease^[37].

There is considerable debate as to whether it is the level of TSH or of T4 itself that results in the physiological effects of thyroid hormone excess. A prospective study in Rotterdam found that individuals with subclinical hyperthyroidism had a greater than threefold increase in risk of developing dementia; with higher levels of T4 conferring greater risk. It is worth noting that none of these patients had a T4 level above the reference range^[36]. This finding is supported by a further retrospective study, which also demonstrated an association between elevated thyroid hormone levels and dementia, not related to the concentration of TSH. It therefore seems likely that the level of T4 is the important determinant^[39]. Furthermore, in a prospective cohort study of 665 Japanese-American men, followed-up for development of dementia after thyroid function was recorded, subsequent autopsy of one fifth of the cohort-including both healthy and demented patients-demonstrated that at higher levels of T4, more numerous intracerebral tangles and plaques are seen, as well as clinical dementia^[40].

Data regarding any association between osteoporosis and subclinical hyperthyroidism is unclear. Some studies show low levels of TSH appear to result in slightly reduced bone mineral density in men and post-menopausal women, but the protective effect of oestrogens means this does not generally apply in pre-menopausal women^[41]. The fifth Tromso population study in Norway, conducted in 2001, compared bone mineral density levels of TSH whilst adjusting for possible confounding factors such as weight and smoking. It discovered that, if TSH was normal, there was no relationship to bone mineral density; however, low TSH was seen in subjects with lower bone mineral density^[42]. T4 levels that are within the normal range are correlated with a lower level of bone mineral density at both the higher and lower ends of the spectrum - that is, in the region of subclinical thyroid disease^[36,43]. These hormone derangements are also associated with increased risk of fracture^[44].

Subclinical hypothyroidism: Subclinical hypothyroidism is a significant problem within the elderly population, and is more common than overt hypothyroidism^[45]. Despite the above discussion relating subclinical hyperthyroidism to cognitive impairment and dementia, patients with subclinical hypothyroidism have also been shown to be more likely to develop such attributes^[46]. This may be due to the effect of T4 itself, or reduced hormone concentration within the brain, resulting in slower information processing and increased susceptibility to cognitive dysfunction^[47]. It is also worth noting that treatment with levothyroxine has

been shown to reduce cognitive impairment and improve mood in patients with mild hypothyroidism^[48]. Currently, although there is evidence that both states can cause cognitive decline, subclinical hyperthyroidism appears to have a stronger association with the development of dementia. A small scale study of 59 patients with multi-diagnosis dementia found a slight increase in TSH serum levels patients with AD compared to other diagnosis dementia patients and with healthy controls, along with a decrease in cerebrospinal fluid (CSF) total T4 levels in both patients with AD and those with other diagnoses compared to healthy controls^[49]. The CSF total T4 levels correlated positively with MMSE test scores and negatively with markers of axonal damage, which the authors hypothesized may mean that central levels of T4 are functionally important in AD^[49].

Despite the association between subclinical hypothyroidism and cognitive impairment, osteoporosis has not specifically been linked to subclinical hypothyroidism. Overtreatment of these patients with thyroxine has in fact been shown to lead to reduced bone mineral density and an increased rate of osteoporosis^[50,51]. This represents an important clinical disadvantage, and clinicians should exert caution in deciding whether or not to treat subclinical hypothyroidism^[51]. Subclinical thyroid disease is common in the elderly population, and has been shown to be associated with a number of co-morbidities including osteoporosis and dementia in the case of subclinical hyperthyroidism. Additional work is required to establish if age-related changes in thyroid hormone concentrations represent a common factor in the aetiology of both conditions. Furthermore, investigating the treatment of subclinical disease, and whether or not it results in a lower rate of dementia and osteoporosis in the elderly, represents an exciting avenue for research in the future.

Alcohol

Excessive alcohol use is well known to result in low bone mineral density and increased risk of fracture^[52]. This has been thought to be due to a direct deleterious effect on osteoblast activity and subsequently a decrease in bone formation^[53], however this mechanism is not likely to be related to the development of dementia. Recently it has been suggested that lower levels of vitamin D in chronic alcoholics may be related to hepatic insufficiency and subsequently impaired metabolism of the substance^[54]. This could in turn affect bone formation. It must be remembered that low to moderate levels of alcohol intake does not reduce bone density; however, there has been no protective effect demonstrated either.

Whilst chronic excessive alcohol use leads to unique forms of dementia (*i.e.*, Korsakoff's syndrome) this is secondary to vitamin deficiencies, especially thiamine. Ethanol toxicity has been shown in rats to cause hippocampal and cortical cell loss, as well as loss of proteins required for neuronal survival^[55]. However, at low to moderate levels of intake there appears to be a protective effect against developing dementia^[56,57]. Interestingly, there was no protective effect seen in individuals with the

APOE4 gene^[56]. The reasons for this protective effect are currently unclear.

It is difficult to assess whether alcohol intake is related to an increased risk of osteoporosis and dementia, especially given the likely protective effect of a moderate alcohol intake against dementia. The multiple comorbidities often experienced by chronic alcoholics (most notably nutrient deficiency) means studies are affected by a number of confounding factors. Varying patterns in form and frequency of alcohol abuse also make analysis difficult. Any link that were to be demonstrated would possibly be due to a secondary impact on another aspect of physiology (such as vitamin D deficiency), as opposed to an innate property of ethanol itself.

Statins

Statins (HMG CoA reductase inhibitors) are currently the target of a large volume of research given their supposed pleiotropic effects. As well as treating dyslipidaemia, statins have been proposed as being effective against malignancy, nephropathy, cataract formation and macular degeneration as well as against osteoporosis and dementia^[58].

The role of statins in reducing the risk of dementia was classically thought to be due to their role in reducing plaque formation, hence reducing vascular insults to the brain and the risk of ischaemic neuronal loss^[59]. Newer studies have proposed a systemic reduction in the inflammatory response, as evidenced by the ability of statins to reduce levels of C-reactive protein^[60]. Statins act on the mevalonate pathway, inhibiting conversion of HMG-CoA to mevalonate^[61]. Mevalonate is a precursor of the interleukin-6 group of cytokines which are implicated in systemic inflammation^[60]. It is possible that a reduction in systemic inflammation by inhibiting this pathway may help to prevent the development of dementia^[62].

Given the interest in the proposed mechanisms, Cochrane reviews have been held into randomised controlled trials of both the prevention and treatment of dementia by statins. They have found that despite marked reductions in serum low density cholesterol levels, statin use neither improves cognitive function in those with dementia nor does it reduce the incidence. The reviews conclude that there is insufficient evidence to recommend statins as either a prophylactic against, or treatment for, dementia^[63,64].

New theories on the development of osteoporosis hold that the mechanism is similar to that whereby lipids are oxidised^[65]. If statins were shown to act directly on this mechanism then a beneficial effect in osteoporosis would also be likely. *In vitro* studies investigating mechanisms by which statins stimulate osteoblast differentiation have demonstrated that they exert their effects *via* the SMAD and the bone morphogenetic protein-2 (BMP-2) signalling pathways^[66]. A recent review of *in vitro* and *in vivo* data suggests that statins also act *via* the RANKL pathway, which has been implicated in both adipogenesis and in changing osteoclastic activity, leading to osteoporosis^[67].

Whilst there are theoretical benefits of statins in both dementia and osteoporosis, they have yet to be demonstrated in clinical studies. A large meta-analysis of hip bone mineral density showed a small but statistically significant benefit in patients taking statins^[68]. However, this advantage does not translate into a decreased risk of fracture, according to a systematic review of studies observing fracture incidence in patients taking statins^[69]. A recent RCT has also failed to demonstrate the benefit of specific statins in decreasing fracture risk^[70]. Further evidence is required before routine statin use can be recommended for the prevention or treatment of either condition.

Androgens and oestrogens

Sex steroids play important roles in reproductive function, and in recent years receptors for these hormones have been identified in a range of body tissues, including bone and the nervous system^[71]. The relationship between ageing, falling levels of sex steroids, and the subsequent reduction in bone mineral density is well described and a cause of much morbidity in the elderly population. Reduction in oestrogen levels in women is known to result in increased osteoclast activity and bone resorption^[72]. The androgens are also known to be important in maintaining bone mineral density, both through intrinsic activity and as a result of aromatization to oestrogens^[73]. Androgen activity gradually reduces in later male life, hence the resulting increase in rates of osteoporosis in older men. Whilst administration of endogenous sex steroids in the form of hormone replacement therapy in post-menopausal women does reduce the risk of fracture, it is no longer recommended for the prevention of osteoporosis due to cardiovascular side-effects^[74]. Newer theories propose that oxidative stress holds an important role in the development of osteoporosis, and that sex steroids are important in protecting against this^[65]. This would represent a possible therapeutic target with statin agents, if such a mechanism is proven.

Androgens and oestrogens have been suggested as being protective against AD, given that cognitive impairment is associated with a decrease in testosterone levels^[75]. Animal studies have shown increased neuronal activity when testosterone supplements are administered, but the data from clinical trials is disappointingly inconclusive^[75]. Additionally, the role of oestrogen in both preventing cognitive decline in intellectually normal women, and in maintaining cognitive function in patients with AD, has been the subject of a number of systematic reviews. Insufficient evidence for any beneficial effect was found for oestrogen administration in all studies reviewed^[76,77]. Moreover, one review of long-term hormone replacement therapy found that in healthy women aged over 65 there was an increased incidence of dementia^[74], although this is unlikely to be due to a direct effect of hormone replacement, and may simply be a result of an increase in frequency of cardiovascular events, a known independent risk factor for developing dementia.

There has been recent animal work looking at the effects of sex steroid analogues, so called selective androgen receptor agonists (SARMs) and selective estrogen receptor agonists, which are thought to allow for the beneficial effects of the sex steroids in protecting against neurodegenerative disorders whilst avoiding detrimental cardiovascular tissue effects which may also contribute to development of dementia^[78]. Such analogues are thought to interfere in the progression of AD by aiding clearance of amyloid beta peptides from neurological tissue^[78]. In the treated mice there were decreased levels of amyloid beta, along with increased levels of amyloid beta clearing enzymes and improved long term memory^[78].

The evidence surrounding changes in sex steroid levels and dementia is inconclusive. There is no firm evidence for a beneficial effect of androgen administration, and the increase in frequency of cardiovascular events causes significant morbidity and may increase the prevalence of dementia itself. This may be due to the significant increase in cholesterol levels associated with falling androgen levels^[79]. Additionally, the low levels of androgens demonstrated in some men with dementia may be unrelated or may be secondary to the disease itself.

DISCUSSION

Despite various possible mechanisms for a link between the two pathologies, it is also quite possible that these associations are coincidental and not related to a common aetiological factor. Only one such investigation into common aetiologies exists in a 2014 study which found raised amyloid beta peptide levels in osteoporotic bone tissue compared to age matched controls in female patients^[80]. The level of amyloid beta expression negatively correlated with bone density levels in this study^[80]. Amyloid beta was found to also have an impact on osteoclast differentiation and activation, implying it may play a role in the pathological processes of osteoporosis^[80]. Authors hypothesized amyloid beta disorders to be systemic disorders resulting in differing tissue manifestations^[80], yet robust evidence remains to be produced regarding this link and regarding the exact aetiology of amyloid beta in AD.

People with dementia are more prone to falls and fractures due to cognitive and behavioural disorders, visual and motor problems, gait and balance disturbances, malnutrition, and the adverse effects of medication^[81]. Thus there may be a higher pick-up rate for osteoporosis amongst this group. However, a population-based study of more than 2600 elderly people found that those with dementia received less preventative treatment for osteoporosis compared to people without dementia^[82]. In patients who have received the appropriate prescription, efficacy may be diminished in patients with dementia due to factors such as medical comorbidities, polypharmacy, lack of adherence, substance abuse, delirium and inadequate social support^[83].

Nevertheless, we hypothesise that dementia and osteoporosis have common aetiologies as significant

counterevidence exists in recent literature. There remains a significant increased prevalence of osteoporosis in AD sufferers in large scale observational studies compared to the general population, with an odds ratio for femoral fracture amongst a French female population the same as that of other severe systemic illnesses (OR = 4, $P < 0.0001$). The mortality and morbidity associated with such fractures in elderly populations prompts continued interest in this area of research^[84]. Furthermore, following femoral neck fracture treatment and subsequent inpatient stays, this subsection of the population has been found to have poor return to previous functional states as measured by residential status, along with poor 30-d mortality compared to patients without dementia^[85]. Other very large scale observational studies have had compelling results in favour of a potential link, with Chang *et al.*^[86] finding a 1.46-fold and 1.39-fold higher risk of dementia (95%CI: 1.37-1.56) and AD (95%CI: 0.95-2.02) in osteoporosis patients studied, whilst adjusting for potential confounders such as comorbid disease. This Taiwanese cohort also demonstrated a negative correlation between treatment for osteoporosis (such as bisphosphonates) and the risk of dementia, with the most marked negative correlation found in those taking bisphosphonates and oestrogens^[86]. However, patients with dementia have repeatedly been found to be least likely to be prescribed osteoporosis treatments which may have such protective effects both in terms of fracture risk and cognitive health^[87]. Despite these recent findings, the same limitations to such large scale retrospective studies apply and further RCTs would be required to provide higher quality evidence of such links despite the varied evidence explored in this paper.

The most compelling evidence for a common aetiology is the APOE4 allele, a major cholesterol carrier, and a well-established genetic risk factor for AD *via* its binding to Amyloid beta peptide and its potential role in deposition of senile plaques^[3]. APOE4 has also been found to be associated with fracture, independent of dementia and falling^[27]. The mechanism behind this effect on fracture risk is postulated to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele, which binds vitamin K in the plasma and promotes its uptake into the liver more rapidly than other APOE variants. Women who express this allele have a higher risk of osteoporotic fractures than other APOE genotypes found in the general population^[1]. This may be multifactorial in its effect and augmented by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. In particular, vitamins D and K are known to play a role in the both bone matrix stability and neuronal protection in the CNS. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies.

Robust evidence of an underlying pathophysiological link between osteoporosis and dementia would potentially transform the care of the older adult. Research to date has tended to be fragmented and of a relatively weak

nature with multiple confounding factors reflecting the difficulties of *in vivo* experimentation in the population of interest. A suggestion for future work would include randomised controlled trials of vitamin supplementation vs placebo, stratified for APOE4 and hormone status. As our understanding of the molecular basis of osteoporosis and dementia improves, new therapeutic targets should become apparent.

COMMENTS

Background

Dementia and osteoporosis are diseases processes with similar epidemiology and increasing prevalence in the elderly, where the two coexist in a subsection of the population especially amongst females. The burden of elderly care continues to be a significant challenge to healthcare systems globally. Alzheimer's disease (AD) is the leading cause of loss of independence and autonomy in the elderly and osteoporotic fractures have a huge impact in this patient population in terms of morbidity and mortality. An odds ratio of 6.9 for fracture prevalence between people with and without AD has been reported. In current understanding of the disease aetiologies no pathological overlap has been identified but a common link has been postulated to exist. The pathogenesis of AD is currently understood to involve development of amyloid plaques causing neuronal death and subsequent phosphorylation of Tau proteins, which ultimately cause further neuronal degeneration and the localisation of these two abnormal proteins in the synapses causes post-synaptic neuronal death via calcium influx. Despite extensive research into AD and its multifactorial pathophysiology, current treatments are limited by cost and efficacy and their action lies in palliation of symptoms. Osteoporosis in contrast is a progressive skeletal disease characterised by reduced bone density and micro-architectural bone destruction leading to increased susceptibility to fracture. Both diseases have multifactorial pathophysiology and have been associated with other metabolic disturbances including decreased vitamin D levels and elevated parathyroid hormone. Other genetic variants such as the APOE4 allele have also been postulated to link their pathophysiology.

Research frontiers

Both osteoporosis and AD form part of frailty syndrome, a collection of signs and symptoms associated with significant disability in the elderly population and increased public expenditure in healthcare and social care systems. This paper hypothesizes that both diseases share a common predisposing aetiology, which may be multifactorial and involve genetic, metabolic, endocrine and environmental factors.

Innovations and breakthroughs

Many studies have been conducted in the last 60 years exploring various aspects of the pathophysiology of both osteoporosis and dementia as both diseases represent significant burdens upon the affected populations. However very few have been higher tier research designs such as randomised control trials or specifically examined an aetiological link as addressed by the research question of this paper. The authors' key findings were that the most compelling evidence of a common yet independent aetiology lies in the APOE4 allele, which is a well-established risk for AD but also carries an independent association with fracture risk and so osteoporosis. The mechanism behind this is thought to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele which may be amplified by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies which are then well associated with increased risk of fracture.

Applications

Discovery of a common aetiological link between the two may prove key in development of novel treatments for these complex medical and social problems. This study found that research to date on this topic has tended to be fragmented and of a relatively weak nature with multiple confounding factors, which may reflect inherent difficulties of *in vivo* experimentation in the

population of interest. Despite many theoretical links between the two diseases, there is a lack of systematic high level evidence and as such the link between the two remains theoretical. This study may help direct design of future large scale studies or RCTs in the affected population groups.

Peer-review

This is an interesting study, and what is reviewed is well done.

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Surgery for calcifying tendinitis of the shoulder: A systematic review

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Abstract

AIM

To systematically search literature and determine a preferable surgical procedure in patients with failed conservative treatment of calcifying tendinitis of the shoulder.

METHODS

The electronic online databases MEDLINE (through PubMed), EMBASE (through OVID), CINAHL (through EBSCO), Web of Science and Cochrane Central Register of Controlled Trials were systematically searched in May 2016. Eligible for inclusion were all available studies with level II and level III evidence (LoE). Data was assessed and extracted by two independent review authors using a specifically for this study designed data extraction form.

RESULTS

Six studies (294 surgically treated shoulders) were included in this review. No significant differences between the three available treatment options (acromioplasty with the removal of the calcific deposits, acromioplasty or solely the removal of the calcific deposits) were detected regarding the functional and clinical outcome. The follow-up ranged from 12 mo to 5 years. Complication rates were low. No reoperations were necessary and the only reported complication was adhesive capsulitis, which in all cases could be treated conservatively with full recovery.

CONCLUSION

We found that all three available treatment options show good functional and clinical outcomes in the short and midterm. However, a favorable procedure is difficult to determine due to the lack of high-quality comparing studies.

Key words: Calcifying tendinitis; Surgery; Systematic review; Acromioplasty; Debridement

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Core tip: All three available surgical treatment options (acromioplasty with the removal of the calcific deposits, acromioplasty or solely the removal of the calcific deposits) show good functional and clinical results and low complication rates. However, more high-quality comparative research is needed to appoint a preferential procedure.

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INTRODUCTION

Calcifying tendinitis (CT) of the shoulder is a common disease. It is one of the most frequent causes of non-traumatic shoulder pain and has a high disease burden. In a healthy population the incidence of subacromial calcific deposits is 2.7%^[1]. In patients with shoulder complaints this number rises to 6.8%. CT mainly affects individuals between 30 and 60 years of age. Males and females are equally affected^[1-3]. The calcific deposits are most frequently (80%) seen in the supraspinatus tendon, at a typical location of 1.5 to 2.0 cm of its insertion on the major tuberculum. CT is primarily treated conservatively, though in about 10% of the cases this fails. Then often surgery is a last resort. The etiology of CT remains unclear and is still a matter of dispute. Some authors state that CT is not related to subacromial impingement^[2]. This is supported by the histological finding in the study of Uthoff *et al.*^[4]. In this study only minimal signs of inflammation in the rotator cuff of patients with CT were seen. Conversely, other authors observed that there was neovascularization and influx of phagocytes around the calcific deposits. As they state this could lead to subsequent edema of the rotator cuff and an increase of the intratendinous pressure. This theoretically can lead to secondary subacromial impingement as the thickened and calcified tendon decreases the subacromial space. Others state that impingement causes rotator cuff tendinitis, which when chronically apparent leads to CT, due to decreased local oxygen tension or hypoxia^[1,2,5,6].

There are several surgical procedures available, mostly in accordance with the above-mentioned theories. In the current orthopedic literature three major surgical strategies have been postulated. The first is an acromioplasty in combination with removal of the calcific deposits, the second is an acromioplasty without removing the calcific deposits and the third surgical procedure is to solely debride the calcific deposits and leave the acromion untouched. However, there is still

some debate what is the most preferable procedure. It remains unclear whether the calcific deposits need to be, completely or partially, removed and if an additional acromioplasty is beneficial.

Therefore, the objective of this study is to determine if there is a preferable surgical procedure in patients with conservative treatment resistant CT. We performed a systematic review with two clear research questions: (1) Is there a difference in functional and clinical outcomes after debridement of the calcifications in comparison with debridement and additional acromioplasty on the short- and mid-term; and (2) Is there a difference in the functional and clinical outcomes after acromioplasty compared to acromioplasty with debridement of the calcifications on the short- and mid-term?

MATERIALS AND METHODS

This review was performed and written down following the principles of the PRISMA statement^[7]. Five relevant electronic databases (MEDLINE through PubMed, EMBASE through OVID, CINAHL through EBSCO, Web of Science and Cochrane Central Register of Controlled Trials) were systematically searched by one review author (FV) in May 2016 for studies in English, German and Dutch. Furthermore, the reference lists of the included articles and available reviews were crosschecked for possible relevant studies. The search was set up using a PICO format [patient (or disease), intervention (drug or treatment), comparison (another drug of treatment) and outcome], from which search terms were deduced, as can be seen in Table 1. Studies eligible for inclusion were Level of Evidence (LoE) II (randomized controlled trials) and LoE III (comparative cohort studies) that compared different surgical procedures for CT of the shoulder. From the selected articles, the authors, their institutions and the journal name were masked, a few weeks before data assessment took place.

Data assessment and management

Risk of bias and the quality of the included studies were assessed independently by two authors (FV, EF). The included RCTs and quasi-RCTs were assessed using the 12 quality criteria of Furlan *et al.* (2008). High-Quality was defined as a "yes" score in $\geq 50\%$ of all items^[8]. The non-randomized studies were assessed using the Newcastle-Ottawa assessment scale^[9]. Disagreements were resolved by consensus, or when necessary a third review author (JWM) was consulted. Data was independently extracted by two reviewers (FV, EF) and crosschecked for accuracy. The reviewers were blinded to the authors of the included articles, their institutions, and the journals in which they were published. Data from each individual study was extracted in a standardized way using a specifically designed extraction form (appendix 1 in supplemental material). Discrepancies were resolved by scrutinizing the original article until a consensus was reached. Extracted data included information such as inclusion and exclusion

Table 1 PICO search strategy

Population	Patients with radiographically confirmed symptomatic tendinitis calcarea of the shoulder (search terms: Shoulder joint, rotator cuff, shoulder, supraspinatus, infraspinatus, subscapular or teres, impingement syndrome, tendinopathy, tendonitis or tendinitis, tendinosis, calcinosis, calcifying, calcification, calcified, calcific, calcarea)
Intervention	Surgery (search terms: Surgery, surgical, orthopaedic surgery, shoulder surgery, acromioplasty, debridement, bursectomy, arthroscopic, Neer)
Comparison	Surgery (search terms: Surgery, surgical, orthopaedic surgery, shoulder surgery, acromioplasty, debridement, bursectomy, arthroscopic, Neer)
Outcome	Functional and clinical outcome
Limits	Language: English, German, Dutch Publication year: 1996-2016 Human

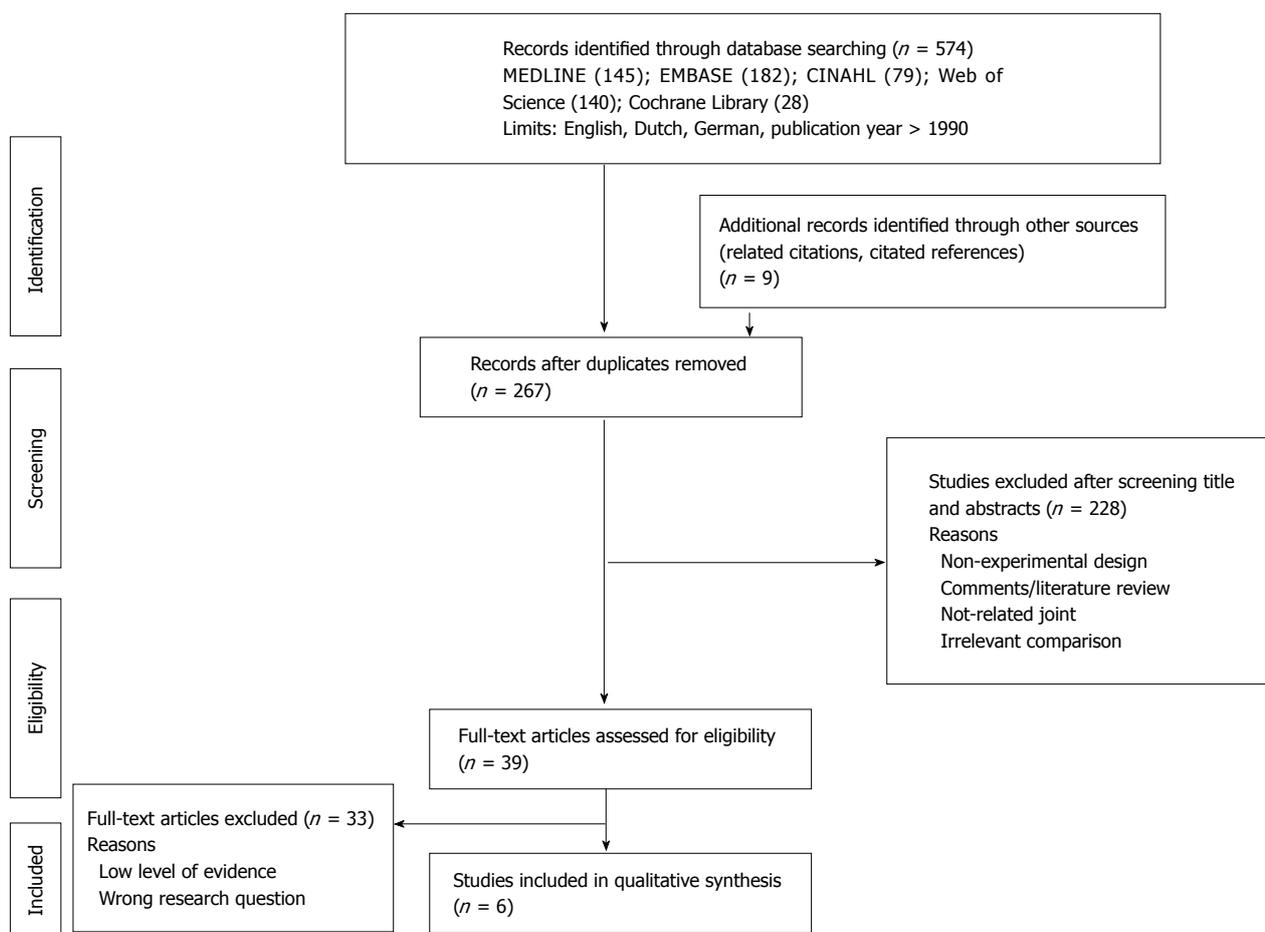


Figure 1 PRISMA flow diagram.

criteria, inclusion period, method of randomization, specific characteristics of the patient groups, specific surgical information, primary and secondary outcomes, baseline characteristics, statistics used, results and complications (appendix 2 in supplemental material). In case of missing information, we tried to contact the authors of the identified studies.

Data analysis

Whenever possible data was pooled. When pooling was not possible, due to clinical heterogeneity of the included studies based on the included intervention and/or study population, data is presented in a quality

synthesis.

RESULTS

Using the above-mentioned search strategy (appendix 3 in supplemental material) 574 potential relevant studies were identified (Figure 1); of which 267 remained after removing the duplicates. After screening of the titles and abstracts 228 studies were excluded. The main reasons for exclusion were that the studies did not concern the shoulder, were non-experimental studies, or made an irrelevant comparison. The full-texts were read in 39 studies. Finally, 6 studies were included in

Table 2 Characteristics of the included studies

Ref.	Study design (LoE)	Population	Mean age (range)	Duration of symptoms in months (range)	Interventions	Outcome measures	Findings	
							Baseline	Follow-up
Rubenthaler <i>et al</i> ^[10]	RCT (II)	38	51.1 (-)	-	Arthroscopic debridement + acromioplasty vs Open debridement + acromioplasty	Patte score, VAS, CMS	No significant differences	16 mo: CMS: 86.0 vs 85.3 (NS) VAS: 1.4 vs 1.8 (NS) Patte score: 84.4 vs 84.6 (NS)
Clement <i>et al</i> ^[11]	RCT (II)	80	49 (32-75)	6.2 (-)	Arthroscopic debridement + acromioplasty vs arthroscopic debridement	VAS, DASH, CMS, SF-12	No significant differences	6 wk: CMS: 62.2 vs 64.1 (NS) DASH: 24.5 vs 24.0 (NS) VAS: 4.4 vs 4.5 (NS) SF-12: 45.7 vs 44.3 (NS) 12 mo: CMS: 82.4 vs 77.5 (NS) DASH: 14.5 vs 14.0 (NS) VAS: 1.6 vs 2.5 (NS) SF-12: 43.0 vs 42.5 (NS)
Hofstee <i>et al</i> ^[12]	Quasi-RCT (III)	40	52.3 (41-62)	14.5 (6-36)	Arthroscopic debridement + acromioplasty vs arthroscopic debridement	DASH, VAS, satisfaction, ROM	No significant differences	36 mo: DASH: 3.14 vs 3.04 (NS) VAS: 4.3 vs 4.2 satisfied, yes: 80% vs 75%
Marder <i>et al</i> ^[13]	Retrospective case-control study (III)	50	44 (27-67)	13 (-)	Arthroscopic debridement vs arthroscopic debridement + acromioplasty	QuickDASH, RTW, UCLA	No significant differences	6 wk: RTW: 60% vs 20% (P = 0.004) 5 yr: QuickDASH: 6.3 vs 11.1 (NS) VAS: not well recorded UCLA: 32.0 vs 32.4 (NS)
Tillander <i>et al</i> ^[14]	Matched pair analysis (III)	50	50 (40-67)	66 (12-216)	Arthroscopic acromioplasty in patients with vs without CT	CMS, satisfaction, radiological	No significant differences	24 mo: CMS: 78 vs 79 (NS) Satisfaction, yes: 72% vs 80% (NS)
Maier <i>et al</i> ^[15]	Comparative cohort study (III)	36	48.9 (29-70)	35.2 (9-84)	Open debridement vs open debridement + acromioplasty	CMS	No significant differences	34 mo: CMS: 74.9 vs 73.4 (NS)

RCT: Randomized controlled trial; CMS: Constant-Murley score; DASH: Disabilities of Arm, Shoulder and Hand score; VAS: Visual Analog Scale for pain; UCLA: University of California-Los Angeles score; RTW: Return to work; -: No information available in included study; NS: Not significant.

this review, concerning 294 surgically treated shoulders with CT.

Characteristics

Study characteristics of the included studies are summarized in Table 2. Of these 6 studies there were two were RCTs (118 participants), one quasi-RCT (40 participants) and three comparative cohort studies (136 participants). The data could not be pooled because of the incompleteness of the extracted data and owing to the diversity in timing of the outcome moments (range, 6 wk-5 years).

Data assessment

The risk of bias was assessed by two independent review authors (FV, EF). Three studies were evaluated with the 12 criteria of Furlan *et al*^[8], and three studies were evaluated

with the Newcastle-Ottawa scale^[9]. Two RCTs were assessed as high-quality RCTs (Table 3), whereas in the non-randomized group one study received the maximum score and the other two studies had a near to maximum score (Table 4). Results of the functional outcome are presented using different outcome measures, namely the Constant-Murley score (CMS), Patte score and the University of California-Los Angeles score (UCLA). The results of the clinical outcome are presented with various outcomes measures, including the Disabilities of Arm, Shoulder and Hand score (DASH) and return to work, as can be seen in Table 2.

Debridement vs debridement with additional acromioplasty

The studies of Rubenthaler *et al*^[10], Clement *et al*^[11], Marder *et al*^[12] and Maier *et al*^[13] aided in answering the

Table 3 Methodological quality scores of the individual included randomized controlled trial's and quasi-randomized controlled trial

Ref.	Adequate randomization?	Allocation concealment?	Blinding patients?	Blinding caregiver?	Blinding outcome assessors?	Incomplete outcome data addressed? dropouts	Incomplete outcome data? ITT-analysis?	No selective outcome reporting?
Rubenthaler <i>et al</i> ^[10]	+	+	+	-	?	+	-	+
Clement <i>et al</i> ^[11]	+	+	+	-	+	+	-	+
Hofstee <i>et al</i> ^[12]	-	-	?	-	?	+	-	+

12 quality criteria of Furlan *et al*^[8]. +: Yes = 1 point; -: No = 0 points; ?: Unclear/unsure = 0 points. High-quality ≥ 50%, Low-quality ≤ 50%.

Table 4 Methodological quality scores of the individual included comparative cohort studies

Ref.	Selection (max = ****)	Comparability (max = **)	Exposure (max = ***)
Marder <i>et al</i> ^[13]	***	**	***
Tillander <i>et al</i> ^[14]	****	**	***
Maier <i>et al</i> ^[15]	***	**	***

Newcastle-Ottawa Scale^[9].

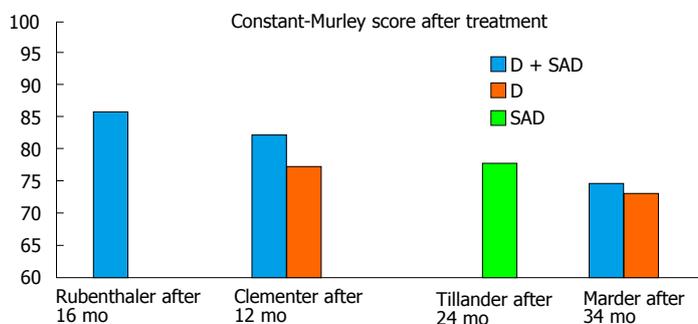


Figure 2 Constant-Murley score after treatment. D: Debridement; SAD: Subacromial decompression.

first research question (Figure 2).

Functional outcome: For the comparison of the functional outcome on the short and midterm only the RCT of Clement *et al*^[11] reported data 6 wk and 12 mo after debridement vs debridement with acromioplasty. They reported no significant difference after 6 wk (mean CMS 62.2 vs 64.1) and 12 mo (mean CMS 82.4 vs 77.5). Rubenthaler *et al*^[10] reported the results after debridement with acromioplasty in an open vs arthroscopic procedure (mean CMS 86.0 vs 85.3). Marder *et al*^[13] and Maier *et al*^[15] reported data of debridement vs debridement with acromioplasty after 5 years and 34 mo, respectively. The mean UCLA of 32.0 vs 32.4 after 5 years did not differ significantly and the mean CMS of 74.9 vs 73.4 after 34 mo did not differ either.

Clinical outcome: The clinical outcome was reported by Clement *et al*^[11] and Marder *et al*^[13] using the DASH score and QuickDASH score. The clinical outcome did not differ significantly in the short and midterm (6 wk: mean DASH 24.5 vs 24.0 and 12 mo: mean DASH 14.5 vs 14.0). After 5 years the mean QuickDASH did not differ significantly either (6.3 vs 11.1).

Acromioplasty vs acromioplasty with additional debridement

The studies of Hofstee *et al*^[12] and Tillander *et al*^[14] were

helpful in answering the second research question. There was no information available for the comparison of the results in the short term.

Functional outcome: Tillander *et al*^[14] reported results of the functional outcome after 24 mo after solitary acromioplasty in patients with and without CT. The mean CMS was 78.0 and 79.0, respectively. As an indication of the functional outcome Hofstee *et al*^[12] reported the ROM after 36 mo. In all six planes the ROM did not differ significantly between patients after acromioplasty in comparison with patients after acromioplasty with debridement.

Clinical outcome: Hofstee *et al*^[12] reported a DASH score of 3.1 vs 3.0 after 36 mo of surgery which was not significantly different.

Complications

Four of the included six studies reported information about adverse events or complications^[10,11,13,15]. There were no intraoperative complications reported, none of the included patients required reoperation. The only complication reported was adhesive capsulitis. In the studies of Clement *et al*^[11] and Marder *et al*^[13], one patient (1.3%) and three patients (6%) showed signs of adhesive capsulitis. These patients could all be treated conservatively and showed full recovery at the

end of the follow-up.

DISCUSSION

CT is often a self-limiting disease which in the majority of the patients can be managed with conservative measures, such as physical therapy, subacromial infiltrations, shock wave therapy or needling. However, in some patients these conservative measures fail and surgery is needed. Based on the results of this systematic review of LoE II and III evidence, we found that all three available treatment options show good functional and clinical outcomes in the short and midterm. However, a favored procedure is difficult to determine due to the lack of high-quality comparing studies.

Regarding the first research question four studies aided in answering this "question"^[10,11,13,15]. The functional and clinical outcome did not differ after debridement vs debridement with an additional acromioplasty. It could be postulated that CT is not correlated with subacromial impingement and an acromioplasty does not seem to be beneficial. This supports the aforementioned theory of Gärtner *et al*^[2]. Of the other outcomes extracted from the included studies, only in the study of Marder *et al*^[13] did significantly more patients return to work after six weeks (Table 2). In the included RCT^[11] an additional acromioplasty was not found to be beneficial. Though, in this study the (patho)anatomy (*e.g.*, classification of Bigliani^[16]) of the acromion was not considered. It has been postulated that if there are any radiological or intraoperative signs of impingement an acromioplasty can be performed^[16,17].

The studies of Hofstee *et al*^[12] and Tillander *et al*^[14] aided in answering the second research question. They found good functional and clinical results 24 and 36 mo after an acromioplasty and an acromioplasty with an additional debridement of the calcifications. They found no significant differences. Short term results were not available. Other variables (VAS and satisfaction) also did not differ significantly. These results support the correlation between CT and subacromial impingement. Whereas, this suggests that the complete or partial debridement of the calcific deposits is not necessary.

All three available treatment options are safe; the complication rates are low and the reported complications were treated conservatively and showed full recovery. In the included studies the percentage of adhesive capsulitis was low, comparing to the current literature where rates as high as 18% are reported^[18-20]. In the included studies in which a debridement was performed the rotator cuff defect was not sutured afterwards, even though no rotator cuff tears were seen in our entire study population.

Some limitations apply to this systematic review. The main limitation is the lack of high-quality, preferably randomized, comparing trials between the different treatment options. Two high-quality RCTs were included of which one did not make the exact comparison we were interested in. The other one was valuable, however

the follow-up was rather short (one year). Therefore, there is a need for more research on this topic. The data could not be pooled due to heterogeneity of the included studies and therefore no quantitative analysis could be made. We analyzed the causes of this heterogeneity. But, we could not improve this sufficiently; therefore data is presented in a narrative fashion. On the other hand, we were able to detect all relevant LoE II and III evidence regarding the surgical treatment options of CT and describe their results in this concise review.

All three available surgical treatment options for patient with conservative therapy resistant CT of the shoulder show good functional and clinical outcome and are safe procedures. Based on this systematic review a preferable treatment option could not be appointed and therefore recommendations cannot be made. Future research should be aimed at comparing all three available options. This is preferably done in a randomized fashion including a short, mid and long term follow-up.

COMMENTS

Background

There still is no consensus on what is the best surgical treatment of therapy resistant calcifying tendinitis of the shoulder. Different authors opt different surgical procedures. The authors tried to identify the surgical treatment with the best functional and clinical outcome.

Research frontiers

Calcifying tendinitis was probably first diagnosed by Plenk *et al* in 1953. Up till to today the exact etiology is still unclear. In the majority of the cases the disease resolves spontaneously or with conservative measures. However, sometimes surgery is necessary. Several authors have pointed out the beneficial effect of an additional acromioplasty with the debridement of the calcific deposits.

Innovations and breakthroughs

Although this disease is extensively studied the exact surgical management has not been clarified yet. There were several comparative studies available but Clement *et al* were in 2015 the first to publish a randomized study on this particular subject. They stated that an additional acromioplasty was not beneficial.

Applications

This review suggests that all three available surgical options are safe and effective. However, a preferable could not be appointed.

Terminology

SAD is a subacromial decompression which is the resection of the anterolateral part of acromion and release of the coracoacromial ligament.

Peer-review

This is a very interesting and well planned study.

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Effect of lengthening along the anatomical axis of the femur and its clinical impact

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Abstract

AIM

To review and study the effect of lengthening along the anatomical axis of long bones and its relation to the mechanical axis deviation.

METHODS

We try in this review to calculate and discuss the exact clinical impact of lengthening along the anatomical axis of the femur on affecting the limb alignment. Also we used a trigonometric formula to predict the change of the femoral distal anatomical mechanical angle (AMA) after lengthening along the anatomical axis.

RESULTS

Lengthening along the anatomical axis of the femur by 10% of its original length results in reduction in the distal femoral AMA by 0.57 degrees. There is no objective experimental scientific data to prove that the Mechanical axis is passing *via* the center of the hip to the center of the knee. There is wide variation in normal anatomical axis for different populations. In deformity correction, surgeons try to reproduce the normal usual bone shape to regain normal function, which is mainly anatomical axis.

CONCLUSION

Lengthening of the femur along its anatomical axis results in mild reduction of the distal femoral AMA. This may partially compensate for the expected mechanical axis lateralisation and hence justify its minimal clinical impact.

Key words: Bone lengthening; Deformity; Femoral lengthening; External fixation; Intramedullary nail; Axis deviation

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Core tip: In deformity correction the aim is to reproduce

the normal anatomical shape of the bone to regain normal function. There is no experimental data to prove the passage of the imaginary mechanical axis and load distribution of the body *via* the center of the hip to the center of the knee. Lengthening along anatomical axis of the bone is expected to cause minimal or no clinical effect on mechanical axis and load distribution on joints.

Emara KM, Mahmoud AN, Emara AK, Emara MK. Effect of lengthening along the anatomical axis of the femur and its clinical impact. *World J Orthop* 2017; 8(5): 431-435 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/431.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.431>

INTRODUCTION

The goal of recent advances in the field of limb lengthening is to increase the patient acceptance and comfort and avoid the common complications of the classic external fixators. One important achievement is the use of totally implantable intramedullary distracting nails for tibia and femur. Among them, the Albizzia nail (DePuy, Villeurbanne, France), Fitbone (Wittenstein, Igersheim, Germany), Intramedullary Skeletal Kinetic Distractor (ISKD, Orthofix Inc., McKinney, TX, United States) and Precise nail (Ellipse Technologies Inc., Irvine, California) were used successfully^[1,2]. These are self-lengthening telescopic intramedullary rods, which could be fully motorized or un-motorized and depend on external apparatus or limb movement to make them extend^[1]. Intramedullary lengthening utilizes the anatomical axis of the bone, in contrast to lengthening with external fixators which occurs along the mechanical axis. In the tibia, no difference would be detected after either ways of lengthening since the anatomical and mechanical axes of the tibia are almost the same^[3]. However, in normal femora, the mechanical and anatomic femoral axes diverge by approximately 5°-9°. This angle is known as the anatomic-mechanical angle (AMA)^[2-4]. When using intramedullary lengthening in femora, lateralization of the overall limb alignment has been observed both theoretically and radiologically^[2-7]. The amount of mechanical axis lateralization has been documented by Burghardt *et al.*^[2], who concluded that each 1 cm lengthening of the femur results in about 1 mm lateralization of the mechanical axis radiologically. However, the exact clinical outcome of such mechanical axis lateralization has not been presented clearly in literature. The purpose of this study is to review the exact effect of lengthening along the anatomical axis on disturbing the normal mechanical alignment of the limb and hence distribution of load along the joint surface. We have reviewed the trigonometric formula to predict the change of the femoral AMA after lengthening along the anatomical axis, and reflected the results on the clinical outcome of mechanical axis deviation.

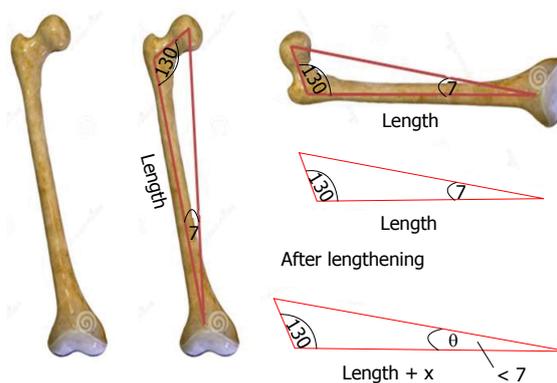


Figure 1 Femoral lengthening along the anatomical axis (length) affects the femoral anatomical mechanical angle (assumed to be 7 degrees). Increasing the femoral length along the anatomical axis would cause decrease in the anatomical mechanical angle (θ).

MATERIALS AND METHODS

Trigonometry was used to calculate the change in the angle between the femoral mechanical and anatomical axes resulting from lengthening along the anatomical axis. The original angle is assumed to be 7°, where “ θ ” is the angle after lengthening the femur a distance of “x” cm (Figure 1).

The angle θ was calculated for different original bone lengths and different lengthening distances. Original bone lengths used in our calculations are average lengths that vary from 21 cm for a 3 years old, up to 44 cm for an adult female and 47 cm for an adult male^[6]. Femur lengths were considered for different ages with a step of 3 years of age, and so 3, 6, 9, 12, 15 years old, adults’ femurs were considered. Lengthening distances that were considered to vary from 3 to 18 cm, adding 3 cm each step (3, 6, 9, 12, 15, and 18) (Figure 2).

RESULTS

Results of the change of the femoral AMA after lengthening were expressed in Table 1. From the calculations, it was deduced that increasing the bone length by 10% its original length results in reduction of the angle between the mechanical and anatomic axes by 0.57°, and increasing the length by 20% reduces the angle by 1.05° approximately.

DISCUSSION

Our hypothesis was that the femoral lengthening along the anatomical axis with a telescopic intramedullary nail induces reduction of the femoral anatomical mechanical angle (AMA) which is normally around 7°. This may compensate for the limb mechanical axis that lateralization that was proven both theoretically and radiologically^[2-4,6], and hence could partially justify the minimal clinical impact of such mechanical angle lateralization after intramedullary lengthening.

A shift of the mechanical axis of the limb has been

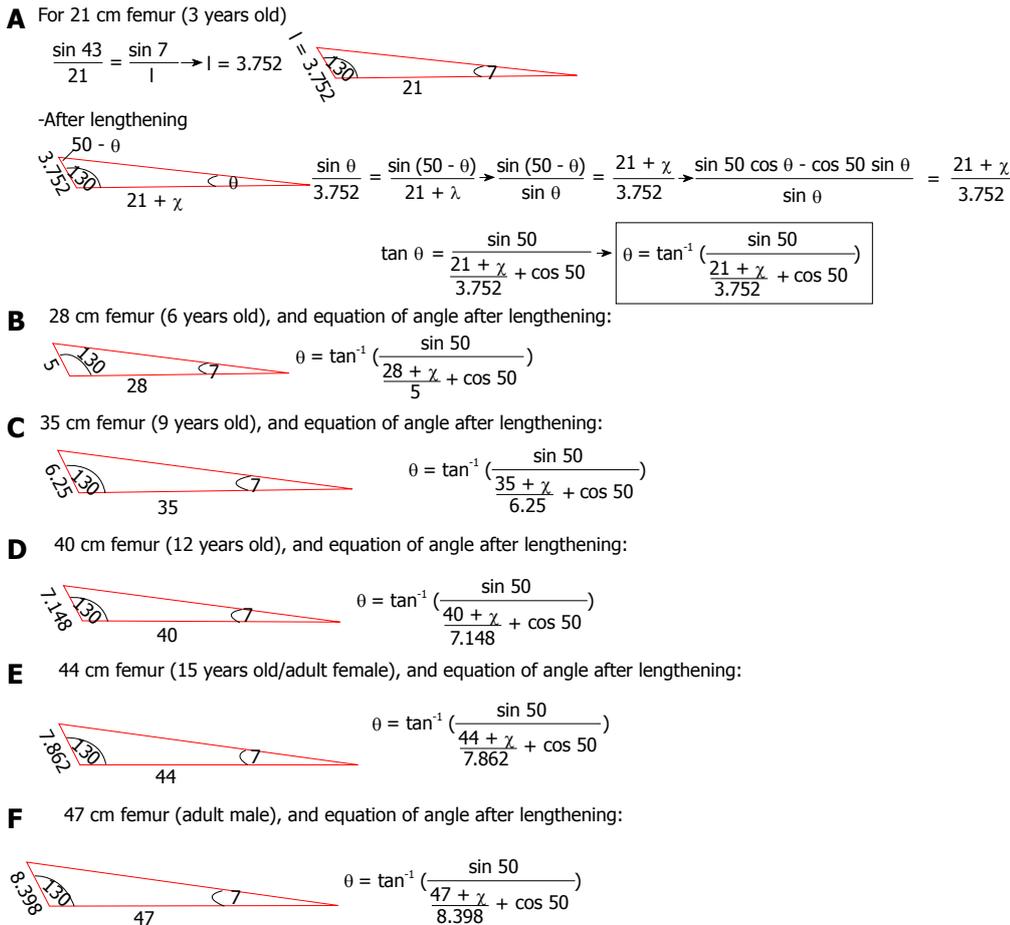


Figure 2 Calculation of the changes in the θ angle after lengthening of different sizes of femora using Law of Sines (A-F).

reported differently in studies about lengthening with a telescopic intramedullary nails^[2,8-11]. Theoretically, Burghardt *et al*^[4] found lateralization of the limb mechanical axis after lengthening along the anatomical axis using trigonometry. Radiologically, Bughdart *et al*^[2] found that 26 of 27 limbs which had intramedullary lengthening with the Precise nail, had a lateral shift of the mechanical axis, and concluded that lengthening of the femur by 1 cm causes lateral shift of the limb mechanical axis by 1 mm. In a similar study about femoral lengthening with the Albizzia nail, Guichet *et al*^[12] found that a lateral shift of the mechanical axis of the limb was seen in all the study cases, with a mean increase in the genu valgum angle by 1.04 degrees, however they could not find a constant correlation between the amount of mechanical axis deviation and the gain in femoral length. Similarly, Baumgart *et al*^[8] found a maximal mechanical axis deviation of 2 mm after using fully motorized intramedullary nails in femoral lengthening, and hence they recommended shifting the distal fragment laterally before reaming, in order to achieve normal mechanical alignment. Other similar studies about intramedullary femoral lengthening either have not commented on the mechanical axis deviation^[9], noticed very rare occurrence of mechanical axis deviation^[5,10] or did not find any mechanical axis alteration nor angular deformities after

lengthening^[11].

On the other hand, all the studies which found a radiological mechanical axis deviation after femoral lengthening with intramedullary nails did not comment on the isolated femoral axes relation changes, which in our case represented by the distal femoral AMA. Clinically, all these studies have described that mechanical axis lateral shift to be inconsequential or clinically insignificant^[2,5,7,9-12]. This might support our hypothesis, that such mechanical axis shift could be partially compensated by reduction in the distal femoral AMA concluded in our study, and hence no clinical consequences could be observed. Also this might be attributed due to the wide variation of the mechanical limb alignment in (normal) individuals. In the study of Ekhoﬀ *et al*^[13], only 2% of normal limbs included in the study have a neutral mechanical axis, and as many as 76% deviate from neutral by $> 3^\circ$ varus when measured using CT. Also, Bellemans *et al*^[14] found that limb alignment differs between males and females as studied by using full-length lower limb radiographs. In this study, 32% of male and 17.2% female knees were in $> 3^\circ$ of constitutional varus. Similarly, Yaniv *et al*^[15] found that varus knee axis deviation is normally present in football players older than 13 years old.

The mechanical axis is supposed to be the line of body weight loading the joints to the ground, and since

Table 1 Changes in the anatomical mechanical angle after lengthening

Femur length (cm)	X	P	θ	$\Delta\theta$
21	3	14	6.21	0.79
	6	28	5.58	1.42
	9	42	5.06	1.94
	12	57	4.64	2.36
	15	71	4.28	2.72
28	18	85	3.97	3.03
	3	10	6.38	0.62
	6	21	5.87	1.13
	9	32	5.44	1.56
	12	42	5.06	1.94
35	15	53	4.73	2.27
	18	64	4.45	2.55
	3	8	6.5	0.5
	6	17	6.07	0.93
	9	25	5.69	1.31
40	12	34	5.36	1.64
	15	42	5.06	1.94
	18	51	4.8	2.2
	3	7	6.56	0.44
	6	15	6.17	0.83
44	9	22	5.83	1.17
	12	30	5.52	1.48
	15	37	5.25	1.75
	18	45	5	2
	3	7	6.6	0.4
47	6	13	6.24	0.76
	9	20	5.92	1.08
	12	27	5.63	1.37
	15	34	5.37	1.63
	18	41	5.13	1.87
	3	6	6.62	0.38
	6	12	6.28	0.72
	9	19	5.98	1.02
	12	25	5.7	1.3
	15	32	5.45	1.55
	18	38	5.22	1.78

X: Distance lengthened (cm); P: Percentage lengthened distance of the original bone length (%); θ : Angle between mechanical and anatomical axes after lengthening (degree); $\Delta\theta$: Change in the angle between mechanical and anatomical axes due to lengthening (degree).

the body centre of gravity could be affected greatly by postural abnormalities that may be present in different patients, marked differences in the limb mechanical axes could be seen in different individuals. The situation is further complicated by differences in the alignment of the limb when measured in a lying position (which is non-weight bearing) and in a weight-bearing standing position^[16]. In a study by Deep *et al*^[17], they found the limb alignment to be dynamic process that differs according to different postures, and also varies between males and females in normal knees. Deep *et al*^[17] found also a greater tendency into varus malalignment in the study group with normal non-arthritic knees, that go into more varus when changing the position from supine to standing. Walcox *et al*^[16] found similar changes in arthritic knees. Again, the presence of nutritional abnormalities in Calcium and vitamin D metabolism could lead high prevalence of mechanical axes varus malalignment in normally looking adolescents^[18]. Again, in general

population and different races, there is a range of varus and valgus deformation that has no clinical effect, and there is no fixed number for the normal anatomical shape of human bone. Some mild change during lengthening can stay in most of the cases within this range. The assumption of fixed normal passage of mechanical loading on the limb is not exactly compatible with reality due to the different positions the normal human body use along the day in normal life. Also there is no objective Empirical data to prove where is the normal passage of mechanical axis in relation to the human joints. Since the aim of deformity correction surgery is to reproduce the near normal anatomical shape of bones to improve function, anatomical axis should be the main guide for surgeons in deformity correction and limb reconstruction.

All these data, beside the fact that even the documented amount of mechanical axis lateralization, 1 mm for each 1 cm lengthening, remains very little, this may further justify that the actual implementation of the mechanical axis deviation on the clinical outcome could be very mild or even non significant.

In conclusion, although mechanical axis lateralization after lengthening along the anatomical axis was documented theoretically and radiologically in literature, we found that lengthening of the femur along the anatomical axis theoretically reduce the distal femur AMA by around 0.57 degrees approximately for lengthening by 10% of the original bone length. This change, along with the high variation of population mechanical limb alignment could justify the minimal clinical effect seen with of such mechanical axis deviation after femoral lengthening along the anatomical axis.

COMMENTS

Background

Bone lengthening and deformity correction surgery consider the mechanical and anatomical axes during the surgical planning and treatment. This review article aim to stimulate critical thinking to some fixed ideas in the community of orthopaedic surgeons, specially pediatric orthopedics and limb reconstruction.

Research frontiers

There are objective data about anatomical shape of bone and the range of normal variation but there is no sufficient data regarding the normal mechanical axis and its variation between normal population.

Innovations and breakthroughs

The authors recommend considering anatomical axis as the main guide for lengthening, and not to over emphasize on mechanical axis, and mild variations in anatomical axis during lengthening.

Applications

Lengthening along anatomical axis is safe and effective.

Terminology

Anatomical and mechanical axis are terms used in deformity correction and bone lengthening.

Peer-review

The authors present a review article about the effects of lengthening along the anatomical axis, using a trigonometric approach. They refer to the topic of

mechanical axis lateralisation in intramedullary limb lengthening and check the clinical relevance.

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Chest pain caused by multiple exostoses of the ribs: A case report and a review of literature

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Abstract

The aim of this paper is to report an exceptional case of multiple internal exostoses of the ribs in a young patient affected by multiple hereditary exostoses (MHE) coming to our observation for chest pain as the only symptom of an intra-thoracic localization. A 16 years old patient with familiar history of MHE came to our observation complaining a left-sided chest pain. This pain had increased in the last months with no correlation to a traumatic event. The computed tomography (CT) scan revealed the presence of three exostoses located on the left third, fourth and sixth ribs, all protruding into the thoracic cavity, directly in contact with visceral pleura. Moreover, the apex of the one located on the sixth rib revealed to be only 12 mm away from pericardium. Patient underwent video-assisted thoracoscopy with an additional 4-cm mini thoracotomy approach. At the last 1-year follow-up, patient was very satisfied and no signs of recurrence or major complication had occurred. In conclusion, chest pain could be the only symptom of an intra-thoracic exostoses localization, possibly leading to serious complications. Thoracic localization in MHE must be suspected when patients complain chest pain. A chest CT scan is indicated to confirm exostoses and to clarify relationship with surrounding structures. Video-assisted thoracoscopic surgery can be considered a valuable option for exostoses removal, alone or in addition to a mini-thoracotomy approach, in order to reduce thoracotomy morbidity.

Key words: Multiple hereditary exostoses; Thoracoscopy; Ribs exostoses; Chest exostoses; Chest pain

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Core tip: This is a report of an exceptional case of multiple internal exostoses of the ribs in a young patient affected by Multiple hereditary exostoses observed for chest pain as symptom of an intra-thoracic localization. Chest pain could be the only symptom of an intra-thoracic

localization, possibly leading to serious complications. Thoracic localization must be suspected when patients complain chest pain. Computed tomography scan is indicated to confirm exostoses and to clarify relationship with surrounding structures. Video-assisted thoracoscopy surgery can be considered a valuable option for exostoses removal, alone or in addition to a mini-thoracotomy approach, in order to reduce thoracotomy morbidity.

Mazza D, Fabbri M, Calderaro C, Iorio C, Labianca L, Poggi C, Turturro F, Montanaro A, Ferretti A. Chest pain caused by multiple exostoses of the ribs: A case report and a review of literature. *World J Orthop* 2017; 8(5): 436-440 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i5/436.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i5.436>

INTRODUCTION

The aim of this paper is to report an exceptional case of multiple internal exostoses of the ribs in a young patient affected by multiple hereditary exostoses (MHE), who came to our observation complaining chest pain as the only symptom of an intra-thoracic localization. MHE is also known as diaphyseal acasia, Osteochondromatosis or multiple osteochondroma. It is an autosomal dominant disorder with growth plate-like exostoses next to long bones and other skeletal elements.

Usually, all affected individuals are diagnosed by age 12 years, but the median age of diagnosis is three years. The risk for malignant degeneration to osteochondrosarcoma increases with age^[1].

The diagnosis of MHE is based on clinical-radiographic results of multiple exostoses in members of a family. The two genes involved are known to cause MHE are EXT1 and EXT2. Mutations in both EXT1 and EXT2 are detected in 70%-95% of affected individuals^[2]. Exostoses of the rib are extremely rare, contributing to approximately 1% of all exostoses in MHE^[3-5]. We report the case of a patient, complaining only chest pain, affected by MHE with three exostoses protruding directly into the thoracic cavity.

CASE REPORT

A 16 years old patient with familiar history of MHE, came to our observation for a right sided knee-pain caused by an exostoses of the distal femur irritating the surrounding aponeurotic structures. The patient had undergone several surgical procedures for exostoses removal on both femur, tibia and fibula, left radius and fourth finger of the right hand, all performed by our Unit. During physical examination, patient reported even having a left-sided chest pain. This pain had increased in the last months with no correlation to a traumatic event and was exacerbated by physical activity and cough. Palpation didn't reveal any subcutaneous swelling. There was no sign of coughing,

sputum, nausea, tremor or fever and his laboratory values were all normal. The chest x-ray revealed the presence of three exostoses located on the right second and twelfth and on the tenth left ribs, not related to the pain complained by the patient. We therefore performed a computed tomography (CT) (Figure 1) of the chest with 3-dimension reconstruction which even showed the presence of three exostoses on the left third, fourth and sixth ribs. All the three exostoses protruded into the thoracic cavity, directly in contact with visceral pleura. Moreover, the apex of the one located on the sixth rib revealed to be only 12 mm away from pericardium. Because of symptoms complained by the patient and the particular location of exostoses with potential serious complication, we therefore decided for surgical intervention.

Surgical technique

The patient received general anesthesia. Unilateral ventilation with a tidal volume of 300 mL was obtained using a double-lumen endotracheal tube.

A lateral decubitus position was used and a 4-cm long mini-thoracotomy incision was performed at the fifth intercostal space in addition to a standard thoracoscopic portal at the eighth intercostal space in order to completely resect exostoses avoiding recurrence and organ injury.

The surgeon identified by thoracoscopy three significant exostoses originating from the ribs within the left side of the chest (Figure 2); one of them hurt the pericardium during cardiac pulsations, as visualized under unilateral right ventilation after exclusion of the left lung. This scratching caused a thickening of the adjacent pericardium and visceral. Each exostoses were completely resected using a chisel and the specimens obtained were sent to the pathologist. In the apex of the chest cavity a single thoracotomy tube was inserted and positioned.

The incisions were closed and the lung was re-expanded to evaluate correct ventilation. The postoperative course was ordinary, and the patient was discharged on the seventh postoperative day. Pathological examination of the specimens obtained were consistent for exostoses, measuring 2 cm in length and 1 cm in width in the third rib, in the fourth one 2 cm in length and 0.5 cm in width and in the sixth one 2.5 cm in length and 1.5 cm in width (Figure 3). At the last 1-year follow-up, patient was very satisfied and no signs of recurrence or major complication had occurred.

DISCUSSION

The most common localization of exostoses is distal femur, proximal tibia, fibula and humerus, bones that develop from cartilage. Angular deformities, leg-length inequalities and pain resulting from inflammation of skin, tendons or nerves often require surgery.

The flat bones like iliac and scapula are less frequently involved. Rarely ribs, spine, metatarsals, meta-



Figure 1 Thoracoscopic findings. Exostosis originating from the costochondral junction of the ribs, with the tip adjacent to the pericardium. The thickening of the pericardium and pleura was caused by scratching with the exostosis during respiratory movements and cardiac pulsations.

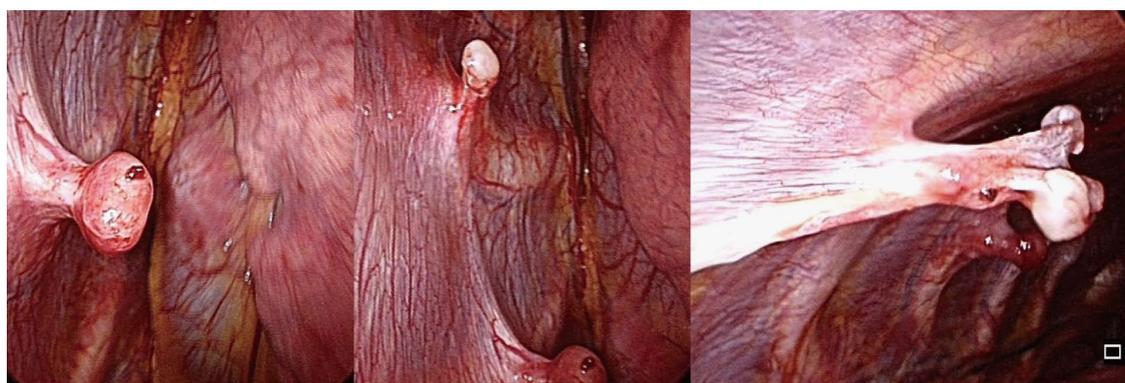


Figure 2 A chest computed tomography scan showing exostoses originating from the left third, fourth and sixth ribs, with a long bony spicule projecting inwards toward the lung.



Figure 3 Macroscopic aspect of exostosis.

carpals, phalanges are involved^[1]. Costal exostoses may be difficult to recognize on the chest using only X-ray and the chest CT scan is usually suitable^[3-5]. Malignant transformation is seen in 0.5%-5% cases of MHE. Axial sites as ribs, spine, pelvic hips and shoulder are sites of increased risk of malignant transformation. Average age at malignant transformation in MHE is 25-30. It is rare before 20 years of age.

Generally, exostoses grow and gradually ossify during skeletal growth and stop growing with skeletal maturity. The proportion of individuals with MHE who have clinical symptoms rises from approximately 5% at birth to 96%

at age 12 years^[1].

MHE doesn't require therapy in the absence of clinical symptoms, but it should be recommended in selected patients. Despite several studies exist in literature regarding costal exostoses, only few Authors have reported surgical management and outcomes of intra-thoracic localization (Table 1).

Most of the cases described concern about a single exostoses, alone or associated to MHE, while very few papers report the management of multiple intra-thoracic exostoses^[3,16,19,27,28]. The majority of cases were treated with a thoracotomy approach, with an increase of less

Table 1 Review of surgically treated intra-thoracic exostoses reports

Ref.	Year	Age	No. of exostoses	Procedure	Outcomes
[6]	1980	9	1	Thoracotomy	Good
[7]	1981	20	1	Thoracotomy	Good
[8]	1989	7	1	Thoracotomy	Good
[9]	1990	14	1	Thoracotomy	Good
[10]	1993	19	1	Thoracotomy	Good
[11]	1994	36	1	Thoracotomy	Good
[12]	1994	3	1	Thoracoscopy	Good
[13]	1997	19	1	Thoracotomy	Good
[14]	1998	15	1	Thoracotomy	Good
[15]	1997	17	1	Thoracoscopy	Good
[16]	2001	21	1	Thoracotomy	Good
[17]	2005	6	3	Thoracoscopy	Good
[4]	2005	15	1	Thoracotomy	Good
[18]	2005	11	1	Thoracotomy	Good
[19]	2006	14	1	Thoracotomy/ thoracoscopy	Good
[20]	2008	17	2	Thoracotomy	Good
		15	1	Thoracotomy	Good
		23	2	Thoracotomy	Good
		12	1	Thoracotomy	Good
		3	1	Thoracotomy	Good
[21]	2009	15	1	Thoracoscopy	Good
[22]	2009	16	1	Thoracoscopy	Good
[23]	2010	17	1	Thoracoscopy	Good
[3]	2011	14	2	Thoracotomy	Good
		6	2	Thoracotomy	Good
[24]	2012	25	1	Thoracotomy/ thoracoscopy	Good
[25]	2013	2	1	Thoracotomy	Good
[26]	2013	5	1	Thoracoscopy	Good
[27]	2012	21	1	Thoracotomy/ thoracoscopy	Good
[28]	2014	16	2	Thoracoscopy	Good
[29]	2014	15	1	Thoracotomy	Good
		5	Multiple intra/ extrathoracic	Thoracotomy	Good
[30]	2015	18	1	Thoracoscopy	Good

invasive surgery such as video-assisted thoracoscopy in the last two decades^[12,15,17,21-23,26,28,30]. However, some Authors have underlined the needs of an additional mini-thoracotomy incision depending on the localization of rib involvement and the dimension of the exostoses^[19,24,27]. Therefore, considering our case, we sought to completely resect exostoses avoiding recurrence and organ injury preferring a 4-cm mini-thoracotomy approach instead of an additional standard thoracoscopic portal.

The outcomes of surgical management were favorable in all previously reported cases with no significant complications, as in our case. Only Cowles *et al.*^[17] reported a persistent post-operative pneumothorax related to a malfunction of chest drainage system, resolved without consequence^[17].

Interestingly, in most of the cases reported the diagnosis was made due to complication, potentially fatal, caused by interference with surrounding structures, as was the choice to surgically treat the exostoses. On the contrary, only two cases are described in literature with pain caused by intra-thoracic localization of exostoses

as the only reason for exostoses removal^[14,29], as in our case.

The patient described in this report revealed only chest pain, but localization and dimension of exostoses could have had a possible risk of dangerous thoracic organ damage or risk of haemothorax due to traumas or vascular wound directly caused by the tip of the exostoses, as widely reported in literature.

Chest pain could be the only symptom of an intra-thoracic exostoses localization, possibly leading to serious complications. Thoracic localization in MHE must be suspected when patients complain chest pain. A chest CT scan is indicated to confirm exostoses and to clarify relationship with surrounding structures. Video-assisted thoracoscopic surgery can be considered a valuable option for exostoses removal, alone or in addition to a mini-thoracotomy approach, in order to reduce thoracotomy morbidity.

COMMENTS

Case characteristics

The patient, a 16 years old Caucasian male, reported having a left-sided chest pain, increased in the last months with no correlation to a traumatic event and was exacerbated by physical activity and cough.

Clinical diagnosis

Palpation don't showed evidence of any subcutaneous swelling and there was no sign of coughing, sputum, vomiting, palpitation or fever.

Differential diagnosis

Neuropathic pain, rib fracture, pneumothorax, haemothorax, pneumonia, pleuritis, chest or pleural or lung neoplastic process were excluded by the clinical and objective sign, laboratory tests and imaging.

Laboratory diagnosis

Hemoglobin level, hematocrit, electrolytes, liver enzymes and coagulation parameters were all normal.

Imaging diagnosis

The chest X-ray and computed tomography (CT) revealed the presence of three exostoses located on the right second and twelfth and on the tenth left ribs, not related to the pain complained and other of the three exostoses on the left third, fourth and sixth ribs.

Pathological diagnosis

The imaging suggested the diagnosis of multiple exostoses of the rib and it was confirmed after the surgical excision by the pathological examination of the specimens.

Treatment

All the exostoses were removed by a thoracoscopy approach with a chisel.

Related reports

Costal exostoses may be difficult to recognize on the chest X-ray. The chest CT scan is usually useful for diagnosis and malignant transformation is seen in 0.5%-5% cases of multiple hereditary exostoses (MHE).

Term explanation

MHE, also known as Multiple Osteochondroma, Osteochondromatosis and Diaphyseal Aclasia, is an autosomal dominant disorder characterized by formation of ectopic, cartilage-capped, growth plate-like exostoses next to long

bones and other skeletal elements.

Experiences and lessons

Thoracic localization in MHE can be suspected when patients complain chest pain and a chest CT scan is indicated to confirm exostoses and to clarify relationship with surrounding structures.

Peer-review

This is an interesting and well presented case report of a rare genetic disease.

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Perioperative blood management strategies for patients undergoing total knee replacement: Where do we stand now?

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Abstract

Total knee replacement (TKR) is one of the most common surgeries over the last decade. Patients undergoing TKR are at high risk for postoperative anemia and furthermore for allogeneic blood transfusions (ABT). Complications associated with ABT including chills, rigor, fever, dyspnea, light-headedness should be early recognized in order to lead to a better prognosis. Therefore, perioperative blood management program should be adopted with main aim to reduce the risk of blood transfusion while maximizing hemoglobin simultaneously. Many blood conservation strategies have been attempted including preoperative autologous blood donation, acute normovolemic haemodilution, autologous blood transfusion, intraoperative cell saver, drain clamping, pneumatic tourniquet application, and the use of tranexamic acid. For practical and clinical reasons we will try to classify these strategies in three main stages/pillars: Pre-operative optimization, intra-operative and post-operative protocols. The aim of this work is review the strategies currently in use and reports our experience regarding the perioperative blood management strategies in TKR.

Key words: Total knee replacement; Transfusion; Total knee arthroplasty; Blood loss; Autologous blood donation; Blood management; Perioperative; Tranexamic acid; Tourniquet; Haemodilution; Anaemia; Transfusion protocol

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Core tip: Total knee replacement is one of the most common elective surgeries in orthopaedics. Blood loss during surgery is putting the patient at risk for a blood transfusion. A number of reviews and meta-analyses have tried to analyze the best blood conservation strategy. Our objective is to review any blood saving method/strategy into the preoperative, intraoperative and postoperative period and analyze their possible

combination. A zero allogenic blood transfusion rate with safe and cost-effective methods should be the aim and an achievable goal.

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INTRODUCTION

Total knee arthroplasty (TKA) is currently the most cost-effective and efficacious way for treating patients with end-stage knee osteoarthritis who suffer from severe pain, activity limitation and for whom conservative treatment is unsuccessful. Based on National registries, TKA is considered to be the most common major orthopaedic surgery performed worldwide^[1]. It's really important to mention that the number of TKA surgeries performed each year increases and is projected to have a five to six-fold increase by 2030^[2].

Blood loss during TKA is putting the patient at risk for a blood transfusion. It's reported that patients undergoing TKA may result in blood loss between 1000 mL and 1500 mL which necessitates subsequent allogeneic blood transfusion (ABT) in 10%-38% of them^[3-7]. Thus, it becomes prudent to minimize the ABTs while trying to maintain hemoglobin (Hb) in a safe and efficient level to help patient's rehabilitation. Many strategies have been used in order to minimize blood loss including preoperative autologous blood donation (PAD), acute normovolemic haemodilution (ANH), autologous blood transfusion (ABT), intraoperative cell saver, drain clamping, pneumatic tourniquet application, and the use of tranexamic acid (TXA)^[8-10].

Although many strategies and algorithms have been proposed for ABTs reduction there is not a consensus about the most efficient/successful combination^[8,11]. This article will try to review the latest strategies, analyze the results and our experience regarding the use of TXA. Summarizing, these strategies can be divided in three stages: Pre-operative, intra-operative and post-operative (Table 1).

PRE-OPERATIVE

The main aim of blood management is to eliminate ABTs and prevent anaemia simultaneously. In order to avoid anaemia's clinical symptoms we need to preserve post-operative Hb values as higher as possible. Therefore, we highlight the significant effect of high pre-operative Hb on the requirement of ABT in TKA.

Detection of anaemia and iron deficiency treatment

Anaemia has been defined by the World Health Or-

ganization as an Hb concentration < 130 g/L for men, < 120 g/L for non-pregnant women^[12]. Regarding patients undergoing TKA it's been reported that 8% to 21% of them were anaemic before the procedure^[13,14].

Pre-operative assessment of patients should be performed at least 30 d (some reviews suggest at least 60 d) before the procedure in order to have enough time to investigate the cause and/or plan the required treatment^[15-17]. In case of low Hb additional lab tests should be carried out including at least full blood count, serum ferritin, transferrin saturation index (TSAT), vitamin B12, folic acid, a marker of inflammation (*e.g.*, serum CRP) and a marker of renal function (*e.g.*, serum Creatinine) (Figure 1)^[18]. Any other low Hb cause apart from iron deficiency anaemia (IDA) should be carefully investigated.

IDA is the main cause of low Hb. It's been reported that IDA counts up to 50% of the patients with Hb lower than 12 g/dL^[19,20]. It's been suggested that patients undergoing TKA should meet WHO's criteria regarding the minimum pre-operative Hb. Otherwise, surgery should be postponed^[15]. Furthermore, a recent, retrospective study demonstrated that preoperative anaemia (haematocrit < 25%) and ABTs are the two "evils" that increased the post-operative morbidity and mortality^[21].

Adult patients with IDA who are candidates for TKA should be treated before the surgery. Either intravenous or oral iron therapy has been found to be effective in the treatment of pre-operative anaemia, meanwhile reducing the rehabilitation's duration^[14,22]. Moreover, the superiority of intravenous iron therapy with respect to oral iron therapy has been reported^[23]. A 3-wk duration, administration of intravenous iron, just before surgery seems to be the most efficient and safe treatment^[24]. Additionally, oral iron may not be efficacious in patients with malabsorption such as coeliac disease^[25].

Erythropoietin

Erythropoietin (EPO) is a great tool in correcting anaemia as it is an essential hormone for red blood cell production. Without it, definitive erythropoiesis does not take place. Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells^[26,27]. Its role in blood loss management has been thoroughly studied, showing a 60% reduction of ABTs in patients who received EPO compared to control group^[28-30]. Three or four weekly subcutaneous injections (600 IU/kg) seems to be the most frequently used protocol with the best results^[31-35]. Weber *et al.*^[36] reports a mean rise in pre-operative Hb of 1.9 g/dL in patients that received EPO. A big disadvantage of EPO is the really big cost which is being estimated to 1500 dollars per patient (4 weekly injections)^[37]. For this reason, EPO use is being suggested when the patient has anemia and meets the criteria for blood transfusion, but declines a blood transfusion because of religious beliefs (*e.g.*, Jehovah's Witness), or the appropriate blood type is not available because of the patient's red cell antibodies^[38]. Adverse events have been reported in 5% of patients that have been treated with EPO. These complications include deep venous thrombosis (DVT),

Table 1 Three pillars of patient's blood management and saving

Pre-operative	Intra-operative	Post-operative
Detection of anaemia and iron deficiency treatment Erythropoietin Perioperative management of antiplatelet agents Transfusion protocol agreement Pre-operative autologous blood donation	MIS and navigated MIS TKA Tourniquet Hypotensive epidural anesthesia Acute normovolemic haemodilution Antifibrinolytic agents Topical fibrin sealants Intra-operative cell salvage Peri/intra-articular (bupivacaine and epinephrine) injections Bipolar <i>vs</i> monopolar sealant Platelet-rich plasma Bone wax Sealing femoral tunnel	Compression and cryotherapy Limb position Post-operative cell saving Drainage clamping

MIS: Minimally invasive; TKA: Total knee arthroplasty.

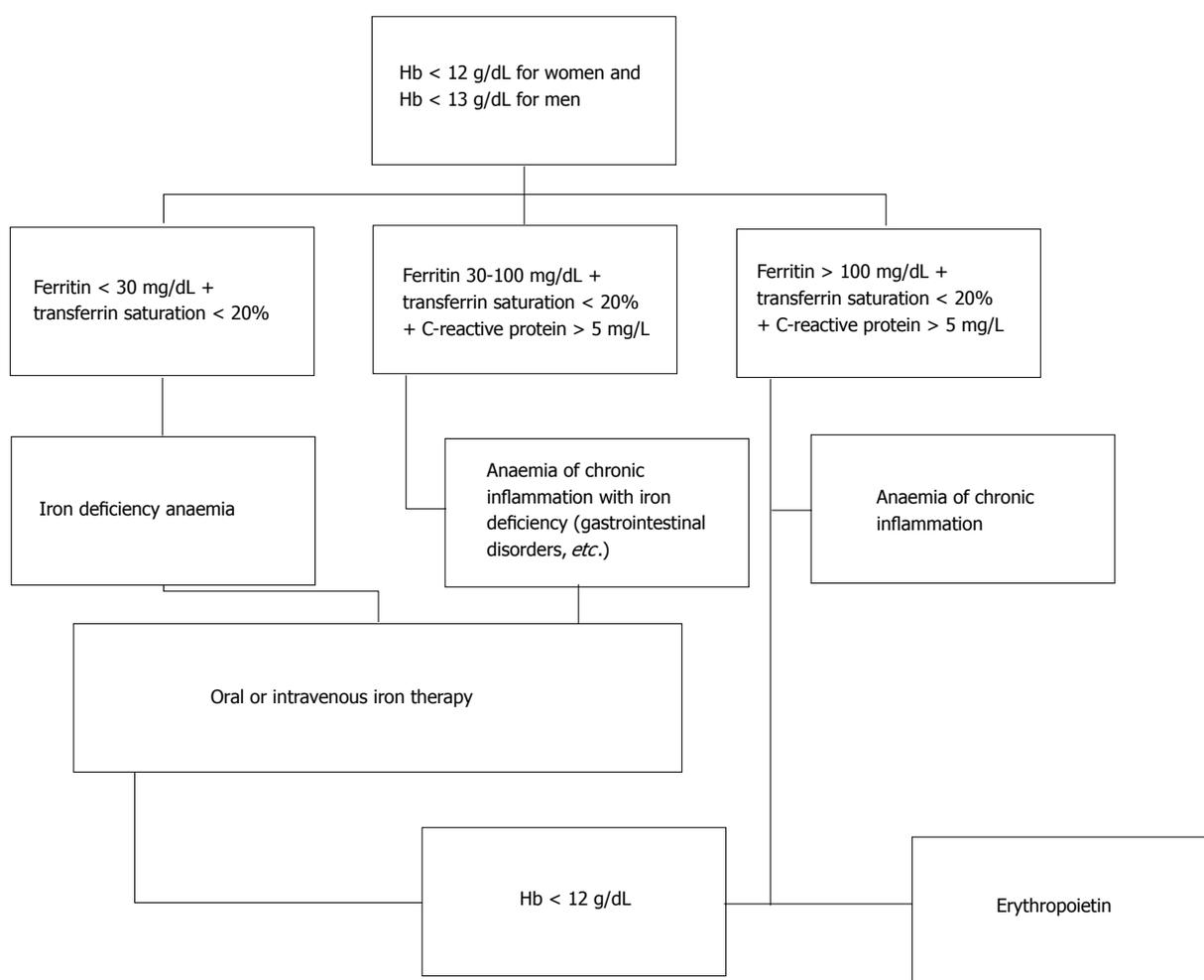


Figure 1 Algorithm proposed for low hemoglobin investigation. Hb: Hemoglobin.

pulmonary embolism (PE), fever, hypokalemia, urinary tract infection, nausea, hypoxia, and vomiting^[39-41]. Briefly, EPO can reduce the need for ABTs in high-risk patients undergoing TKA; however, it was not found to be cost-effective compared to other blood conservation methods^[42].

Cardiovascular disease is common in patients planning to undergo to TKA. Antiplatelet agents, used as monotherapy or in combination, have a key role in preventing cardiac and vascular events^[43]. Many of these patients have already undergone previous percutaneous coronary intervention (PCI) with stent implantation. American Heart Association's/American College of Cardiology Foundation's guidelines suggest dual antiplatelet therapy with

Perioperative management of antiplatelet agents

aspirin and an adenosine diphosphate (ADP) inhibitor (e.g., clopidogrel) for at least 1 mo after bare-metal stent implantation and for 1 year after drug-eluting stent implantation in order to avoid late thrombosis^[44]. There is a distinct proof that elective surgeries like TKA should be avoided (if it's possible) within the first year of stent implantation, as it's been reported a 5- to 10-fold increase in acute stent thrombosis^[45]. Of course, after the first year most of these patients continue with single antiplatelet therapy^[46].

Our main concern about antiplatelet agents is the perioperative bleeding that can occur during the procedure. Recent review reports bleeding increase up to 50% in patients with dual antiplatelet therapy. Regarding the monotherapy, the same review found that blood loss increased 2.5%-20%^[47]. From an anaesthesiologist's perspective, the incidence of spinal haematomas associated with epidural or spinal anaesthesia is the main reason for antiplatelet's discontinuation. Regarding the literature, 61 cases of spinal haematomas associated with epidural or spinal anaesthesia are reported between 1906 and 1994^[48].

The two most prescribed antiplatelet drugs (with different mechanism of action) are aspirin and clopidogrel. Regarding the aspirin, guidelines suggest its discontinuation 7-10 d before surgery without major consequences. Post-operatively, aspirin should be resumed preferably within 24 h (when bleeding risk is low). Conversely, patients who are in high cardiovascular risk should not stop aspirin therapy in the perioperative period^[49]. Clopidogrel acts by inhibiting the ADP receptor on platelet cell membranes. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) suggest discontinuation of clopidogrel 5 d prior to surgery and if additional DVT prophylaxis is needed a low molecular weight heparin (LMWH) should be used.

The key point is that both the continuation and the discontinuation of antiplatelet therapy can be associated with major risks. Therefore, (especially in dual antiplatelet therapy) the management of these medications in the perioperative setting should be discussed between the cardiologist, orthopaedic surgeon, and anaesthesiologist. This "team" should weigh the patient's risk of thrombosis with the risk of surgical bleeding to determine the right choice for him and if/when dual antiplatelet therapy can safely be discontinued.

Transfusion protocol agreement

ABTs are responsible for many complications like human immunodeficiency virus (HIV)'s, hepatitis B and C transmission (despite donor screening), whereas allergic reactions may cause minor reactions (e.g., fever) to fatal ABO blood group incompatibility^[50,51]. Therefore, it's really crucial to analyse and update the transfusion protocols that are being used in hospitals and especially in orthopaedic departments. We'd like to notice that although transfusion is a post-operative process, we include it in pre-operative measures as an agreement/protocol about the "transfusion

trigger" should be achieved before the surgery.

The main factor that should be investigated is the so called "transfusion trigger". It's the Hb threshold at which the physician decides to transfuse the patient. Many protocols/rules like 10/30 have been used in the past; but it's not the case any longer^[52]. Low transfusion trigger point seems to be effective in reducing ABTs^[53,54]. Reviews suggest transfusion triggers (Hb levels) between 8 g/dL and 9 g/dL (excluding severe cardiovascular disease, renal failure, and hematologic disorders)^[55,56]. Unquestionably, symptomatic anaemia resulting in tachycardia, change in mental status, cardiac ischemia or shortness of breath should always be treated followed by ABT. Based on literature, in our department we use a mini transfusion algorithm/protocol (Figure 2). This protocol has already documented significant reductions in the rates of red cell transfusion and worthwhile blood conservation. Noticeably, this strategy seems to be really cost-effective.

Briefly, a blood management protocol with restrictive typing and screening, cross-matching, and transfusion should be adopted by national health systems in order to reduce the wastage of unused blood units and the rate of ABTs without increasing patients' morbidity or mortality.

Pre-operative autologous donation

In 1980, the recognition that ABTs were associated with potential risks like viral transmission (e.g., HIV) and bacterial infection prompted the development of PAD programs^[57,58]. In 1992, PAD accounted for nearly 8.5% of all blood collected in United States. Nevertheless, pre-donation decreased to 3.5% of the blood units collected by 1997^[59].

PAD's main target is providing a resource of safe blood for patients that are candidates for scheduled surgery (like TKA). Meanwhile, this process increases the patient's total red blood cell (RBC) mass due to the PAD-induced stimulation of erythropoiesis before elective surgery.

Many studies and meta-analyses concluded that PAD strategy managed to reduce the use of ABTs by 40%-52%, increase the overall transfusions (allogeneic and autologous) by 30%. On the contrary, it's really important to mention that patients' Hb concentration decreased by more than 1 g/dL from before starting PAD to immediately prior to surgery^[60-62]. PAD's poorly cost-effectiveness (about 300\$ per unit), combined with new blood saving strategies and new drugs has led to a decline in its use^[63,64]. In our days, the use of PAD has therefore lost its acceptance and is no longer being used in TKA patients.

INTRA-OPERATIVE

Plentiful methods, strategies, technologies and drugs have contributed in blood loss minimization and ABTs' reduction. Some of them have gained ground during the last decades and others didn't manage to prove their effectiveness. Intra-operative blood saving seems to play the most important role between the strategies and techniques indicated in the three pillars of patient

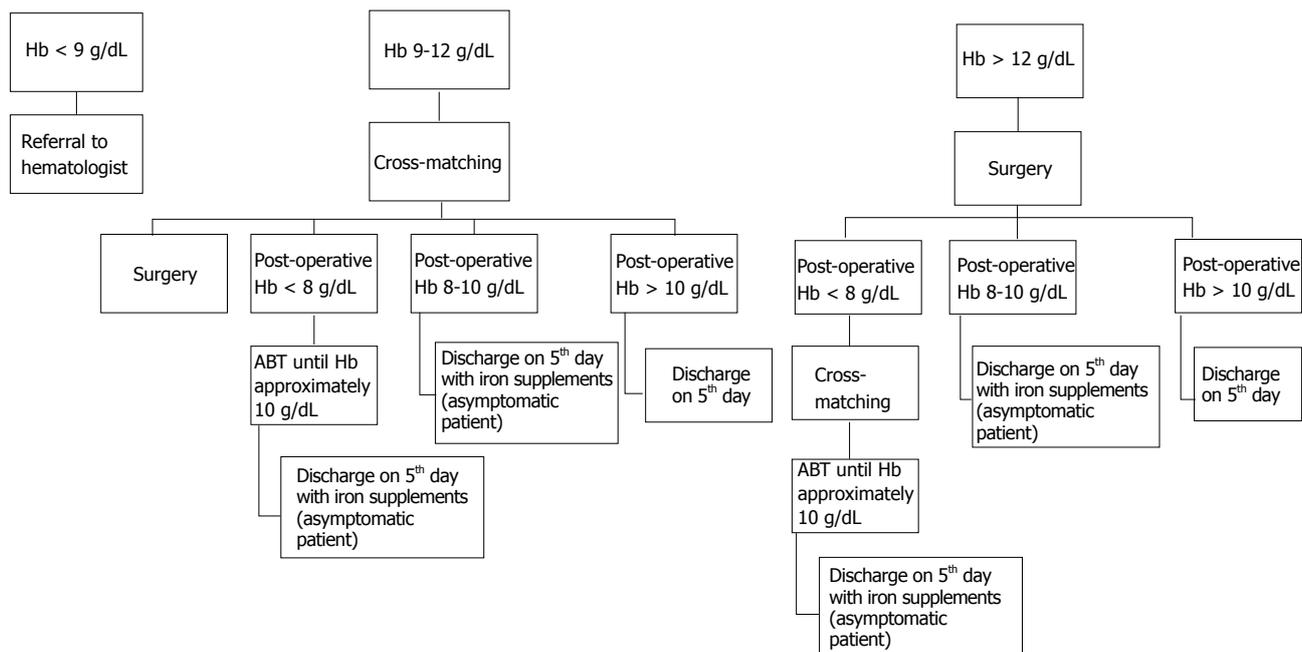


Figure 2 Algorithm used in our department regarding the allogeneic blood transfusion strategy. Hb: Hemoglobin.

blood management.

Minimal invasive and/or navigated minimal invasive TKA

Many of the patients that have decided to have a TKA might consider a minimally invasive procedure with or without navigation. This type of surgery uses smaller incisions and less cutting of the tissue surrounding the knee. The advantage of such a surgery except for the smaller incision is the promising recovery, a shorter hospital stay and less blood loss.

A meta-analysis revealed the superiority of minimal invasive (MIS) to the standard parapatellar approach in visual analog score (VAS) and range of motion (ROM) in the short term (postoperative 2 wk)^[65]. No differences were noticed in straight leg raise, hospital stay, post-operative complications and blood loss. Comparable results pointed out between MIS TKA and MIS navigated TKA^[66]. In conclusion, MIS TKA has proved the ability to couple the benefits of less invasive surgical approach without compromising the long-term established success of conventional TKA, especially in blood loss.

Tourniquet

A tourniquet is a compressing device, used to control venous and arterial circulation to an extremity (lower extremity in TKA) for a period of time. Although the majority of orthopaedic surgeons still use it widely, its role is controversial. Tourniquet's use was believed to be effective in decreasing intraoperative blood loss. However, reactive blood flow after tourniquet's release seems to balance out the total blood loss compared to the non-tourniquet TKA method^[67]. A meta-analysis of thirteen randomized controlled trials (RCTs) demonstrated that non tourniquet use in TKA has better clinical outcomes, less complications and better ROM in early postoperative

period. The most important finding of this meta-analysis is that the true blood loss in TKA was not reduced using a tourniquet^[68]. Therefore, it can be explicitly deduced that TKA with a tourniquet reduces the intra-operative blood loss but postoperatively increases the hidden blood loss^[68]. To sum up, tourniquet's effectiveness and safety in TKA should be carefully considered when surgeon decides to use it.

Hypotensive epidural anesthesia

In April of 1989 Sharrock *et al*^[69] published the first description of hypotensive epidural anesthesia. To date, HEA is not a popular method in elective orthopaedic surgery like TKA. HEA was developed to combine the advantages of epidural anesthesia (airway problem, reduced rate of DVT) with the benefits of induced hypotension.

Its mechanism of action is well-described. A sympathetic blockade (including cardiac sympathetic fibers), using local anesthetic at an upper lumbar interspace (T12-L1/L1-L2), causes a reduction in arterial pressure. Mean arterial pressure (MAP) is maintained at 50-55 mmHg with end result the reduction of blood loss. It's really important to mention that concurrently, a low dose of epinephrine is being infused (till MAP reaches 75-80 mmHg) achieving circulation's stabilisation^[70,71].

Although HEA's use seems to be really advantageous, without complications, it's not a "first line" method regarding blood loss in TKA. A few studies have proved its safety and efficacy in total hip arthroplasty (THA), but further studies are needed to assess its use in TKA^[70,72,73].

Acute normovolemic haemodilution

Acute normovolemic haemodilution (ANH) is a technique in which whole blood is removed from a patient, while

circulating volume is maintained with crystalloid fluid. It is performed shortly before or shortly after induction of anaesthesia. A close monitoring of the patient is necessary and when Hb level drops down to 8-9 g/dL ANH is being halted^[74]. Postoperatively, sufficient blood is administered to maintain patient's Hb over 8-9 g/dL.

Many studies suggest ANH's use in elective orthopaedic surgeries as it contributes in ABT's reduction^[75-77]. In contrast, there are studies that noted no significant difference between control and ANH group^[78-81]. Undoubtedly, more studies would be needed to prove/rebut its efficacy in blood loss management.

Antifibrinolytic agents

The most famous blood saving management of the last decade is the use of antifibrinolytic agents. TXA, ε-aminocaproic acid (EACA) and aprotinin are the most commonly used antifibrinolytic agents^[82-84].

TXA and EACA are lysine analog antifibrinolytics that reversibly bind both plasmin and plasminogen. TXA is a current trend in TKA and THA. Many studies have proved its efficacy without an increased risk of complications (DVT, PE, and wound infection). Latest studies and meta-analyses focused on the best route of administration combined with multiple dose regimens^[85-88]. Regarding the route of administration and plasma concentration, maximum plasma concentration of TXA is reached within 5-15 min after intravenous (IV) injection, 30 min after intramuscular (IM) injection and 2 h after oral tablets^[89]. IV TXA seems to be more effective compared to topical administration. However, the topical administration seems to outcompete IV in patients with high risk of thromboembolic events^[90]. On the contrary, a recent meta-analysis showed no statistically significant difference in total blood loss, drain output, transfusion requirements and thromboembolic complications between topical TXA and IV-TXA in TKA^[91].

The most efficacious regimen is still under debate, but multiple IV boluses regimens (pre/intra/post-operatively) prove to have a better result compared to a single IV dose^[92]. Nevertheless, two RCTs concluded that intra-articular regimen of TXA is as effective as three doses IV regimen in preventing blood loss without any difference in thromboembolic complications^[93,94]. In addition to all these studies some authors have noticed that the combination of IV and intra-articular TXA is more effective than either regimen used alone^[95,96]. All these conflicting results suggest that more well-conducted randomised controlled trials are needed to produce strong evidences about it. In our orthopaedic department two RCTs have already been completed, showing the high effectiveness of TXA's both in TKA with tourniquet and TKA without tourniquet and one more is currently running^[87,88]. The aim of the current study is to determine whether or not repeated dosing of IV TXA reduces (additionally) the post-operative reduction in hemoglobin, hematocrit, number of transfusions, and post-operative blood loss following primary TKA.

Studies comparing EACA to TXA on the reduction of

perioperative bleeding and on the number of transfusions needed showed no significant differences between the two antifibrinolytic agents. The only advantage of TXA compared to EACA is its lower price^[97].

Aprotinin, a nonlysine antifibrinolytic agent, was more effective at decreasing blood loss but was associated with increased cardiovascular complications (increased risk for myocardial infarction) and was therefore removed from the market in 2008^[98-100].

Topical fibrin sealants

Fibrin sealant is comprised mostly of fibrinogen and human thrombin which form a stable fibrin clot and can mimic the last phase of physiological blood coagulation cascade. Many studies have proved their efficacy without increasing the risk of DVT, PE, hematoma, wound infection or other complications for patients undergoing TKA^[101,102]. However, their main disadvantage is the high cost compared to other blood management methods (like TXA)^[103,104]. Moreover, newer studies appear to confute the initial hypothesis of fibrin sealants' haemostatic role. All these studies report no effect of fibrin sealant in terms of blood or transfusion savings after TKA^[105-107].

Intra-operative cell salvage

Intraoperative blood salvage, also known as cell salvage, is a medical procedure involving recovering blood lost during surgery and re-infusing it into the patient^[108]. Many devices and processes have been developed to assist in salvaging the patient's own whole blood since the 1970s, when it was popularized in major thoracic or abdominal procedures^[109]. Unwashed blood revealed poor results as it may contain hemolyzed RBC, clotting factors and cytokines^[110,111]. Therefore, cell separation and washing showed better results with an autologous red cell concentrate with normal function and no complications^[112].

Literature's evidence strength is really limited regarding the safety and effectiveness of this method. Current studies have low level of evidence which means that they are incompetent to compare the post-operative infection rates with and without cell salvage use. A general outcome of these studies is that intra-operative cell salvage reduce ABTs but more studies needed to clarify the importance and the risk of this method^[113-115].

Peri/intra-articular (bupivacaine and epinephrine) injections

Epinephrine is the agent of choice for topical haemostatic vasoconstriction^[116]. Anderson *et al.*^[117] injected bupivacaine and epinephrine just before wound closure (one-third pericapsular, two-thirds peri-incisional). They managed to prove a 32% less drain output in study group. However, no statistically significant differences were noticed in the transfusion rate between the two groups. Moreover, a new study by Yang *et al.*^[118] reports controversial results, as the initial hypothesis regarding the haemostatic role of intra-articular epinephrine after

TKA is not being supported by the various bleeding parameters.

Bipolar vs monopolar sealant

Monopolar electrocautery is a device that delivers electrical current to patient's tissue through a pen-like stylus. Intra-operative temperatures can be higher than 300 °C, resulting in smoke and eschar formation^[119]. Opposed to monopolar electrocautery, bipolar sealing delivers radiofrequency energy combined with continuous-flow saline in order to prevent temperatures higher than 100 °C. Although bipolar sealant is being used for decades in oncology, thoracic, spine and brain surgery it seems to be a novel approach in TKA^[120-123]. However, latest studies (including RCTs) and the results of the comparison between bipolar and monopolar sealers used in TKA report no significant difference in postoperative drain output, postoperative Hb level and transfusion requirement^[119,124,125].

Platelet-rich plasma

Platelet-rich plasma (PRP) has been used in surgeries to promote cell regeneration since 1987^[126]. Today, PRP injections is being safely used in many fields like cosmetics, sports medicine, orthopaedics, and fasciomaxillary^[127,128].

PRP is defined as plasma with a platelet level above peripheral blood concentration. There are two methods to obtain it: (1) ready PRP kits (higher cost); and (2) a wide variation of reported protocols for standardization and preparation of PRP (most of them use two-step centrifugation protocol)^[129,130]. The final volume contains platelets and factors (*e.g.*, platelet-derived growth factor and transforming growth factor- β) whose haemostatic and wound-healing effects have been well-described^[131-134]. Gardner *et al.*^[135] in their retrospective study report less blood loss during the post-operative period. Despite that a consensus about the high concentration of growth factors and its efficacy in wound healing has been reached, its haemostatic role is still debatable^[136,137].

As a final point, we'd like to note that understanding of basic principles of centrifugation is of vital importance in preparation of PRP. Many protocols have been described with different consistency of PRP yield. Thus, it is advisable to standardize individual, cost-effective preparation protocols, which are easy to adapt in clinical practice^[130].

Bone wax

Bone wax is a waxy substance used to help mechanically control bleeding from bone surfaces during surgical procedures. It consists of a mixture of beeswax, paraffin and isopropyl palmitate^[138]. Although its use in elective orthopaedic surgery hasn't been well-demonstrated, Moo *et al.*^[139] suggest bone wax's application in TKA for reducing total blood loss and maintaining higher hemoglobin levels.

It's remarkable to mention that complications like allergic reaction, inflammation and foreign bodies formation need extra attention by the physicians^[140]. Undoubtedly, further studies are needed to confirm its safety and efficacy

in TKA.

Sealing femoral tunnel

In recent decades most of the orthopaedic surgeons use an intramedullary alignment system regarding the placement of the femoral component in TKA^[141]. The intramedullary (IM) femoral rod that is being used damages the cancellous bone and its vascularization resulting in high blood loss. Nowadays, many surgeons seal this tunnel with autologous bone in order to minimize the bleeding. Although autologous bone grafting is a safe and non-time consuming process, its efficacy regarding the reduction in blood loss is still debateable^[142,143]. Additionally, studies report that the use of an extramedullary (EM) femoral alignment guide system resulted in reduction of the drained blood and consequently in lower transfusion rates^[144,145]. Our only concern is the influence of IM and EM femoral cutting guides on survivorship of the TKA, as IM seems to demonstrate superiority over the EM^[146].

POST-OPERATIVE

Last but not least, post-operatively blood saving methods are integrated in order to reduce blood loss and blood transfusion, and promote the rehabilitation of patients. Post-operative strategies include compression, cryotherapy, use (or not) of drainage systems, cell saving systems and post-operative leg position.

Compression and cryotherapy

Knee swelling after TKA is common and most of the time impairs early rehabilitation. Use of an inelastic compression bandage after TKA seems not to reduce total blood loss. However, it offers a slight but non-significant improvement regarding the postoperative pain and early functional outcomes^[147,148]. On the other hand many studies report no difference in compression method^[149-151].

Recently Desteli *et al.*^[152] and Kullenberg *et al.*^[153] reported that cryotherapy was beneficial in minimizing blood loss after TKA. Many cryotherapy devices have been used in the past (gel packs, circulating ice water) in order to help patients' rehabilitation^[154,155]. However, Adie *et al.*^[156] in their systematic review and meta-analysis does not support the routine use of cryotherapy after TKA.

Limb position

Another option in order to reduce blood loss after TKA is the limb position. Different knee flexion positions (*e.g.*, hip elevation by 60° combined with 60° knee flexion) have been reported to have promising results with respect to reducing perioperative blood loss^[157-159]. Based on these studies, we conclude that post-operative knee flexion is an easy, inexpensive and effective method in blood loss reduction.

Post-operative cell saving

It's been calculated that 50% of the total blood loss in a TKA occurs post-operatively^[6]. Therefore, post-operative

cell saving and return of unwashed, filtered blood from drains represents an alternative to ABTs method^[160]. This system consists of a collection bag and an autologous transfusion bag (filtered blood collected). Re-transfusion can take place in the first 6 h after the end of surgery in order to avoid bacterial infection^[161-163]. After this period it can be used as a vacuum drain. Its cost-effectiveness and efficacy seems to be maximized in patients with pre-operative Hb between 12 g/dL and 15 g/dL, whereas in patients with Hb < 12 g/dL post-operative cell saving system should be combined with other blood-saving techniques in order to increase its efficacy^[164].

Drainage clamping

Although it is commonly believed that a suction drain, placed intra-articularly reduces the formation of a haemarthrosis and enhances rehabilitation, many studies have yielded controversial results regarding its use^[165-169]. Senthil Kumar *et al*^[170] in report that most of the post-operative blood loss occurs in the first few hours and especially in the first four hours. As a result, drainage's clamping should help in minimizing blood loss acting like a tamponade. Although drainage's use is still debatable, many different drainage's clamp intervals have been described^[168,171-173]. In a prospective study, Yamada *et al*^[174] noted that extended drainage's clamping increased complications significantly. There is no consensus about the best protocol but it's noticeable that drainage's clamping combined with TXA can reduce blood loss after TKA^[175]. Surprisingly and in contrast with the above literature, 2010 Tai *et al*^[176] found no advantage of using the "clamping" method compared with non-drainage at all.

CONCLUSION

It's more than clear that TKA is a surgery with a blood loss reaching up to 1500 mL. Undoubtedly, the consequent ABTs and/or anaemia occurring post-operatively are causes of increased morbidity, cardiovascular risks, length of stay, decreased vigor and slow rehabilitation. Over recent decades, many blood saving strategies and methods have been described. Nevertheless, there are no concise guidelines, as few/limited studies have compared the relative efficacy of these techniques.

The common target of all blood saving methods is the cost-effective decrease of ABTs. The aim of this review was to evaluate current evidence regarding the efficacy, the safety and the cost-effectiveness on the various pre/intra/post-operative management strategies for patients undergoing TKA. As we described above there is a plethora of methods that can be used in the different periods of the surgery. Many studies have successfully/unsuccesfully described the advantages/disadvantages of each method with/without their limitations. We faced many controversial results in the majority of these strategies. For that reason larger prospective randomized studies comparing not only the individual strategies, but also their combination, are needed.

Scrutinizing the recent literature, we conclude that there is no "consensus success story" about a common efficient/safe blood management strategy in TKA. And if we hazard a guess, we'd say that this consensus cannot be achieved. The current trend is the patient-specific strategy (PSS). This idea is based on the notion that each patient has a different impact on the risk of requiring a transfusion. For example the PSS in a healthy man with Hb > 13 g/dL who undergoes TKA could be a "do nothing" (except Hb reaches transfusion trigger). Conversely, a Jehovah's Witness patient and/or a patient with significant cardiopulmonary compromise should be monitored carefully and more blood management strategies should be considered in order to avoid ABTs. In other words, the above methods that have been analyzed, the advantages and the disadvantages of each method, are just the different parameters that every surgeon should take on board in order to achieve the best result in a specific patient.

The take home message after our in-depth search is that the first important step in blood management is the thorough pre-operative evaluation of each patient. Consideration should be given to the existing physiologic/pathologic variables of the patient and the concomitant actions that should be taken in order to allow prompt optimization of the patient's physiologic status. The 2nd principal arm of effective blood management is the restriction of ABTs' to patients meeting well-established transfusion criteria. Nowadays, this trigger has been decreased to 8 g/dL. The old common belief that all patients with Hb below 10 g/dL should be transfused, has been surpassed. However, when clearly the blood is indicated (clinical signs and symptoms of anemia), administration should not be delayed. Additionally, the use of TXA perioperatively (with different routes of administration) is a widely accepted, effective and safe method in reducing perioperative blood transfusion. These three steps are the "baseline" in our daily practice regarding the perioperative care of the surgical patient.

In our daily practice, it's been proven to be really challenging and unfeasible to apply the same practices in all patients. In simple terms, no single method achieved to provide significantly superior results over another in ABTs' reduction. Primarily, every orthopaedic surgeon should be able to plow through and understand each method separately. Consequently, he must tailor these methods to result in an individualistic blood saving model.

In conclusion, an appropriate combination of the above blood management strategies could further result in ABT's reduction. Additionally, we should highlight the importance of a team approach (*e.g.*, orthopaedic surgeon, anesthesiologist, hematologist) in order to optimize the patients perioperatively and succeeding in the best result.

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Sternal metastasis - the forgotten column and its effect on thoracic spine stability

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Abstract

Sternal metastases are not studied extensively in the literature. There is a paucity of information on their role in metastatic disease. The concept of the fourth column was described by Berg in 1993, and has been proven in case report, clinically and biomechanical studies. The role of the sternum as a support to the thoracic spine is well documented in the trauma patients, but not much is known about its role in cancer patients. This review examines what is known on the role of the fourth column. Following this we have identified two likely scenarios that sternal metastases may impact management: (1) sternal pathological fracture increases the mobility of the semi-rigid thorax with the loss of the biomechanical support of the sternum-rib-thoracic spine complex; and (2) a sternal metastasis increases the risk of fracture, and while being medical treated the thoracic spine should be monitored for acute kyphosis and neurological injury secondarily to the insufficiency of the fourth column.

Key words: Fourth column; Sternal fracture; Sternal metastasis; Sternal-rib-thoracic spine complex; Spine stability

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Core tip: The sternal-rib complex provides additional support to the thoracic spine. The role of sternal fracture affecting the stability of the thoracic spine is well established in trauma, to date however its role in metastatic disease is unclear. Biomechanical studies highlight its importance and the presence of sternal metastasis should be considered when assessing the stability of the thoracic spine in metastatic disease.

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INTRODUCTION

Cancer remains the second leading cause of death in the United States, with 589430 cancer related deaths each year^[1]. In Europe, collective data from 40 countries has yielded an annual incidence of 3.45 million new cases per year, with 1.75 million cancer related deaths^[2]. With early detection and increased treatment options, prolonged survival in patients with metastatic disease will result with increased incidence of skeletal related events (SREs) that will require orthopaedic intervention. The skeleton is the third most common site for metastatic disease to occur in the body, with only the lungs and liver with a higher incidence. Within the skeletal system, the spine is the most common site of metastases. The thoracic spine is most prone to metastatic disease as it contains the greatest volume of bone marrow per vertebrae^[3]. Bone metastases are associated with a considerable degree of morbidity both due to pain and SREs. SREs are defined as a pathological fracture, a requirement for surgical intervention and palliative radiotherapy to a bone lesion, hypercalcaemia of malignancy, and spinal cord compression. Metastatic spinal cord compression occurs in 3.4% patients with cancer per year in the United States^[4] is a source of considerable morbidity. Breast, prostate, renal, lung, and haematopoietic tumours most commonly metastases to the spine and are discussed elsewhere in more detail. But what of sternal metastases which occur in the setting of spinal metastatic disease. Do they have an effect on the spine and its stability?

Sternal metastases are a rare phenomenon^[5,6] and there is a paucity of information published regarding their incidence and also their effect on spine stability. Best medical therapy, such as external beam radiotherapy or chemotherapy, is advocated for the vast majority of cases^[7] however when a pathological fracture occurs, then there is potential for delayed union and deformity. When present with concomitant thoracic spinal disease then the role of the sternum-rib-thoracic spine complex in thoracic spine stability, as the fourth column, is an important consideration. Berg^[8] first proposed the fourth column in 1993, as an adjunct to the three-column theory of spine stability of Denis^[9]. To date no study has looked at the role of the sternum in thoracic spine stability in the presence of a sternal metastasis. Hence the focus of this review is to identify what is known on the topic of sternal metastasis in the setting of spinal metastatic disease, and their potential effect on spine stability.

STERNAL METASTASES - WHAT IS KNOWN?

There has been little focus on the incidence and

association of sternal metastatic disease in recent years. A necropsy study by Urovitz *et al*^[5] from 1977 remains the largest single study on the topic. In a patient population of 415 patients, the incidence of sternal metastases was found to be 15.1%, of which 30.2% had a sternal fracture^[5]. These fractures also demonstrated delayed or nonunion features and were associated with greater deformity than traumatic sternal fractures^[5]. Conflicting reports on the commonest location and most prevalent tumours exist. Urovitz *et al*^[5] identified the body of the sternum as the commonest site of metastases with breast, lymphoma and myeloma the most prevalent primary oncological processes. This was contrary to what was previously described by Kinsella *et al*^[6] who concluded that the manubrium was most at risk, and that thyroid, renal and breast carcinoma were the most common. These findings are summarized in Figure 1.

Once sternal metastases have developed, best medical therapy with either radiotherapy, hormonal therapy or chemotherapy is recommended as per the primary diagnosis^[7]. This is regardless of location and size of the metastatic disease as the sternum is a non-weight bearing bone and treatment is not altered by whether the lesion is osteoblastic, osteolytic or mixed on imaging^[7]. The treating oncologist should closely evaluate the response of treatment, especially pain relief. If pathological fracture occurs, continued medical therapy is advocated and only those patients who fail best medical therapy are to be referred for consideration for surgical intervention^[7]. Sternal metastasis in isolation may be treated by a number of mechanisms. Usually in the setting of isolated metastatic disease, the tumour may be excised and the sternum may be reconstructed with titanium mesh^[10], locking titanium plate^[11] or even an allogenic transplant^[12]. In the palliative setting, kyphoplasty of sternal metastasis has been advocated for pain relief^[13]. Unfortunately, all recommendations are for sternal metastases in isolation and do not take into account the sternum-rib-thoracic spine complex in combination. Specifically, there are no recommendations for the prophylactic surgery on the sternum to prevent fracture in a patient with concurrent spinal metastatic disease.

SPINAL METASTASIS

Spinal metastases can be treated medically, with radiotherapy and or spinal surgery and treatment must be individualized to accommodate for tumour type, performance status of the patient, life expectancy and neurological status. It is a fundamental realization that any intervention with regards spinal metastases is palliative. There are four primary indications to intervening in metastatic disease of the spine: Neurological compromise, spinal instability, unrelenting pain and in the case which histological diagnosis must be established. Historically radiotherapy became the first-line treatment for most patients^[14]. Recent advances in imaging, surgical technique and instrumentation systems have improved

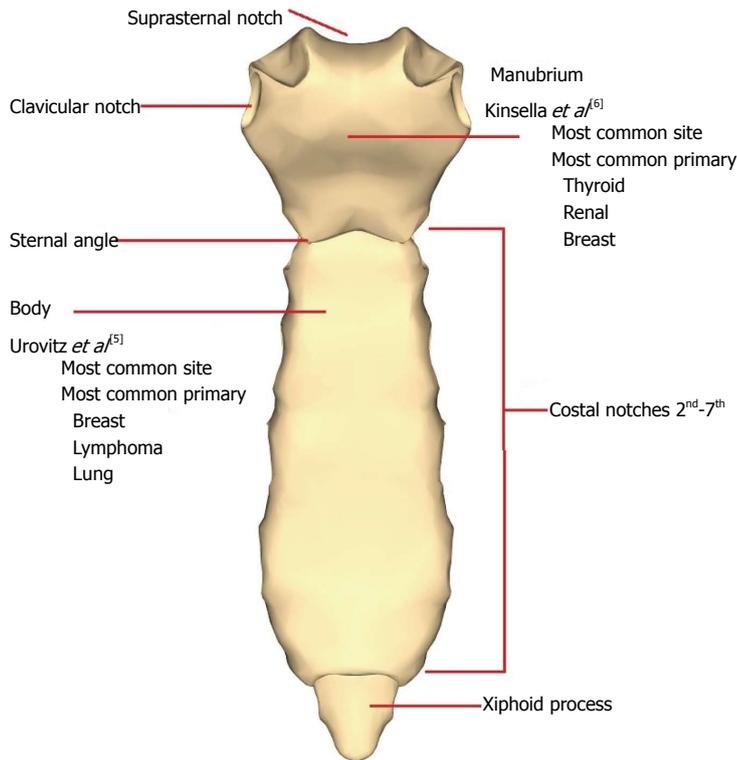


Figure 1 Sternum.

outcomes from surgery. Patchell *et al*^[15] in a randomized control trial showed that surgery followed by radiotherapy to be superior to radiotherapy alone. These findings were reproduced in a large multicentre observational study^[16]. There is a multitude of evidence on surgery in neurological compromise including spinal cord compression, in which cases the spine needs to be decompressed and stabilized^[17-19]. The sternum in this setting does not play a role in the management strategy as the evidence supports intervention regardless of sternal disease. Likewise, management of intractable pain and the need for histological diagnosis is not altered by whether disease is present in the sternum. Spinal stability however is directly affected by the sternum in biomechanical studies of the spine^[20] and thus it follows that it has the potential to affect stability in the metastatic spine, but remains to be investigated fully.

STABILITY WITH SPINAL METASTASIS

Assessing the spine stability in metastatic disease however is more difficult, and especially in the setting of impending instability, the sternum could play a role. From the literature we know that defining instability in the spine using trauma criteria is not directly applicable to the setting of metastatic disease^[21]. This is because the injury does not follow typical patterns seen in trauma, and involves different biological healing potential and patient factors^[22]. As we have no evidence on the topic then we must be cautious when applying observations from traumatic sternal and spinal injuries to the oncological setting as we assess the thoracic spine as a whole with the sternum-rib-thoracic spine complex.

The Spine Oncology Study Group (SOSG) defines stability as the "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive stability and/or neurological compromise under physiological loads"^[22]. It is the major goal of any spinal surgery in oncology to preserve or restore the spine's stability. Regardless of indication, surgery is generally reserved for patients with a life expectancy of greater than 3 mo^[23]. To determine a patient's life expectancy, multiple scoring systems have been developed. Tokuhashi *et al*^[24] developed one example of a scoring system to evaluate prognosis of metastatic spine tumour patients. This was further assessed by Enkaoua *et al*^[25] regarding its reliability, and demonstrates a median survival of 5.7 mo with a score ≤ 7 mo vs 23.6 mo for a score of ≥ 8 . Regardless of scoring systems however, establishing survival of patients is subjective and must take into account multiple patient and disease factors before a decision on suitability for surgery is made.

Surgeons rely on their clinical experience as well as internationally accepted scoring systems to determine a spine's stability and appropriate treatment. The SOSG have provided a classification system for spinal instability - The Spinal Instability Neoplastic Score (SINS) - which was developed from existing evidence based medicine and expert consensus opinion^[22]. Factors included in the score include location, pain, alignment, vertebral body collapse, posterior element involvement and type of bone lesion (Table 1). The SINS has been shown to have good inter- and intraobserver reliability in determining stability. Stability is derived from overall score out of a max score of 18. Neoplastic disease is

Table 1 Spinal Instability Neoplastic Score

	Score
Spine location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile (C3-C6, L2-L4)	2
Semi-rigid (T3-T10)	1
Rigid (S2-S5)	0
Mechanical or postural pain	
Yes	3
No (occasional pain but not mechanical)	1
Pain-free lesion	0
Bone lesion quality	
Lytic	2
Mixed lytic/blastic	1
Blastic	1
Radiographic spinal alignment	
Subluxation/translation	4
<i>De novo</i> deformity (kyphosis/scoliosis)	1
Normal	0
Vertebral body involvement	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% involvement	1
None of the above	0
Posterior involvement	
Bilateral	3
Unilateral	1
None	0

deemed unstable with a score of 13-18, stable with a score of 0-6 and indeterminate instability or possibly impending with a score of 7-12. The specificity and sensitivity of the SINS for unstable or potentially unstable spines is 95.7% and 79.5% respectively. The SINS provides a useful tool for assessing spinal disease and aids in the decision making for surgical intervention but is not binding. Unfortunately the sternum is not considered in the SINS in its current format, and thus the fourth column becomes the forgotten column when considering spine stability in metastatic disease.

Further scoring systems exist which can also aid in the decision making process. As survivorship improves with neoplastic conditions so does the incidence of metastatic disease in the axial skeleton. Predicting the survivorship of patients with metastatic disease is important in the planning of surgical intervention. The Oswestry Spinal Risk Index (OSRI) is a simple, reproducible measure of survivorship looking at primary tumor pathology and the patient's general condition^[26]. It has been externally validated twice and provides accurate prediction of a patients survivorship which can be used in the decision making process^[27,28].

ROLE OF THE FOURTH COLUMN IN METASTATIC DISEASE

Biomechanically, the inherent stability of the thoracic spine is augmented by the sternum and rib cage, which increases the moment of inertia and stiffens the spine against rotary forces^[29]. There is a multitude of evidence

from case reports, retrospective reviews and biomechanical studies on the importance of the sternum and ribs in the presence of thoracic spine injury in acute trauma but none on metastatic disease. The association between sternal fractures and spine injuries is well documented in the literature^[8,30-32]. In clinical practice a spinal injury must be suspected to exist in the presence of a sternum fracture, even at discordant levels.

A 50-year literature review by Fowler^[30] concluded that 43% of sternum fractures had associated spinal fractures. Berg postulated that the sternum and ribs represents a fourth column of structural support for the thoracic spine in addition to the three described by Denis^[8]. The three column model divides the osteoligamentous structures of the spinal column into an anterior, middle and posterior column^[9]. Involvement of 2 of the 3 columns resulted in potentially unstable spinal injury at risk of progressive deformity and neurological compromise^[9]. The additional fourth column theory was based on two cases of displaced sternal fractures with minimally displaced thoracic spine injuries leading to progressive kyphosis^[8].

This pattern of injury is often associated with neurological compromise, with increasing degrees of kyphosis being observed. Golpalakrish and Masri reported 83% of patients with sternum and spine fracture combinations had complete neurologic injury and were paraplegic^[32]. Vioreanu *et al*^[31] in 2005 reported an incidence of 1.4% of sternal fracture with vertebral fracture, which rises to 9.2% when the subset of thoracic fractures is examined in isolation. There is a clear association of neurological compromise in these patients with all six patients suffering neurological injury of which four patients had complete injuries^[31].

However, neither Berg nor Vioreanu *et al*^[31] described the behavior of a three-column injury with an intact sternum or "fourth column". A case report by Shen describes how the sternum provided sufficient stability for the conservative management of a three-column unstable injury pattern in an ankylosing spondylitis patient without neurological compromise^[33]. The authors concluded that the case confirmed the existence and clinical relevance of the fourth column proposed by Berg. An *in vitro* cadaveric study estimated that the sternum-rib complex accounts for up to 78% of thoracic stability^[34]. Watkins *et al*^[20] examined the biomechanics of the fourth column in 10 human cadaveric thoracic spines using multidirectional flexibility tests. They found that an indirect flexion-compression fracture of the sternum decreased the stability of the thoracic spine by 42% in flexion-extension, 22% in lateral bending and 15% in axial rotation^[20]. This is evidence of the importance of the sternum in stability of the thoracic spine, and why the thoracic spine is considered a semi-rigid structure^[22]. Following from this we can conclude that sternal and thoracic spine injury is a potentially unstable combination.

Metastasis of the sternum and their role on stability is not addressed in the Spinal Instability Neoplastic

Score (Table 1). There are two areas where they have a potential role, which needs to be further explored. The thorax (T3-T10) is termed semi-rigid in the location score secondary to the biomechanical benefit of the sternum and rib cage, and is only scored 1 out of a possible 3. Concomitant sternal metastasis with pathological fracture would affect the semi rigid nature of the thorax with loss of the stability provided by the fourth column. The flexion-extension stability of the spine is reduced by 42%^[20] in this setting regardless of thoracic disease, with rotational and lateral bending also affected. We must ask the question - with the loss of the biomechanical benefit of the sternum, should the thoracic now be considered "mobile" and the location score increased to 2 to reflect this? Secondly, in the presence of metastases without pathological fracture, a lytic lesion of the sternum would be at risk for impeding fracture and should be observed closely. If the spine is deemed stable, close follow up of both the sternal and thoracic metastatic disease is required as early de novo kyphosis deformity would add an additional 2 points to a patients score and may change management. The association between kyphosis and loss of sternal integrity is well established in case reports and carries a significant risk of neurological injury^[8,30,32].

In addition, sternal metastasis may be painful but this would not impact on the SINS pain score. Local pain may be related to the sternal metastases themselves but back pain in the setting of concurrent sternum and spine disease which worsens with movement and loading of the spine and is relieved by recumbence would suggest that it is mechanical in nature and thus increase the patients score, as set out by the SOSG^[22].

CONCLUSION

In conclusion, the thoracic spine should not be examined in isolation. The sternum is a pivotal support in thoracic spine stability and should not be overlooked when assessing a patient's thoracic spine. Assess spinal stability in the metastatic diseased spine is a complex and multifactorial process. The sternum provides essential support to the thorax spine and pathological fracture or impending fracture in the sternum has the potential for acute deformity of the thoracic spine that could lead to neurological injury. No evidence exists on the sternum role in metastatic spinal stability to date and thus hard conclusions cannot be made. We recommend that sternal metastatic disease be assessed in conjunction with spinal metastatic disease, and that treatment be tailored to individual cases. Further study is needed to fully evaluate the role of the sternum in spine stability with metastatic disease. A biomechanical study looking at the location and involvement of the sternum and the subsequent risk of fracture and deformity is needed to quantify the risk to the spine. Following this there may be a role for modification of the SINS once their role has been fully investigated. For now, clinical judgment is recommended until further evidence is provided in the literature.

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Role of fetuin A in the diagnosis and treatment of joint arthritis

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Abstract

Osteoarthritis is a slowly progressive disease which includes the intervention of several cytokines, macrophage metalloproteinases reaction, leading to the degradation of the local cartilage but also having an impact on the serum acute phase proteins (APPs). Subsequently, biomarkers seem to be essential to estimate its progression and the need for any surgical intervention such as total arthroplasty, but also can be used as therapeutic agents. Recently, among APPs, fetuin A drew attention regarding its possible anti-inflammatory role in animal models but also as a therapeutic agent in the inflammatory joint disease in clinical trials. In contrast with other APPs such as C-reactive protein, fetuin A appears to be lower in the serum of patients with degenerative joint disease in comparison with the healthy ones, and also acts as an antagonist of the anti-proliferative potential of transforming growth factor- β (TGF- β) cytokines. Because of its lower serum levels in arthritis, an unregulated binding of TGF- β and bone morphogenetic proteins takes place leading to further arthritic lesions. The purpose of the present review is to assess the current evidence regarding the multipotent role of the alpha-2-HS-glycoprotein or as also known Fetuin-a in animal models but also as a biomarker of the degenerative joint arthritis in clinical trials.

Key words: Fetuin A; Arthritis; Alpha-2-HS-glycoprotein; Bone morphogenetic protein; Inflammation; Glycoprotein; Treatment

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Core tip: Fetuin A, an acute phase glycoprotein, recently drew scientific attention regarding its anti-inflammatory role. In the case of arthritis, clinical studies have shown

its therapeutic potential as well as its anti-inflammatory role as it has been indicated by animal models. In this manuscript, we intend to review the current evidence concerning its anti-inflammatory and therapeutic role in degenerative joint disease.

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INTRODUCTION

Osteoarthritis, which is also known as degenerative arthritis, is a deteriorating musculoskeletal condition that includes the decrease in the articular cartilage but also leads to a progressive subchondral erosion of the bone^[1]. It is assumed that the joint arthritis consists of an inflammatory response which is introduced by several cytokines which are produced by the local reaction of macrophages, such as interleukin (IL)-1a, IL-8, IL-10 and matrix metalloproteinases (MMPs). These agents are measurable in the serum but also in the joint synovial fluid and all lead to cartilage breakdown^[2]. Additional to the imbalance of the cytokines driven inflammatory process, the collagen of type 1 is transformed to collagen of type 2, while at the same time a decrease in the joint chondrocytes also takes place. It is widely accepted that the activity of IL-1 has a leading role in the arthritis inflammatory process leading to the production of MMPs which further leads to cartilage degradation. Acute phase proteins (APPs), such as C-reactive protein, are also elevated in patients with severe osteoarthritis^[2,3].

Regarding APPs, fetuin A has recently draw attention regarding its possible anti-inflammatory role^[4]. The complete structure of the complex oligosaccharides of fetuin A has been established^[5]. Thanks to ion exchange chromatography following pronase digestion, identical molar ratios of sialic acid, mannose and N-acetyl-glycosamine of 3:3:3:5 was revealed (Figure 1).

Fetuin A is also known as alpha-2-HS-glycoprotein (AHSG) for the human homologue and was first declared as a fetus major plasma protein. During the fetus growth, it is expressed in the liver, kidney, gastrointestinal tract, skin and brain^[6]. Concerning the adults, among APPs, fetuin A is produced by the liver and has recently drawn attention regarding its possible anti-inflammatory role in injury or infection, classifying it as a negative APP due to a regulation of pre-inflammatory cytokines such as tumor necrosis factor (TNF), IL-1, IL-6 and interferon (IFN)- γ , but also as a positive APP thanks to the mediation of HMGB1^[7].

The aim of this mini review is to investigate the possible role of fetuin A in the inflammatory response, in processes such as the joint osteoarthritis.

ETIOPATHOLOGY OF ARTHRITIS

The joint homeostasis seems to take place due to a balance between catabolic factors of the adult joint cartilage (IL-1 and TNF) as well as the anabolic ones [insulin like growth factor (IGF), bone morphogenetic protein (BMP) morphogens such as BMP-7 and cartilage-derived morphogenetic proteins (CDMPs)], transforming growth factor- β (TGF- β) and fibroblast growth factors (FGFs). CDMP-1 is expressed in the deeper damaged areas of the cartilage of osteoarthritic joints where it leads to an increase of the local chondrocytes but also promotes the local production of proteoglycans^[8,9].

Among the morphogens above, BMP-7 leads an important role for the maintenance of the joint homeostasis. Normally, BMP-7 emerges in the upper matrix of articular cartilage adhering to the expression of BMP receptors (BMPR- I A, I B, and II). BMP-7 has many roles in the inflammatory disease of the joint, including the preservation of surfaces of the articular cartilage by promoting the expression of the chondrocyte phenotype of dedifferentiated cells, increasing synthesis of tissue inhibitor of metalloproteinase (TIMP). Moreover, leads to the expression of IGFI, and cytoskeletal proteins of the chondrocytes^[10]. It is also known that multipotent mesenchymal stem cells (MSCs) that express BMPs and BMPRs have been isolated from adult human synovial membrane^[11]. So, it is assumed that morphogens from the TGF- β family seem to be involved in the remodeling of the arthritic cartilage. Components of synovial joints, such as the bone marrow, the synovium and the periosteum, contain MSCs that are capable of inducing chondrogenesis. It is suggested that the unregulation and likely the up regulation of the activity of TGF- β and BMP are likely to make MSCs in numerous joint sites to form excessive amounts of tissues of cartilage, bone and fibre, leading to fibrosis and osteophyte formation, characteristics of joint osteoarthritis. So, any imbalance between the factors above is likely to establish the degenerative joint disease (DJD) which with further progression may lead to the need of a total joint replacement^[12]. However, the bone itself has a leading role in the pathogenesis of osteoarthritis. The level of bone remodeling plays a critical role under mechanical loading conditions, as demonstrated by consistent experimental studies. Yet, new clinical biomarkers have being developed to assess the bone phenotype of osteoarthritic patients. This stratification strategy is likely to better identify groups of patients who would benefit from bone-acting drugs to decrease disease progression and improve pain and disability^[13].

FETUIN-A (AHSG) IN DJD

As it was stated above, APPs such as C reactive protein is mentioned to be elevated due to arthritis, depending on the severity of the disease^[14]. Fetuin A protein is also mentioned to be influenced by the inflammation as an APP^[15,16], in addition to other biomarkers which have

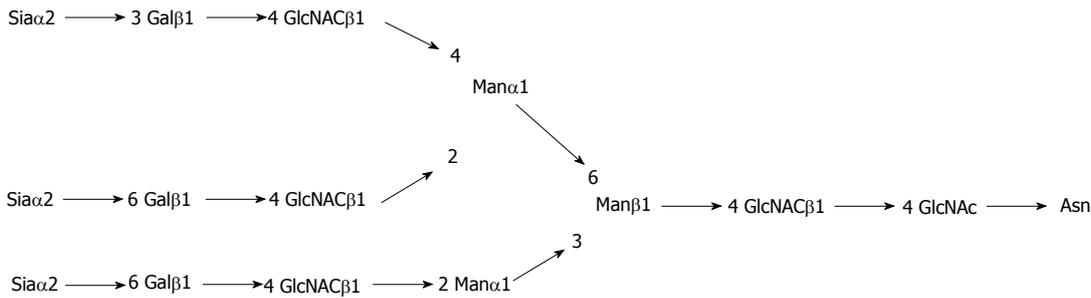


Figure 1 Structure of fetuin A.

been recently studied. For example, serum cartilage oligomeric matrix protein was also found elevated in cases of knee joint osteoarthritis^[17,18]. Interestingly, recent research has shown lower serum levels of AHSB in patients with DJD, accompanied with lower BMP levels than the healthy ones^[12].

Studies have shown that AHSB is a negative acute phase reactant and its level is correlated with CRP circulation in the serum inversely^[19]. Further research has also shown a close association between fetuin A and metabolic syndrome^[20], obesity and dyslipidemia^[21], or even blood pressure regulation^[22]. Additionally, it has been linked closely with type 2 diabetes mellitus and many authors have suggested that it may be an independent risk factor for the expression of the disease. Specifically, patients with high levels of serum AHSB may have increased risk of incident diabetes^[23,24]. Mixed results have been drawn regarding the role of fetuin A in the cardiovascular disease. However, all studies have shown a positive or negative effect of the circulating levels and the presence of the disease^[19,25,26]. With no exaggeration, one can admit that AHSB is indeed a multifunctional protein^[16]!

AHSB is an antagonist of the TGF- β /BMP, as it is mentioned that it antagonizes the osteogenic as well as the anti-proliferative actions of TGF- β cytokines *in vitro*. More specifically, the 18-19 amino acid region in the AHSB molecule is identical to the TGF- β receptor type II (TBR II) and appears to be the BMP antagonist site. This domain is also designated the TGF- β receptor II homology 1 domain (TRH1), which is essential for the cytokine binding and as a result leads to the non binding with the TBR II^[27]. So, inflammatory diseases characterized by low serum AHSB, such as DJD, leads to an unregulated binding of TGF- β and BMP, having further fibrosis, osteophyte and ectopic bone formation as a result^[28].

During the progression of the arthritis, a down regulation of the liver production of AHSB leads to it lower serum levels^[12]. Another explanation for that is likely to be the elevated figures of MMPs which are produced by the inflamed tissues, Especially, MMP-1, 3 and 9 are increased in inflamed joints. However, recent studies suggest that AHSB can be eliminated by MMPs, either systematically or locally in the joint^[29]. As a result, this could lead to increased activity of the BMPs that would also lead to further progression of the arthritis.

Regarding the prevention of DJD, it is important to

state that the therapeutic interventions and goals should take place during the early stages of the arthritis, as chondrocytes are still able to respond to the anabolic factors^[9]. The existence of a therapeutic window should be established regarding the concentration and the exposure of BMP-7. Moreover, in order to maintain the joint homeostasis it is important that other proteins such as AHSB that are down-regulators of the BMPs, should be available in order to enhance the protective role of the cytokines above.

As for the therapeutic potential of AHSB in the DJD, Rittenberg *et al.*^[30] described in 2005 the regulated release of intrarticular injections on experimental level of BMP7 by co-injection of its regulatory molecules such as AHSB in clinical trials. Moreover, besides to the regulation of BMPs, therapeutic potential of AHSB is also based on its ability to eliminate the inflammation and the local tissue destruction. In 1998, Wang *et al.*^[31] proved through examination of murine cell cultures that AHSB can be used by the local macrophages as an opsonin for macrophage deactivating molecules. Furthermore, Wang *et al.*^[32] in 2010 established the protective role of AHSB in the ischemic cerebral inflammation in animal models of rats, as well as the the suppression of sepsis mediators in late stages of sepsis in the same animal model. Also, TNF increase from lipopolysaccharide stimulated macrophages was inhibited significantly in an animal model of inflammation which was carried out by Wang *et al.*^[33] in 1997. Consequently, the co-administration of AHSB and BMPs is able to set a therapeutic intervention for the degenerative bone disease, taking into account the anti-inflammatory role of the agents above.

CONCLUSION

In conclusion, joint arthritis' diagnosis and treatment as well as its pathophysiology have been studied during the years. However, further research seems to be essential for more effective prevention. The protein Fetuin A has the potential to be used as a biomarker of the disease, as well as a therapeutic agent for the DJD. As a result, physicians should be aware of the fetuin A as a marker of activity and also to be informed in order to have a correct approach to the patients disease and treatment, but also for additional inflammatory diseases. Besides, additional clinical studies are likely to validate the measurement of BMPs as well as AHSB serum levels as a diagnostic means in the

clinical entity of DJD. The identification of AHSG levels in combination with the clinical evaluation of the patients, are not only likely to diagnose the disease in even subclinical stage but also to reduce the need for any further joint salvage procedures, such as total arthroplasty.

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Retrospective Study

**Emergent reintubation following elective cervical surgery:
A case series**

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Author contributions: Schroeder J designed and performed the research, analyzed the data and wrote the paper; Salzmman SN analyzed the data and wrote the paper; Hughes AP designed the research and provided clinical advice; Beckman JD designed the research and provided clinical advice; Shue J analyzed the data and provided research advice; Girardi FP designed the research and provided clinical advice.

Institutional review board statement: This retrospective case series has received approval from the authors' institutional review board.

Informed consent statement: For the patients presented in this case series, a waiver of patient informed consent and U.S. Health Insurance Portability and Accountability Act (HIPAA) authorization were sought. Information contained in this case report contains no personal identifiers to ensure patient confidentiality and protections. Under these provisions, the Institutional Review Board (IRB) at our institution provided approval of this study (IRB#2014-062).

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Abstract**AIM**

To review cases of emergent reintubation after cervical surgery.

METHODS

Patients who were emergently intubated in the post-operative period following cervical surgery were identified. The patients' prospectively documented demographic parameters, medical history and clinical symptoms were ascertained. Pre-operative radiographs were examined for the extent of their pathology. The details of the operative procedure were discerned.

RESULTS

Eight hundred and eighty patients received anterior- or combined anterior-posterior cervical surgery from 2008-2013. Nine patients (1.02%) required emergent reintubation. The interval between extubation to reintubation was 6.2 h [1-12]. Patients were kept intubated after reintubation for 2.3 d [2-3]. Seven patients displayed moderate postoperative edema. One patient was diagnosed with a compressive hematoma which

was subsequently evacuated in the OR. Another patient was diagnosed with a pulmonary effusion and treated with diuretics. One patient received a late debridement for an infected hematoma. Six patients reported residual symptoms and three patients made a complete recovery.

CONCLUSION

Respiratory compromise is a rare but potentially life threatening complication following cervical surgery. Patients at increased risk should be monitored closely for extended periods of time post-operatively. If the airway is restored adequately in a timely manner through emergent re-intubation, the outcome of the patients is generally favorable.

Key words: Cervical surgery; Complication; Airway compromise; Reintubation; Hematoma

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Core tip: The rate of cervical spine surgery has increased over the last years. Airway compromise is a rare but potentially life threatening complication following this type of procedure. This case series represents a single institution's experience of 9 cases requiring emergent reintubation after anterior- or combined anterior-posterior cervical spine surgery. Besides reporting patient characteristics and operative details, our approach to evaluating and treating these cases is presented. In addition the literature addressing reintubation after cervical spine surgery is reviewed.

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INTRODUCTION

Degenerative conditions of the cervical spine result from disk degeneration and the subsequent osteophytic bone formation extending along the affected vertebrae^[1-3]. The uncinat processes as well as the ligamentum flavum may hypertrophy^[1]. All of these mechanisms constitute the body's natural response to restore stability and alignment of the cervical spine. Less commonly, cervical kyphosis, compensatory subluxation and the ossification of the posterior longitudinal ligament are factors which may contribute to a progression of the disease resulting in a wide spectrum of clinical signs and symptoms^[4].

Overall, up to 89%-95% of men and women aged 60 and above will have degenerative changes visible in their cervical spine imaging, C5-6 being the most commonly affected level^[5-7]. Dependent on the degree of nerve root- and spinal cord compression, patients may present with

neck pain, radiculopathy or paresthesias of the upper extremities, or signs of myelopathy such as gait- and fine motor control impairment and weakness^[8,9]. In cases of myelopathy, severe radicular pain, and patients with progressive neurologic deficits, cervical spine surgery is performed as these patients generally have debilitating sequelae^[10].

The safety profile of cervical spine surgery is high, however a mortality rate of 0.14% and an incidence of major complications of 3.93% have been associated with cervical surgery. Patient age > 74 years, a primary diagnosis of cervical spondylosis with myelopathy and large cervical procedures such as long posterior fusions or combined anterior and posterior fusion were found to be predictive of an increased risk of complications^[11].

A more dangerous complication is breathing insufficiency, resulting in urgent reintubation. It has been reported in 0.14%-1.9% of patients undergoing cervical surgery^[12-14]. Postoperative reintubation has been correlated with advanced age, chronic pulmonary disease, pre-operative hypoalbuminemia and anemia, recent weight loss, a high serum creatinine, three or more cervical levels operated on and prolonged surgical time^[12-15]. As urgent reintubation is a lifesaving procedure, timely management is critical in order to avoid grave morbidities and mortalities.

We present a detailed case series of a single institution's experience with postoperative reintubation in patients receiving anterior- or combined anterior-posterior cervical surgery.

MATERIALS AND METHODS

Study population

Data was reviewed from a prospectively maintained hospital database of 880 patients who underwent cervical spine surgery over a 5 year period (2008-2013) at a single institution. Nine patients that required emergent postoperative reintubation following previous extubation were identified.

Data collection

Data was retrospectively collected on patient demographics, past surgical- and medical history, evidence of osteopenia or osteoporosis, primary diagnosis, and surgical details. Data was collected using intra-operative and discharge reports through SRS (SRSsoft, Montvale, NJ, United States). The patients prospectively documented clinical findings and the diagnostic details of their pre-operative imaging were recorded.

RESULTS

The incidence of emergent reintubation following anterior- or combined anterior-posterior cervical surgery was found to be 1.02%.

Patient characteristics

Detailed patient parameters are presented in Table 1. The

Table 1 Patient demographic parameters

No.	Gender	Age (yr)	BMI	Smoking Status	Comorbidities
Case 1	Male	53	29.3	Never	Hyperlipidemia
Case 2	Female	70	26.7	Never	hypertension, Von willebrand disease, hypoglycemia, visual migraines
Case 3	Male	44	23.7	Current, 15 P-Y	-
Case 4	Male	58	26.5	Former, 15 P-Y	Diabetes mellitus type I , asthma
Case 5	Female	58	22.9	Never	Rheumatoid arthritis, hypertension, GERD
Case 6	Male	56	27.7	Never	Coronary artery disease, hypertension, benign prostate hyperplasia
Case 7	Female	71	29.3	Current, 8 P-Y	COPD, pulmonary hypertension, obstructive sleep apnea, GERD
Case 8	Female	51	25.6	Never	-
Case 9	Female	61	21	Never	GERD

P-Y: Pack-years; GERD: Gastroesophageal reflux disease; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease.

average age of the patients was 58 [44-71]. The average BMI of the patients was 25.86 [21-29.3]. The male to female ratio was 4:5. Three patients had a history of tobacco consumption, with two patients remaining active smokers with an average number of 11.5 pack years [8-15]. The patients' medical histories were significant for systemic heart disease in five patients, and for pulmonary disease in two patients. One patient suffered from rheumatoid arthritis. Overall, five patients had multiple systemic comorbidities. One patient's surgical history was significant for a prior emergent posterior cervical decompression from C2-5 for a spontaneous epidural hematoma.

Initial evaluation and diagnostic studies

Five patients complained of myelopathic gait changes. Neck pain was the main complaint of four patients, with three patients each reporting additional shoulder pain or paresthesias. Two patients suffered from upper extremity weakness and numbness, whilst one patient each complained a loss of fine motor control and arm- or hand pain. 8 patients exhibited evidence of a cord signal change in their MRIs.

Initial surgical management

Operative details are presented in Table 2. The average length of surgery was 7.67 h [4.5-11.5], with an average of 3.78 cervical levels fused [2-6]. Three cases were combined anterior and posterior cervical surgeries. The average estimated intraoperative blood loss was 639 mL [150-1100]. No intra-operative complications were recorded in any of the patients. Four patients were kept intubated after completion of the case and extubated on average on the postoperative day number 2 [1-4]. Five patients were extubated at the end of the case. All patients were kept in the post-anesthesia care unit after surgery to monitor airway compromise.

Respiratory distress diagnosis and intervention

Details on postoperative airway management are presented in Table 3. The average interval between extubation to reintubation was 373.3 min [60-720]. The symptoms leading to a pulmonary reevaluation and emergent reintubation varied. Four patients presented with progressive onset of dyspnea, in some cases in combination with stridor,

dysphagia or dysphonia. Three patients had no physical complaints but developed hypoxemia with an oxygen saturation ranging from 70%-80%. Two patients developed a spontaneous severe cough. One of the patients was still intubated and inadvertently extubated himself whilst convulsively coughing, leading to his emergent reintubation.

In general, patients were reintubated nasally after topical lidocaine using a flexible fiberoptic bronchoscope to allow for assessment of airway swelling and vocal cord function. Reintubations were easily performed, however, all were done by experienced attending anesthesiologists. None of the patients required tracheostomy for initial reintubation.

The patients were kept intubated after their emergent reintubation for a mean of 2.3 d [2-3]. Urgent fibroscopic ENT examination and imaging identified a compressive hematoma in one patient that was evacuated in the OR. One patient was diagnosed with pulmonary edema and subsequently desaturated and was transferred to the intensive care unit. The remaining seven patients showed no clear signs of respiratory obstruction, with only moderate pharyngeal edema being identified in diagnostic imaging. Due to the severity of their symptoms, four of the patients with this diagnosis received decadron - three of them in combination with racemic epinephrine.

Follow-up

The patients were followed for an average 21.7 mo [2-26.9]. Residual complaints are summarized in Table 4. One patient who was not diagnosed with a hematoma upon emergent airway reevaluation leading to reintubation required a late debridement for an infected hematoma. Three patients made a complete recovery. The remaining six patients reported residual primary complaints of neck pain, paresthesias, numbness and radicular pain. One patient reported a new onset of headaches. None of the patients complained of persistent dysphagia or dysphonia. Overall, none of the patients experienced any clinical sequelae of their reintubation.

DISCUSSION

In this series of 880 patients undergoing cervical surgery, the overall incidence of emergent reintubation following anterior- or combined anterior-posterior cervical surgery was 1.02%.

Table 2 Primary operative details

No.	Cord signal change (MRI)	Symptoms	Operated levels	Approach	Operative time (min)	Estimated blood loss (mL)
Case 1	Yes	Neck- and hand pain, gait change, paresthesias	C3-7	Anterior	360	750
Case 2	Yes	Upper extremity weakness, shoulder pain, paresthesias	C2-6	Combined	690	750
Case 3	Yes	Right arm pain	C3-7	Anterior	390	850
Case 4	Yes	Shoulder pain, paresthesias	C3-7	Anterior	570	800
Case 5	Yes	Gait change, numbness, weakness	C4-T3	Combined	600	950
Case 6	Yes	Neck pain, numbness, gait change	C3-7	Anterior	330	300
Case 7	Yes	Neck pain, gait change	C2-T6	Combined	660	1100
Case 8	No	Neck pain, shoulder pain	C4-6	Anterior	270	150
Case 9	Yes	Neck pain, shoulder pain, gait change, decreased fine motor control	C3-7	Anterior	270	100

MRI: Magnetic resonance imaging.

Table 3 Postoperative airway management

No.	Primary post-op extubation (d)	Time to reintubation (min)	Symptoms preceding reintubation	Diagnosis	Length of reintubation (d)	Therapeutic measures
Case 1	1	360	Dyspnea, stridor	Pharyngeal edema	2	Decadron
Case 2	1	600	Hypoxemia (70%)	Hematoma	3	Surgical evacuation
Case 3	0	60	Coughing white, thick mucous	Pulmonary edema	2	Decadron, epinephrine, diuretics
Case 4	0	60	Hypoxemia (80%)	Pharyngeal edema	3	-
Case 5	1	600	Dyspnea, stridor	Pharyngeal edema	3	Decadron, epinephrine
Case 6	0	60	Coughing whilst intubated: Inadvertently extubated	Pharyngeal edema	2	-
Case 7	4	720	Hypoxemia (70%-80%)	Pharyngeal edema	2	-
Case 8	0	420	Dyspnea, dysphagia, dysphonia	Pharyngeal edema	2	-
Case 9	0	480	Dyspnea	Pharyngeal edema	3	Decadron, epinephrine

The early signs and symptoms of airway compromise varied. Some patients developed a spontaneous severe cough, progressive dyspnea, stridor, dysphagia or dysphonia. However, some patients had no apparent physical complaints but developed hypoxemia, leading to reintubation. The timely diagnosis of the airway compromise and the subsequent management thereof resulted in a lack of longterm morbidity and mortality related to the complication. Pharyngeal edema was the leading pathology causing postoperative airway compromise.

Postoperative airway compromise is a rare complication of anterior- or combined anterior-posterior cervical surgery. Nandyala *et al.*^[15] examined 8648 patients from the American College of Surgeons National Surgical Quality Improvement Program database. They found that 0.62% of patients analyzed in their study who had undergone cervical spine surgery required prolonged ventilation. An additional 0.64% was reintubated postoperatively. Emergent reintubation was correlated with advanced age and a greater comorbidity burden, demonstrating

similar findings as our case series. Marquez-Lara *et al.*^[12] examined a patient sample which underwent anterior cervical surgery from the Nationwide Inpatient Sample database. They reported an incidence of reintubation of 0.56% and reaffirmed the correlation of reintubation with old age and an increased comorbidity burden. Additionally, they reported a correlation with fusions of three or more levels. Hart *et al.*^[16] experienced a high postoperative incidence of airway edema requiring continuous intubation or emergent reintubation in 45% of cervical surgeries crossing the cervicothoracic junction. All but one of the patients presented here demonstrate at least one of the risk factors reported in the literature such as multi-level fusions, pulmonary disease, advanced age or prolonged surgical time^[12-15].

A variety of conditions have been implicated as the cause of postoperative airway compromise in cervical surgery. Emery *et al.*^[17] presented a series of seven patients who required emergent reintubation following upper-airway compromise after multi-level corpectomies

Table 4 Follow-up

No.	Residual complaints
Case 1	Persistent neck pain and numbness
Case 2	Trapezius pain, paresthesias
Case 3	Residual neck pain
Case 4	-
Case 5	-
Case 6	-
Case 7	Intermittent neck pain, radiculopathy of the right arm
Case 8	Not reported
Case 9	Intermittent neck pain, paresthesias, headaches, numbness and paresthesias of the left thumb and index finger

for myelopathy with a mortality rate of 28.6%. They believed that the cause of the conditions was predominantly hypopharyngeal and supraglottic swelling. Additional studies have discussed their experience with retropharyngeal postoperative hematoma, cerebrospinal fluid collection, angioedema and hardware dislodgement as causes of respiratory distress^[18-22]. The point in time at which the airway compromise occurs has been described as a possible indicator of the etiology. Wound hematomas and pharyngeal edema normally occur within the first hours after the procedure, while respiratory compromise after three days indicates pathologies including abscess formation, cerebrospinal fluid leak or hardware failure^[23]. An optimization of inter-departmental cooperation and the capability of emergent imaging may expedite the diagnosis, resulting in a timely intervention and re-establishment of airway control. In our case series, the diagnosis was made with the help of ear, nose, and throat specialists evaluating the patients combined with an emergent intubation by trained anesthesiologists. Seventy-seven point seven percent of the patients requiring reintubation were subsequently diagnosed with a radiographically not impressive pharyngeal edema. This finding is concurrent with the reports found during our review of the literature.

Few studies discuss the treatment or prevention of airway compromise. Hart *et al*^[16] examined the effect of the implementation of a fluid management protocol in cervical surgery crossing the cervicothoracic junction. They found that none of the patients who received limited intraoperative fluid resuscitation with crystalloids and a maintenance of constant blood pressure after the implementation of the protocol experienced postoperative airway compromise vs the 45% of patients who had experienced complaints previously. We found that our strict adherence to hospital protocol of keeping the patient in the step down unit for 24 h, uninterrupted postoperative monitoring of the vital signs of the patient, as well as continuous regular examinations of the patient contributed to prompt airway management resulting in a lack of mortality amongst these patients.

Sabaté *et al*^[24] examined the implications of post-operative pulmonary complications and reported an increased incidence of mortality, length of stay, readmissions,

and costs. Our case series gives a limited account of the clinical progression of the patients as well as long term follow up examining the clinical sequelae of their complication. It lacks an analysis of risk factors or a prospective examination of the pathophysiology of the complication. Given the overall increases in cervical surgery over the past years due in part to the aging population and novel technological developments, the clinical as well as the economic burden of this potentially life-threatening complication merits more detailed examination^[25]. This is also important since an increasing number of cervical spine surgeries are being performed in the outpatient setting^[26,27].

In conclusion, careful monitoring, timely intervention, and a standardized protocol of intervention in patients with respiratory failure after cervical surgery can provide patients with a favorable long term outcome. Extended care in a monitored environment is recommended for multi-level anterior and anterior posterior complex cervical cases.

COMMENTS

Background

The rate of cervical spine surgery has increased over the last years. Airway compromise is a rare but potentially life threatening complication following this type of procedure.

Research frontiers

There is a paucity of literature on incidence, risk factors and management of postoperative airway compromise following cervical spine surgery.

Innovations and breakthroughs

The incidence of emergent reintubation following anterior- or combined anterior-posterior surgery was found to be 1.02%.

Applications

Patients at increased risk should be monitored closely for extended periods of time post-operatively.

Peer-review

The authors present a detailed paper on reintubation after cervical surgery. This is an important issue as reintubation frequency is in literature less than 1% of the cases. They give valuable information of the seven cases in several tables, combining that important information with a very concise paper, ending in useful conclusions. Therefore this is a very interesting, well-written and succinct paper.

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Retrospective Study

Two-stage surgical treatment for septic non-union of the forearm

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Abstract

AIM

To investigate the effectiveness of a two-stage surgical procedure for the treatment of septic forearm non-union.

METHODS

Septic non-unions are rare complications of forearm fractures. When they occur, they modify the relationship between forearm bones leading to a severe functional impairment. Treatment is challenging and surgery and antibiotic therapy are required to achieve infection resolution. It is even harder to obtain non-union healing with good functional results. The aim of this study is to present a two stages surgical treatment for septic forearm non-union with revision and temporary stabilization of the non-union until infection has cleared and subsequently perform a new synthesis with plate, opposite bone graft strut and intercalary graft. We retrospectively reviewed 18 patients with a mean age at the time of primary injury of 34.5 years (19-57 years) and a mean follow-up of 6 years (2-10 years). All patients presented an atrophic non-union with a mean length of the bone defect of 1.8 cm (1.2-4 cm). Complications and clinical results after surgical treatment were recorded.

RESULTS

Mean time to resolution of the infectious process was 8.2 wk (range 4-20 wk) after the first surgery and specific antibiotic therapy. All the non-union healed with an average time of 5 mo (range 2-10 mo) after the second step surgery. Cultures on intraoperative samples were

positive in all cases. No major intraoperative complications occurred. Two patients developed minor complications and one needed a second surgical debridement for infection resolution. At the last follow-up functional results were excellent in 5 (27.8%) patients, satisfactory in 10 (55.5%) and unsatisfactory in 3 (16.7%) patients. No activities of daily living (ADLs) limitations were reported by 12 (66.6%) patients, slight by 3 (16.6%) and severe limitation by 3 (16.6%) patients. Mean visual analog scale at the last follow-up was 1 (0-3).

CONCLUSION

The two-step technique has proven to be effective to achieve resolution of the infectious process and union with good functional results and low rate of complications.

Key words: Forearm fractures; Non-union; Delayed union; Infection; Open fracture; External fixation; Bone graft

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Core tip: Forearm non-union represent a challenging condition for the orthopaedic surgeon. Septic forms are even more difficult to overcome. However, in the present study we found that good clinical results can be achieved using a dual stage surgical technique with the first aim to resolve the infection process and subsequently achieve bone union.

Perna F, Pilla F, Nanni M, Berti L, Lullini G, Traina F, Faldini C. Two-stage surgical treatment for septic non-union of the forearm. *World J Orthop* 2017; 8(6): 471-477 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i6/471.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i6.471>

INTRODUCTION

Septic non-union are defined as the absence of evidence of fracture healing and persistence of infection at the fracture site for 6 to 8 mo^[1,2]. Current fixation techniques in forearm fractures with the application of the AO principles have proven to be quite effective to achieve healing with a reported non-union rate below 5%^[3-6], and infection rate following open reduction and internal fixation (ORIF) for diaphyseal forearm fractures ranges between 2% and 6%^[7-10].

Forearm non-unions generally occur as a consequence of inadequate initial reduction, unstable fixation or too early limb mobilization. Whereas in case of septic non-union multiple others factors like open injuries, significant soft tissue trauma, highly comminuted fractures, inadequate surgical fixation, patient characteristics and infection may be involved^[7,11-13].

Forearm has the function to support and guide the hand movements through the pronation and the supination at the radio-humeral joint, and at the proximal

and the distal radio-ulnar joints. A non-union of one or both the forearm bones modifies their relationships evolving towards proximal and/or distal joints impairment and forearm dysfunction. Furthermore, segmental bone defects in radius, ulna, or both may worsen functional impairment of the elbow and wrist with also difficulties in positioning the hand in space. Finally, a forearm non-union may compromise the strength in lifting objects and gripping.

Surgical treatment of septic forearm non-union may present many difficulties in addition to the well-known difficulties related to the treatment of bone infection, because of the poor bone quality resulting from the septic process, the bone necrosis and the scar adhesion of the soft tissue due to multiple previous surgeries^[7,9]. Septic non-unions of the forearm are mostly atrophic non-unions, presenting both mechanical failure and severe biological impairment, and in these cases the bone gap and the bad trophic conditions make the surgical restoration of the shape and the function of the forearm even harder. Proper planning of the treatment should consider first to eradicate the infection, then to promote bone healing, restoring as much as possible bone length and shape, with the aim to restore a physiologic function of the upper limb, minimizing possible impairment of elbow and wrist range of motion, forearm pronation and supination and grip strength.

A series of patients affected by septic forearm non-union who underwent surgical treatment was retrospectively reviewed as part of this study with the aim of presenting a protocol for treatment of septic forearm non-union in two surgical steps: (1) revision of the non-union and temporary stabilization with external fixation, followed by antibiotic therapy until healing of the infection; and (2) new synthesis with plate and opposite bone graft strut, with interposition of intercalary bone graft to fill the bone gap. Results and complications at mid to long-term follow-up are reported.

MATERIALS AND METHODS

From January 2002 to December 2015 a total of 34 patients presenting septic forearm non-union were treated in our institution and retrospectively reviewed. Inclusion criteria of this study were: (1) patients with septic diaphyseal forearm non-union; (2) patients with a complete clinical and radiologic documentation of the whole treatment; and (3) patients with at least 2 years' follow-up. Exclusion criteria were as follow: (1) presence of other fractures in the same limb at the time of the primary forearm injury; and (2) patients with neurological impairment on the same side of the non-union. Sixteen patients did not satisfy the inclusion criteria and were therefore excluded from the study. This left a total of 18 patients eligible for this retrospective review.

There were 15 men and 3 women with a mean age at the time of our observation and treatment of 34.5

years (range 19-57 years). The initial trauma was caused by road accident in 13 cases, injuries by machines in 4 and accidental fall in 1 case. The fracture involved the radius alone in 5 patients, the ulna alone in 11 patients and both the radius and the ulna in 2 patients.

The dominant limb was involved in 12 cases. An open fracture was present in 6 cases. The initial treatment consisted in ORIF with plate and screws in 10 patients, 3 of them presenting a Gustilo I open fracture treated within 24 h from the trauma, one of these treated with also intramedullary nailing (ulna) along with plate and screws (radius); fixation with intramedullary rod in 4 patients; external fixation in 3 patients and close reduction in 1 patient. Fourteen of the 18 patients underwent to further surgery after initial treatment, before our observation.

All patients were evaluated clinically in terms of pain and functional impairment, with blood tests including ESR and C-reactive protein (CRP), and with standard X-rays of the forearm in orthogonal projections. Septic non-union was considered on the basis of the absence of bone healing on radiographs after at least 6 mo from the initial treatment in presence of septic signs such as altered blood test with increase of white blood cell and/or ESR and/or CRP, presence of fistula or obvious soft tissue damage over the non-union site, positive specimens available from previous surgery. All patients presented an atrophic non-union with a mean length of the bone defect of 1.8 cm (range 1.2-4 cm) measured on radiographs.

The performed surgical treatment included two stages. The initial treatment consisted in the removal of the fixation devices, debridement and freshening of the non-union site removing fibrous and necrotic tissue in order to obtain healthy bone ends. The scar of the previous surgery was used to perform the skin incision when possible. Otherwise radius exposure was performed through dorsal Thompson approach, while ulna was exposed through direct posterior approach. The medullary canal of the bones was opened to allow good blood supply to the non-union site. Segmental bone defect up to 3 cm after the debridement were left free; conversely, in cases of bone loss greater than 3 cm and large infectious outbreak, a gentamicin-loaded cement spacer was applied. Samples of infected tissue from the wound, the bone and the deep soft tissue adjacent the non-union were cultured and bone specimens were sent to the pathology for analysis. New synthesis with mono-axial external fixator was performed in order to keep the length of the bone segment and the shape and the function of the forearm.

A targeted antibiotic therapy based on the culture performed on intraoperative samples was set, each patients received a specific antibiotic therapy according to the sensibility of the culture to the antibiotic therapy. Dosage, duration and any drug changes were discussed and decided by our infectious diseases consultant considering the patient's comorbidities, liver and kidney function and response to therapy. Monthly, all patients were evaluated clinically, radiographically and with blood

tests, these repeated every two weeks. When normal values of ESR and CRP were observed, antibiotic therapy was interrupted and after 4-6 wk without antibiotic therapy, if ESR and CRP were still normal, and there weren't clinical signs of infection, resolution of the infection was considered.

The second surgical stage consisted into removal of the external fixator and new synthesis with plate and opposite homologous bone graft strut with intercalary graft inserted between the bone ends to restore proper bone length. Intraoperative specimens from the surgical site were taken again and cultured to further confirm the resolution of the infection. Segmental bone defects were quantified and length of the bones were measured using the image intensifier according to Szabo and Weber^[14]. The mean length of the intercalary graft was 2.3 cm (range 1.5-5 cm). In case of both bone non-union, fixation of the ulna was performed first in order to properly restore length and alignment of the forearm^[15]. No antibiotic therapy was performed after the second surgical stage because all the patients were considered cured from infection. Standard prophylaxis at anaesthetic induction was performed according to the guideline of our hospital.

A long-arm cast with elbow 90° flexed and forearm in intermediate rotation was applied after surgery and maintained for 3 wk. Subsequently an articulate elbow brace was applied for another 3 wk allowing flexion-extension of the elbow and physiotherapy was prescribed. Patients were checked monthly until there was radiographic evidence of bone healing, and thereafter, yearly for a mean postoperative follow-up of 6 years (range 2-10 years).

A combined clinical and radiographic evaluation was used to assess the healing of the non-union. Clinical parameters of healing were: (1) absence of pain or tenderness on palpation; (2) painless grip strength recovery; and (3) painless recovery of elbow and wrist range of motion. Whereas radiographic criteria were: (1) bridging of the non-union seen at three cortices; and (2) obliteration of the non-union line or cortical continuity.

The forearm, elbow and wrist flexion, extension, supination, and pronation were assessed using the Anderson system which classifies results as excellent, satisfactory and unsatisfactory. Excellent result was considered in case of united fracture with loss of less than 10° of elbow or wrist flexion-extension or less than 25% of forearm pronation-supination; satisfactory result was considered in case of healed fracture with loss of less than 20° of elbow or wrist flexion-extension or less than 50% of forearm pronation-supination; unsatisfactory was considered in case of healed fracture with a loss greater than 20° of elbow or wrist flexion-extension or greater than 50% of forearm pronation-supination whereas persistent non-union or malunion was considered a failure^[3].

The return to activities of daily living (ADLs) and to job was evaluated in terms of time to return and possible limitation (no limitation, slight and severe limitation).

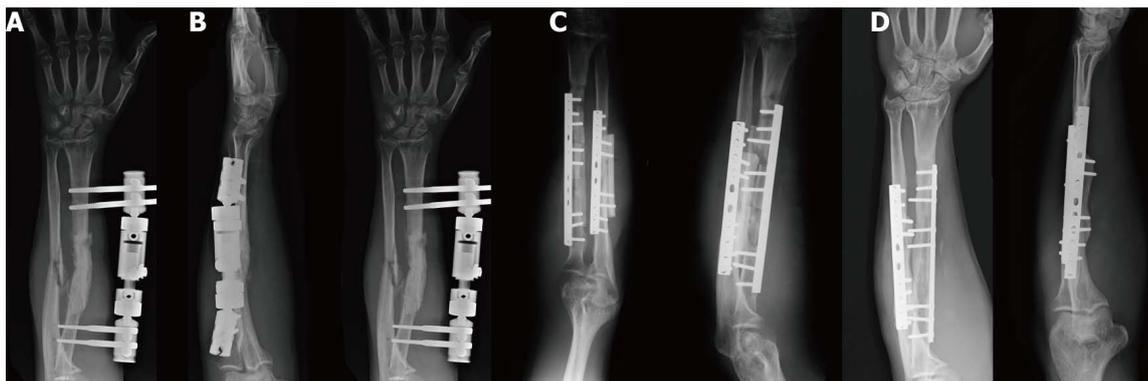


Figure 1 Radiographic aspect of a both radius and ulna non-union in a 25-year-old man. A: Occurred after a Gustilo I open fracture undergone open reduction and internal fixation by plate and screws and intramedullary nailing; B: Once a septic non-union was diagnosed, removal of fixation devices and surgical debridement were performed and an external fixator was applied; C: Eight weeks after the surgical toilette the infection has resolved and thus new synthesis with plate, opposite strut and intercalary bone graft was performed; D: At follow-up both non-unions appear healed with noticeable remodelling of the bone graft.

Visual analog scale (VAS) was used to evaluate any residual pain.

RESULTS

The average follow-up was 6 years (range 2-10 years). At the last follow-up all non-unions healed with evidence of graft integration and bone remodelling (Figure 1).

Cultures on intra-operative samples (harvested during the first surgery) were positive in all patients finding *S. aureus* in 9 patients, *S. epidermidis* in 4 patients, *P. aeruginosa* in 2 patients, both *S. aureus* and *P. aeruginosa* in one patient, both *S. aureus* and *P. acnes* in one patient and both *S. hominis* and *K. pneumoniae* in one patient. The mean time to resolution of the infectious process was 8.2 wk (range 4-20 wk) after the first surgery and specific antibiotic therapy. Average time of healing of the non-union was 5 mo (range 2-10 mo) after the second surgery (Table 1).

No major intraoperative complications occurred. In three patients skin wound healed by secondary intention and one of them required a skin graft. One patient suffered an incomplete transient palsy of posterior interosseous nerve that completely resolved 6 mo after surgery. One patient developed radio-ulnar impingement with prono-supination impairment and underwent further removal of the hardware with functional improvement. After first surgery one patient needed a second surgical debridement and to change the antibiotic therapy due to resumption of infection seen clinically and through blood tests.

At the last follow-up forearm functional results according to the Anderson scale were excellent in 5 (27.8%) patients, satisfactory in 10 (55.5%) and unsatisfactory in 3 patients (16.7%), no failures were recorded. Patients resumed ADLs at a mean of 3 mo after surgery. No limitations were reported by 12 (66.6%) patients, slight limitation by 3 (16.6%) and severe by 3 (16.6%). The original work activity was resumed at a mean of 5 mo after surgery, without limitations in 9 (50%) cases, slight limitation in 6 (33.3%), and with severe

limitation that required to change the type of activity in 3 cases (16.6%). At the last available follow-up mean value of pain according to VAS was 1 (range 0-3) (Table 2).

DISCUSSION

In this study a two-step protocol for surgical treatment of septic forearm non-unions is presented including: (1) extensive surgical debridement of the non-union and temporary external fixation followed by targeted antibiotic therapy; and (2) new synthesis of the non-union with plate and screws, opposite homologous bone graft strut and intercalary allograft after the healing of infection. This technique allowed to achieve good radiographic and clinical outcome, healing of all non-unions with 83.3% of excellent and satisfactory results, and low rate of complications.

The treatment of septic forearm non-unions must consider first the resolution of the infectious process and then the achievement of the fracture union providing a proper reconstruction of the fractured bones and hence adequate function of the forearm. Septic forearm non-unions are mainly atrophic with severe biologic impairment of the bone and the soft tissues. Commonly there may be a various amount of bone gap characterized by scarring, bone sclerosis and absorption, and poor blood supply. All these problems make more challenging to achieve bone healing and good clinical outcomes. Various surgical options are reported in the literature for the treatment of aseptic forearm non-unions^[6,7,9,11-13], but there is paucity of studies concerning the treatment of the septic ones. Baldy dos Reis *et al*^[16] using autologous bone graft and compression plate reported a high rate of good functional results (29 cases out of 31), but their study included mixed cohorts of patients with both septic and aseptic non-unions and a direct comparison with our study is difficult. In a retrospective review of 35 patients presenting forearm non-unions, 11 septic, Ring *et al*^[9] reported a success rate of 100% using plate fixation and autologous cancellous bone-grafting, recovering a mean

Table 1 Patient and fracture data and treatment

Patient	Age (yr)	Bones involved	Open/closed	Initial treatment	Specimens	Time to infection resolution (wk)	Bone defect and intercalary graft size (cm)	Time to healing (mo)
1	27	Radius	Closed	Intramedullary rod	<i>S. epidermidis</i>	6	2.2	5
2	31	Ulna	Open	ORIF	<i>S. aureus</i>	4	1.8	4
3	41	Radius	Closed	ORIF	<i>S. aureus</i>	6	1.5	2
4	24	Ulna	Closed	ORIF	<i>S. hominis</i> + <i>K. pneumoniae</i>	8	2.0	4
5	19	Ulna	Closed	Intramedullary rod	<i>S. epidermidis</i>	6	1.8	3
6	42	Ulna	Closed	ORIF	<i>P. aeruginosa</i>	8	2.0	6
7	39	Ulna	Open	ORIF	<i>S. aureus</i>	6	1.6	3
8	34	Radius	Closed	ORIF	<i>S. aureus</i> ¹ + <i>P. aeruginosa</i>	20	2.2	4
9	45	Ulna	Closed	Intramedullary rod	<i>S. aureus</i>	8	1.7	3
10	25	Radius + Ulna	Open	ORIF + intram. rod	<i>S. aureus</i> + <i>P. acnes</i>	8	2.2	8
11	57	Ulna	Open	External fixator	<i>S. aureus</i>	10	4.0	7
12	38	Ulna	Closed	ORIF	<i>S. epidermidis</i>	6	1.8	4
13	20	Radius + Ulna	Open	External fixator	<i>S. aureus</i>	6	2.8	8
14	31	Ulna	Closed	Close reduction	<i>S. aureus</i>	10	2.0	4
15	52	Radius	Closed	ORIF	<i>S. aureus</i>	12	2.5	5
16	40	Ulna	Open	External fixator	<i>S. epidermidis</i>	6	5.0	10
17	22	Ulna	Closed	Intramedullary rod	<i>S. aureus</i>	6	1.8	4
18	34	Radius	Closed	ORIF	<i>P. aeruginosa</i>	12	2.5	6

¹Bacterial resistant strain, second debridement performed. ORIF: Open reduction and internal fixation.

Table 2 Results

Patient	Age (yr)	Follow-up (yr)	Anderson	ADLs limitations	Job limitations	VAS
1	27	6	Excellent	No	No	0
2	31	4	Satisfactory	No	No	0
3	41	8	Satisfactory	No	No	0
4	24	3	Satisfactory	Slight	Slight	1
5	19	10	Satisfactory	No	No	0
6	42	4	Satisfactory	Slight	Slight	2
7	39	10	Satisfactory	No	Slight	1
8	34	8	Excellent	No	No	0
9	45	4	Excellent	No	No	0
10	25	6	Satisfactory	No	Slight	2
11	57	4	Unsatisfactory	Severe	Severe	2
12	38	5	Excellent	No	No	0
13	20	8	Satisfactory	Slight	Slight	2
14	31	8	Satisfactory	No	No	0
15	52	2	Unsatisfactory	Severe	Severe	3
16	40	4	Unsatisfactory	Severe	Severe	3
17	22	6	Excellent	No	No	0
18	34	8	Satisfactory	No	Slight	1

VAS: Visual analog scale.

bone defect of 2.2 cm. The results reported by Ring *et al*^[9] limited to the 11 septic non-unions seem to confirm the results presented in this paper with a 100% of union rate, however Ring *et al*^[9] study lacks of an adequate description of the surgical procedure and of the treatment of the infection. Similar results are reported by Prasarn *et al*^[7] in a retrospective analysis of 15 infected forearm non-unions. Prasarn *et al*^[7] achieved union in all patients using a two-stage surgical procedure with extensive debridement followed by plate and screws fixation with autologous iliac crest bone graft. Differently to the protocol detailed in this paper, Prasarn *et al*^[7] repeated surgical debridement every 48-72 h: It's the authors' opinion that this procedure could be considered hard and painful to

bear for the patient and expensive in terms of overall cost of the whole treatment. Furthermore, Prasarn *et al*^[7] used an autologous iliac crest bone grafting that presents high morbidity on the donor site and it increases the surgical time. It's the authors' belief that the homologous bone graft may present more advantages than the autologous one, mainly consisting in: (1) short surgical time; (2) possibility to customize the graft according to the patient's characteristics; and (3) neglectable differences in terms of osteoinductive and osteoconductive properties compared to autologous bone graft^[6,17]. Furthermore, a cortical strut graft may provide additional stability than a metal plate alone, and thus improvement of the non-union healing may be postulated. Moreover, a stable fixation usually

allows earlier recovery of active motion of the limb.

One of the limit of the present study is related to the supposed risk of disease transmission with homologous graft, but bacterial infection due to contaminated bone have been rarely reported in literature with an overall risk similar to other major orthopaedic procedures^[17]. It's the authors' opinion that the biomechanic advantages related to the homologous graft are greater than its estimated risk of disease transmission, even if the authors are also aware that a case-control study would be necessary to establish the real advantages from an autologous graft rather than a homologous. Another limit of this study is related to the relatively small average length of the bone defect of 2.2 cm, so the authors are not able to determine if our protocol could bring the same good results also in case of massive bone defect. In these cases the use of vascularized fibular graft has been described with successfully results^[18-21], reporting though major disadvantages related to the risk of infection and thrombosis of the graft vessels^[22], technical difficulties of the procedure and comorbidity on the donor site^[23]. Recently Zhang *et al.*^[24] retrospectively analysed the results of a series of 16 patients affected by septic forearm non-union treated with external fixation and bone transport. The union in all patients was achieved with average good clinical results, nevertheless this technique requires high patient's compliance due to the demanding and long treatment and moreover some concerns about the effectiveness of this treatment may still be raised when it is applied on likely avascular post-infected tissue^[18-20]. Others limitations of this study are mainly related to be retrospective, to the relatively small number of patients, the non-homogeneous series and the absence of a control group.

In the authors' experience some technical precautions must be respected. First, placing the plate and the opposite graft too close to the interosseous membrane must be avoided in order to prevent impingement between radius and ulna and prono-supination impairment. Second, care should be taken to ensure adequate coverage of the bone and the graft by muscles with the aim to enhance blood supply and surgical wound healing. Third, adequate extensive debridement should be performed in order to expose healthy bone ends and to promote biological stimulation. Finally, the new synthesis must be performed only after complete resolution of the infection, documented by clinic and radiographic signs and blood tests.

Septic forearm non-unions are rare and challenging to treat. The infection represents an obstacle to the healing process that frequently requires prolonged treatment, deferred therapeutic interventions and good patient's compliance.

The two steps technique for the treatment of septic forearm non-unions based on revision of the non-union and temporary stabilization with external fixation, targeted antibiotic therapy and finally new synthesis with plate and homologous bone graft has proven to be effective in achieving union. Good clinical results have been obtained in the majority of cases with low rate of significant complications. Despite the unsatisfactory

functional results in 16.7% of the patients according to the Anderson scale, the study presented in this paper obtained resolution of the infectious process and healing of the non-unions in all cases. Accurate debridement and postoperative targeted antibiotic therapy are mandatory to eradicate the infection and thus to allow bone healing. The synthesis with plate and opposite bone graft strut, with intercalary graft, can ensure both stability and biological enhancement so as to promote healing of the non-union and restore good function of the forearm. Despite the average good results of the present study, considering its aforementioned limitations, prospective randomized controlled trial would be desirable to better define the best strategy for treatment of septic forearm non-unions.

COMMENTS

Background

Septic non-union of the forearm represent a challenging condition because of the poor bone quality due to the septic process and the forearm function impairment. Septic non-unions of the forearm are mostly atrophic non-unions, presenting both mechanical failure and severe biological impairment, and in these cases the bone gap and the bad trophic conditions make the surgical restoration of the shape and the function of the forearm even harder. Only few reports are available in literature on this topic because of its infrequency.

Research frontiers

Aim of this study was to evaluate the effectiveness of a two-stage surgical procedure for the treatment of septic non-union of the forearm.

Innovations and breakthroughs

In this study, a two-step protocol for surgical treatment of septic forearm non-unions is presented including: (1) extensive surgical debridement of the non-union and temporary external fixation followed by targeted antibiotic therapy; and (2) new synthesis of the non-union with plate and screws, opposite homologous bone graft strut and intercalary allograft after the healing of infection. Good radiographic and clinical results have been recorded with an average follow-up of six years. Only limited studies are reported in literature on the same topic, moreover with various limitations such as: Groups heterogeneity and lack of information on the technique used. In the present study, we tried to focalize attention on a homogeneous group of patients and to carefully report the technique used exploring its advantages and disadvantages.

Applications

This study suggests a new surgical technique for septic forearm non-union treatment. Readers may use it as a stimulus to change their clinical practice or to assess new research frontiers.

Terminology

Septic non-union are defined as the absence of evidence of fracture healing and persistence of infection at the fracture site for 6 to 8 mo.

Peer-review

This is a well written paper.

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Observational Study

Upper extremity disorders in heavy industry workers in Greece

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Abstract**AIM**

To investigate the disability due to musculoskeletal disorders of the upper extremities in heavy industry workers.

METHODS

The population under study consisted of 802 employees, both white- and blue-collar, working in a shipyard industry in Athens, Greece. Data were collected through the distribution of questionnaires and the recording of individual and job-related characteristics during the period 2006-2009. The questionnaires used were the Quick Disabilities of the Arm, Shoulder and Hand (QD) Outcome Measure, the Work Ability Index (WAI) and the Short-Form-36 (SF-36) Health Survey. The QD was divided into three parameters - movement restrictions in everyday activities, work and sports/music activities - and the SF-36 into two items, physical and emotional. Multiple linear regression analysis was performed by means of the SPSS v.22 for Windows Statistical Package.

RESULTS

The answers given by the participants for the QD did not reveal great discomfort regarding the execution of manual tasks, with the majority of the participants scoring under 5%, meaning no disability. After conducting multiple linear regression, age revealed a positive association with the parameter of restrictions in everyday activities ($b = 0.64$, $P = 0.000$). Basic education showed a statistically significant association regarding restrictions during leisure activities, with $b = 2.140$ ($P = 0.029$) for compulsory education graduates. WAI's final score displayed negative charging in the regression analysis of all three parameters, with $b = -0.142$ ($P = 0.0$), $b = -0.099$ ($P = 0.055$) and $b = -0.376$ ($P = 0.001$) respectively, while the physical and emotional components of SF-36 associated with movement restrictions only in daily activities and work. The participants' specialty made no statistically significant associations with any of the three parameters of the QD.

CONCLUSION

Increased musculoskeletal disorders of the upper extremity are associated with older age, lower basic education and physical and mental/emotional health and reduced working ability.

Key words: Upper extremity disorders; Heavy industry; QuickDASH; Movement restrictions; Occupational diseases

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Core tip: To our knowledge, this is the first study to use the QuickDASH questionnaire for the evaluation of the physical functionality of the upper extremities in the heavy industry sector. Furthermore, it has proved that the presence of musculoskeletal disorders is negatively associated with the reported working ability of the participants, as well as their physical and emotional health. These data will assist in taking measures for the prevention of occupational accidents and injuries in manual labor.

Tsouvaltzidou T, Alexopoulos E, Fragkakakis I, Jelastopulu E. Upper extremity disorders in heavy industry workers in Greece. *World J Orthop* 2017; 8(6): 478-483 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i6/478.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i6.478>

INTRODUCTION

Working in the heavy industry sector can cause the manifestation of occupational diseases and injuries, having a direct impact on the employee, the employer and the state's economy. It can lead to permanent disability or even the death of a worker, the loss of working hours and the reduction of production, as well as the indebtedness of pension funds due to compensations and disability pensions^[1]. According to the World Health

Organization's (WHO) data, one third of all occupational illnesses are musculoskeletal disorders, with 23.3% being located in the upper extremities^[2].

The mechanism involved in the manifestation of musculoskeletal disorders of the upper arm include the use of intense muscular strength, vibrations, painful working positions and rapid and repeated movements, which all result in the great manual strain of the upper extremities^[3-5]. Several questionnaires have been suggested for the measurement and evaluation of the physical functionality and the restriction of movement of the upper arm, amongst them the Quick Disabilities of the Arm, Shoulder and Hand (QD) Questionnaire.

The purpose of this study was to analyze disability due to musculoskeletal problems of the upper extremity in heavy industry workers and to identify relationships between movement restrictions in work, everyday and leisure activity and specific individual and job-related characteristics as well as the working ability of the population under study.

MATERIALS AND METHODS

The population under study consisted of 802 employees, both white- and blue-collar, working in a shipyard industry in Athens, Greece. The white-collar category consisted of secretaries, managers-engineers (civil-, mechanical-, chemical-, metallurgy-, electrical-), draughtsmen, accountants, clerks, computer operators, nurses, electricians with license, inspectors, supervisors, store workers, material suppliers, tool repairs, security men and fire watchmen, while the blue-collar population included manual labor workers, *i.e.*, sand (grit) blasters (simon operators), painters, welders, flame cutters, riggers, dry-dock laborers, fitters, platters, plate fitters, crane operators, chippers, riveters, carpenters and technicians.

Data were collected through the distribution of questionnaires as part of the employees' periodic medical examination in the occupational health department during the period 2006-2009. All employees gave their informed consent for their participation. At the beginning of this study the participants were asked to answer questions regarding individual and job-related characteristics such as age, duration of employment, specialty and basic education. The questionnaires used were the QD Outcome Measure and the Work Ability Index (WAI) for the evaluation and recording of their symptoms and their ability to perform specific tasks, as well as the Short-Form-36 (SF-36) Health Survey, for the assessment of the respondents' general health.

The QD questionnaire evaluates the musculoskeletal symptoms of the participants, as well as their ability to perform certain activities. It consists of three sections. The first section includes eleven five-point scale questions regarding the execution of everyday tasks. The other two parts of the questionnaire are optional and involve 8 five-point scale questions in total, which measure performance during the execution of the participants' usual work demands and sport/music activities. The

Table 1 Individual and job-related characteristics of the population under study (n = 802)

	n (%)
Sex	
Male	763 (95.1)
Female	39 (4.9)
Age (yr)	
< 40	407 (50.7)
40-50	301 (37.5)
> 50	94 (11.7)
Marital status	
Married	63 (7.9)
Single	739 (92.0)
Basic education	
University/PhD	83 (10.3)
Technical school	503 (62.7)
Elementary/high school	216 (27)
Specialty	
White-collar workers	91 (11.3)
Blue-collar workers	711 (88.7)

scores of the three items of the QD range between 0 (no disability) and 100 (most severe disability)^[6,7].

The WAI questionnaire evaluates the participants' ability to work. It consists of seven dimensions, which cover the participants' current work ability compared with their lifetime best, their work ability in relation to the demands of the job, the number of current diseases diagnosed by a physician, their estimated work impairment due to diseases, the amount of sick leaves during the past year, their own prognosis of their work ability in two years time and their mental resources. The total WAI score results from the sum of the subscores of the seven parameters (7-49 points) and is divided into four categories: Poor (7-27 points), medium (28-36), good (37-43) and excellent (44-47) work ability^[8].

The SF-36 health survey includes 36 descriptive questions that involve the evaluation of eight parameters of the physical and mental/emotional health of the correspondent. In particular, it includes questions regarding the physical functionality, the bodily pain, role restrictions due to physical or emotional problems, mental state, social functionality and general perception of the patient's health, as well as questions regarding the participant's subjective opinion of the change in the state of his/her health. By summing up the scores of the eight parameters, two further categories are formed the physical and the mental/emotional component of the SF-36. In particular, the physical component consists of the four parameters of physical functionality, bodily pain, general perception of health and role restrictions due to physical health, while the remaining four parameters form the emotional component. The final score for each component ranges from 0 to 100, with a high score predicting a more favorable situation^[9,10].

Descriptive analysis took place for the available measurements per occupational category. Linear regression analysis was performed to evaluate the influence of possible determinants on the physical dysfunction of the upper

extremity. Coefficients (b) with 95% confidence intervals (95%CI) were calculated as measure of association. For the initial selection of potential factors that influence the ability to perform certain activities, univariate regression analysis was used with a significance level of $P < 0.05$. Subsequently, all independent variables that showed significant associations were considered for inclusion into the multiple linear regression model. Data entry and analysis were conducted by means of the SPSS v.22 for Windows Statistical Package.

RESULTS

The population under study consisted of 802 heavy industry employees, mostly male (95.1%) and under 50 years of age (88.2%). The majority (88.7%) were blue-collar workers, while only 27% were compulsory education graduates (Table 1).

The answers given by the participants for the QD did not reveal great discomfort regarding the execution of manual tasks. The final scores and the mean values for each of the three categories, everyday, work and sports/music activities, are shown in Table 2, with the majority of the participants scoring under 5%, meaning no disability. Full disability wasn't recorded in any of the categories, with the highest scores reaching 77.27%, 87.5% and 75% respectively. Comparing the mean values, the work category scores were slightly lower than the other two, with a 1.704 mean value (Table 2).

The univariate analysis linear regressions that were conducted for the parameters of the QD - daily activities, work and leisure - revealed statistically important associations with WAI's final score and SF-36 two components, physical and emotional. Furthermore, age was linked with everyday and work restrictions of movement of the upper arm, while basic education showed statistically important correlation with the sports/music parameter. The participants' specialty made no statistically significant associations with any of the three parameters of the QD.

After conducting multiple linear regression, age revealed a positive association with the first parameter of everyday restrictions ($b = 0.64$, $P = 0.000$), but was rejected in the regression model of the work parameter. Basic education remained statistically significant regarding restrictions during leisure activities, with $b = 2.140$ ($P = 0.029$) for lower educated workers. WAI's final score displays negative charging in all three analyses, while the physical and emotional components of SF-36 associated with movement restrictions in daily activities and work (Tables 3-5).

DISCUSSION

The general health of every person depends largely on the nature of their work, on the working environment and on the physical and psychological burden involved in their job. Reasonably, the heavy industry sector is associated with increased morbidity, affecting the level

Table 2 Final scores and mean values of the three categories of the QuickDASH Questionnaire

	Mean value	Score (0-100)	n (%)
Everyday restrictions (n = 802)	2786	< 5	681 (85.1)
		5-50	118 (14.5)
		> 50	3 (0.4)
Work restriction (n = 802)	1704	< 5	731 (91.2)
		5-50	66 (8.2)
		> 50	5 (0.6)
Sports/music restrictions (n = 364)	2490	< 5	324 (89)
		5-50	33 (9.1)
		> 50	7 (1.9)

< 5 = no disability, 5-50 = slight disability, > 50 = medium to full disability.

Table 3 Multiple linear regression of upper arm disability during everyday activities

	P-value	b	95%CI	
			Lower	Upper
Age	0	0.64	0.28	0.1
Physical SF-36	0	-0.157	-0.194	-0.12
Mental SF-36	0	-0.061	-0.093	-0.028
WAI	0.08	-0.142	-0.246	-0.037

Covariates of the final model (P < 0.05), b = unstandardized coefficient. CI: Confidence interval; SF-36: Short-form-36; WAI: Work Ability Index.

of workers' health, increasing the number of absences from work and thus reducing productivity. The upper extremities are a part of the body that receives intense strain during manual labor, resulting into frequent injuries and causing transient or even permanent disabilities. Therefore, it is important to investigate the links between musculoskeletal disorders of the upper arm and the individual and job-related characteristics of heavy industry workers.

The QD questionnaire was used in the present study as a measuring tool of the physical functionality and the musculoskeletal disorders of the upper extremities, which constitute a main stress point of the body in heavy industry workers. In all three parameters which involve movement restrictions in daily activities, work and leisure, the results showed a positive outcome, since the majority of the participants denied any restrictions in the functionality of their upper extremities. This could be attributed to efficient prevention strategies being applied in the specific shipyard industry, which prevent the impairment of an upcoming disability.

The statistically important association of the everyday restriction parameter with age was expected and comes to match previous studies^[11]. Workers over 40 years of age are linked with greater difficulty in executing daily activities, because of their reduced strength and their increased musculoskeletal disorders. The fact though that the same association wasn't noticed for the work parameter of the QD is a paradox. Especially given certain specialties in the heavy industry sector involve

Table 4 Multiple linear regression of upper arm disability during work

	P-value	b	95%CI	
			Lower	Upper
Physical SF-36	0	-0.066	-0.102	-0.03
Mental SF-36	0.008	-0.042	-0.073	-0.011
WAI	0.055	-0.099	-0.2	-0.002

Covariates of the final model (P < 0.05), b = unstandardized coefficient. CI: Confidence interval; SF-36: Short-form-36; WAI: Work Ability Index.

Table 5 Multiple linear regression of upper arm disability during sport/music activities

	P-value	b	95%CI	
			Lower	Upper
Elementary/high school education	0.029	2.14	0.223	4.056
WAI	0.001	-0.376	-0.593	-0.16

Covariates of the final model (P < 0.05), b = unstandardized coefficient. CI: Confidence interval; WAI: Work Ability Index.

great strain of the joints of the upper extremities, and in combination with the reduced stamina and osteoarthritis lesions that accompany older age, there should be a statistically significant association with the final score of the work QD. A possible explanation for this outcome could be the tactic of the industry to place younger workers in positions that require great manual strain. However, this result could also be justified by a possible reluctance of the participants to express their true opinion regarding their physical functionality under the fear of dismissal.

Both parameters of the SF-36, physical and mental/emotional, are negatively associated with everyday and work restrictions of the upper limb^[12]. Lower values of the physical component of the SF-36 are interpreted as restriction of movement and bodily pain, similar to the higher scoring of the QD. In the same way and in agreement with other studies, depression, fatigue and emotional restrictions that are expressed through the emotional component of the SF-36 are associated with greater upper extremity disability and a higher QD score^[13].

The strongly negative association of WAI's final score with all three parameters of the QD can be explained accordingly, although no previous studies have been conducted to support our findings. Work ability is highly affected by any dysfunction of the upper limbs due to repetitive and stereotyped movements and maintenance of awkward positions for prolonged periods of time, both in white- and blue-collar workers. Additionally, blue-collar workers are often exposed to vibration or heavy loads, while white-collar workers perform more computer-based tasks and have more constrained posture, which can also lead to cumulative musculoskeletal disorders. According to previous studies, chronicity, fatigue and pain

severity are the primary factors that determine care-seeking and sickness absenteeism and subsequently lead to financial consequences and productivity loss due to medical expenses and workers' compensations^[14-17].

The basic education of the participants proved to be statistically significant only regarding the sports/music parameter, with compulsory education graduates being associated with greater disability of the upper arms. Lower educated workers are usually occupied in positions with more intense manual strain, which could justify the high scores in movement restrictions, in contrast with university graduates, who are usually white-collar employees^[18]. Moreover, lower educated workers are usually related to lower incomes, which comes to agree with previous studies declaring that socioeconomic deprivation is associated with poorer health status^[19].

It is very interesting though, that the same association wasn't noticed for the other two parameters of the QD, everyday activities and work. This could be attributed to similar levels of strain of the upper extremities in both educational categories and by extension in both working categories, since the majority of blue-collar workers have a lower educational level, while white-collar workers are usually university graduates. The difference lies in the mechanisms that lead to movement restrictions in these two categories and not in the level of discomfort or the severity of pain that is caused. Musculoskeletal disorders in the heavy industry sector, both acute and cumulative, can be caused by various mechanisms such as repetitive movements, maintenance of awkward postures, vibration exposure and handling of heavy loads. Office work, which is usually computer-based, can also lead to cumulative musculoskeletal disorders, since it involves stereotyped movements of the upper arm and a more restricted posture for prolonged periods of time^[20].

The positive outcomes of this study are very encouraging and could be attributed to the proper appliance of prevention strategies by the shipyard industry and the occupational doctors. Prevention and early interventions are in the benefit of both the employer and the employee, in order to reduce disabilities, as well as sickness absences^[21].

COMMENTS

Background

The heavy industry sector has been linked with occupational accidents and injuries, a great percentage of which involving musculoskeletal disorders of the upper extremities. This can lead to permanent disability of a worker, the loss of working hours and the reduction of production, influencing both, employer and employee. The Quick Disabilities of the Arm, Shoulder and Hand (QD) Questionnaire provides an effective tool for the assessment of the physical functionality of the upper arm and the recording of musculoskeletal problems in manual labor.

Research frontiers

Various studies have aimed to investigate the prevalence of musculoskeletal disorders of the upper extremities and possible aggravating factors in the industry sector. To the author's knowledge, this is the first study to use the QD questionnaire and correlate it with the working ability and the general physical and emotional health status of a heavy industry worker.

Innovations and breakthroughs

The present study is the first to use the QD questionnaire for the evaluation of physical dysfunction in heavy industry and to demonstrate its effectiveness in recognizing musculoskeletal disorders of the upper arm. Age and lower basic education have been highlighted as aggravating factors. Furthermore, important negative associations have been made with working ability and the physical and emotional health status of the workers.

Applications

The provided data may assist industries in planning prevention strategies to reduce occupational injuries of the upper extremities and motivate occupational physicians into using the QD questionnaire as a screening tool for physical dysfunctions of the upper arm. This study forms a base for future research investigating larger groups of heavy industry workers to provide the most reliable data on upper extremity disabilities.

Peer-review

This manuscript is well-written. The introduction and purpose statement were appropriate. The methods were clearly described. Overall, presentation of the results was appropriate and conclusions appear to be appropriate given the data collected and analysis conducted.

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Observational Study

Medial tibial plateau morphology and stress fracture location: A magnetic resonance imaging study

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Abstract**AIM**

To determine the location of medial tibial plateau stress fractures and its relationship with tibial plateau morphology using magnetic resonance imaging (MRI).

METHODS

A retrospective review of patients with a diagnosis of stress fracture of the medial tibial plateau was performed for a 5-year period. Fourteen patients [three female and 11 male, with an average age of 36.4 years (range, 15-50 years)], who underwent knee MRI, were included. The appearance of the tibial plateau stress fracture and the geometry of the tibial plateau were reviewed and measured on MRI.

RESULTS

Thirteen of 14 stress fractures were linear, and one of them stellated on MRI images. The location of fractures was classified into three types. Three fractures were located anteromedially (AM type), six posteromedially (PM type), and five posteriorly (P type) at the medial tibial plateau. In addition, tibial posterior slope at the medial tibial plateau tended to be larger when the fracture was located more posteriorly on MRI.

CONCLUSION

We found that MRI showed three different localizations of medial tibial plateau stress fractures, which were associated with tibial posterior slope at the medial tibial plateau.

Key words: Magnetic resonance imaging; Runner; Stress fracture; Tibial plateau; Tibial posterior slope

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Core tip: Stress fracture of the medial tibial plateau is a rare injury. No studies have investigated detailed magnetic resonance imaging features of this fracture type. We found three distinct location types of isolated stress fractures of the medial tibial plateau. Posterior tibial slope serves as an indicator to determine the fracture site at the medial tibial plateau.

Yukata K, Yamanaka I, Ueda Y, Nakai S, Ogasa H, Oishi Y, Hamawaki J. Medial tibial plateau morphology and stress fracture location: A magnetic resonance imaging study. *World J Orthop* 2017; 8(6): 484-490 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i6/484.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i6.484>

INTRODUCTION

Stress fractures of the lower extremity commonly occur in athletes and military personnel. The tibial shaft is the most common location for stress fractures during running and marching activities, whereas the medial tibial plateau is a relatively uncommon site. Engber *et al*^[1] reported a series of 36 patients (57 fractures) including 21 bilateral in 1977. Harolds^[2] also reported 105 fractures in 71 soldiers in 1981. They documented that this fracture type is difficult to detect on initial roentgenograms at the onset of symptoms. This injury is easily misdiagnosed because the location of pain and tenderness is very similar to the meniscal injury and pes anserinus bursitis, which are common problems in running activities.

Bone scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) are widely used for early detection of stress fractures. Among them, MRI has been found to be more sensitive than CT and more specific than scintigraphy^[3]. Clinical case reports have described that MRI is a more sensitive method for evaluating stress fractures of the medial tibial plateau compared with X-rays^[4-6]. T2- and STIR-MR images are useful for detecting edema of the cancellous bone that usually presents as a linear fracture line at the medial tibial plateau^[7]. However, no studies have investigated more detailed MRI features of medial tibial plateau stress fractures.

The purpose of this study was to determine the detailed MRI appearance of medial tibial plateau stress fractures including localization and morphology. We found three different types of location in stress fracture of the medial tibial plateau. Thus, the geometry of the tibial plateau in patients with stress fractures of medial tibial plateau and the relationship with the fracture location were also evaluated.

MATERIALS AND METHODS

Patients

The study protocol was approved by the institutional

review board, and the requirement for informed consent was waived. For the present study, we searched the key words "tibial plateau" and "stress fracture" using a database of our institutes' medical records between April 2010 and March 2015, and identified 22 patients. The authors reviewed all medical records. No fractures were observed on MRI in 3 patients, and MRI was not taken in 4 other patients. We excluded these 7 patients in the present study. In addition, one patient was excluded because of a fracture of the medial tibial plateau for which a traumatic event of the affected knee could be identified. Finally, we selected a total of 14 patients [eleven men and three women; mean age, 36.4 years (range, 15-50 years)] with eight right and six left medial tibial plateau stress fractures (Table 1). All patients did not have any relevant medical co-morbidities, such as rheumatoid arthritis, metabolic disease, or osteoporosis in the medical record review, although we did not evaluate bone mineral density (BMD) in the present patients.

The main complaint of all patients was pain in the medial aspect of the proximal part of the tibia, without any traumatic events. On physical examination, tenderness was consistent with the pain site. All cases had no limitation of knee range of motion for reasons other than pain. We did not identify an apparent joint effusion in any patients. All cases did not report sudden onset of discomfort. Thirteen cases were associated with long-distance running (jog or marathon), and one case was associated with rope jump. The delay between symptom onset and seeking medical service ranged from 0 to 120 d (average, 21.9 d).

X-rays and MRI examinations

Initial anterior-posterior and lateral plain radiographs of the affected knee were taken within 2 wk of onset of symptoms (average, 7.9 d) in 12 of 14 patients. No fracture lines on X-rays were observed in these patients.

MRI scans were completed in all 14 patients. MRI of the knee was performed with a 1.5-T MRI scanner (EXCELART Vantage, TOSHIBA, Japan) using a knee coil. Proton density (PD) weighted MRI (TR/TE, 3750/18) and T2-weighted MRI scans (4100/90) sequences were performed in coronal, sagittal, and axial planes according to our routine knee MRI protocol. MRI parameters for all sequences were as follows: FOV, 16-16 cm; 1 excitation; matrix size, 256 × 368; section thickness, 3 mm for coronal, sagittal, and axial planes; and intersection gap, 1 mm. MRI revealed a linear or stellate PD and T2-low weighted image at the medial tibial plateau in all 14 cases (Figure 1). We did not identify any other associated findings on the MRI scans like osteoarthritis, ligament or meniscal pathology, or articular cartilage lesions.

Classification and measurements on MRI

Stress fractures of the medial tibial plateau were characterized on the basis of its regional location and morphology (linear or stellate). We classified fracture locations using both sagittal and coronal T2-weighted images. Images between the image slice that had the

Table 1 Clinical and radiological information in patients with stress fractures of the medial tibial condyle

MRI classification	Case No.	Age (yr)	Gender	Affected side	Activity	MRI after onset (d)	Fracture pattern	Medial slope (degrees)	Posterior slope (degrees)
AM type	1	48	Male	Right	Jog	16	Linear	4.7	4.5
	2	29	Male	Right	Jog	12	Linear	1.7	4.9
	3	15	Male	Left	Jog	13	Linear	6.1	5.5
PM type	4	46	Male	Right	Jog	14	Linear	3.3	9.9
	5	48	Male	Left	Marathon	0	Linear	2.4	6.7
	6	29	Male	Right	Jog	12	Linear	0.9	7
	7	44	Female	Left	Jog	9	Linear	4.5	7.7
	8	30	Female	Right	Rope jump	13	Linear	3.3	7.8
P type	9	40	Male	Left	Jog	14	Linear	0.9	8.2
	10	33	Male	Right	Jog	18	Linear	5.4	10.1
	11	50	Male	Right	Jog	99	Linear	4.8	12.2
	12	20	Male	Left	Jog	25	Linear	-0.2	12.4
	13	39	Male	Left	Jog	127	Stellate	2.2	11
	14	38	Female	Right	Jog	17	Linear	0.9	11.4

MRI: Magnetic resonance imaging.

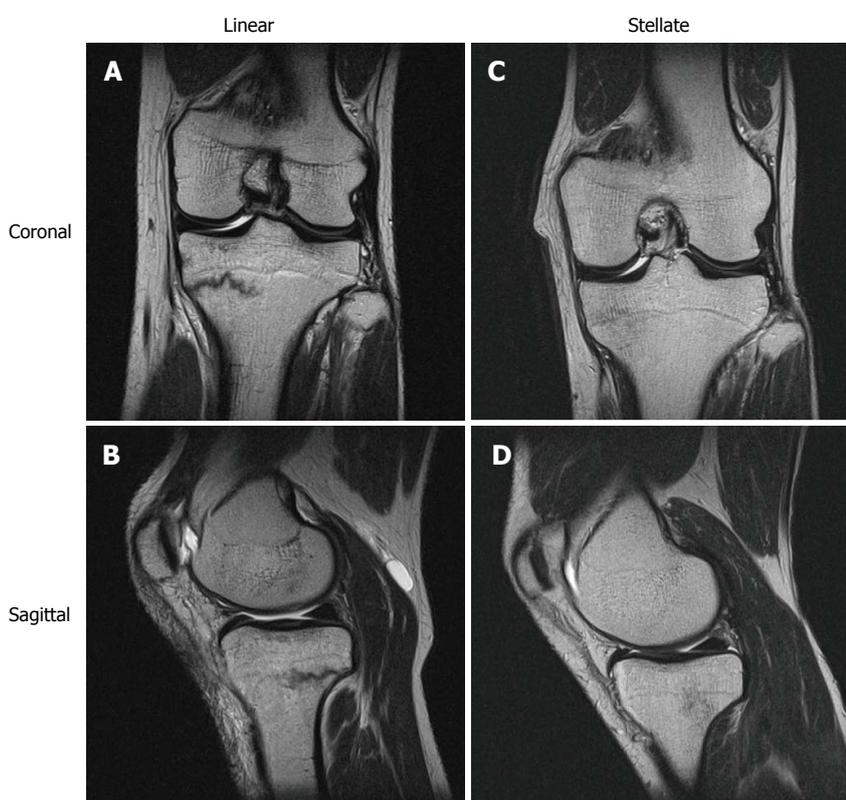


Figure 1 Representative magnetic resonance imaging images of T2-weighted coronal and sagittal views of linear type (A and B) and stellate type (C and D) in stress fractures of the medial tibial plateau.

tibial insertion of both the anterior and posterior cruciate ligaments, to the most medial slice that included the tibial condyle at the fracture level, were 7 or 8 slices in the present cases. At first, we divided the fracture locations into the following two types: Anterior (more images that included a fracture line at the anterior tibial cortex) and posterior (more images that included a fracture line at the posterior tibial cortex). Next, they were divided into two subtypes (medial or not) based on whether the most medial slice included a fracture line or not.

In addition, to investigate the relationship between the fracture location and the geometry of the medial tibial plateau, we measured the posterior tibial slope

and medial tibial slope at the medial tibial plateau on the sagittal and coronal planes of T2-weighted images using ImageJ software according to the measurement reported by Hashemi *et al*.^[8]. Briefly, the transverse image passing through the tibiofemoral joint was used to identify the coronal plane that passed closest to the centroid of the tibial plateau and the sagittal plane that included both anterior and posterior cruciate ligaments. The longitudinal axis of the tibia in the coronal and sagittal planes was defined by determining the midpoint of the medial-to-lateral and anterior-to-posterior widths of the tibia at two points located approximately 3 cm apart and as distally in the image as possible (Figure 2). The medial slope in

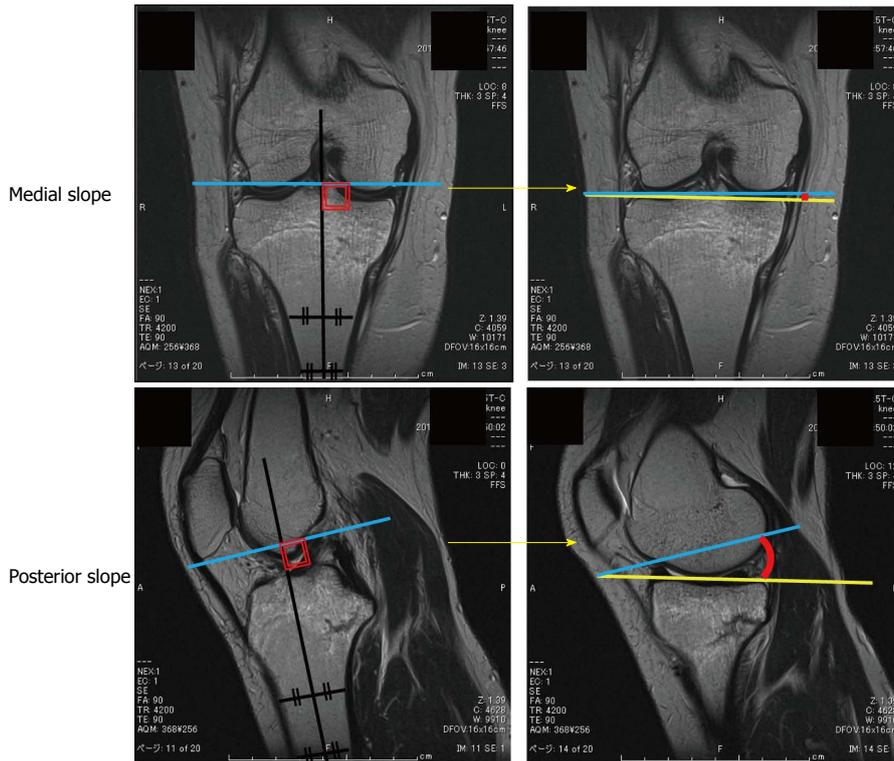


Figure 2 Magnetic resonance imaging illustrating the method used to determine the medial and posterior slopes. The angles of tibial medial and posterior slopes were represented by a segment of red circle between blue and yellow lines.

the coronal plane and the sagittal slope of the medial tibial plateau in the sagittal plane were then measured as the angle between a line joining the peak points on the medial-to-lateral, and the anterior-to-posterior aspects of the plateau and the longitudinal axis. The measured value was rounded off to the first decimal place. Two orthopaedic surgeons (KY and YU) separately measured both tibial posterior and medial slope of fourteen MRIs in a blind manner. Two investigators evaluated the parameters twice with a 1-wk interval. To test intra- and inter-observer reliability, the intraclass correlation coefficient (ICC) was calculated for two assessors.

Statistical analysis

All statistical analyses were performed with R2.8.1. Intra-interobserver agreement was assessed by ICC. The data was analyzed by Kruskal-Wallis and *post-hoc* Mann Whitney with Holm’s correction for determination of differences between three groups, and presented as the mean ± SE. *P* value < 0.05 was considered statistically significant.

RESULTS

MRI of the affected knee demonstrated a PD-low and T2-low linear fracture line at the medial tibial plateau in 13 of 14 patients (Figure 1A and B). One patient had a stellate pattern at the posteromedial part of the tibial plateau (Figure 1C and D). In this case, a linear fracture line might have disappeared because initial MRI was taken at 127 d after the onset. Location of the medial tibial plateau stress fractures was divided into three groups; 3 fractures at the anteromedially

(AM) type (Figure 3A-C), 6 posteromedially (PM) type (Figure 3D-F) and 5 posteriorly (P) type (Figure 3G-I). There were no fractures with anterior (A) type. We further investigated the correlation between the fracture type and tibial plateau geometry. Intra-interobserver agreement for the detection of the medial slope and posterior slope at the medial tibial plateau on MRI was very good (tibial posterior slope; intra ($r = 0.972$; 95%CI, 0.917-0.990), inter ($r = 0.933$; 95%CI, 0.811-0.978), tibial medial slope; intra ($r = 0.935$; 95%CI, 0.814-0.978), inter ($r = 0.895$; 95%CI, 0.715-0.965). The posterior slope in P type was average 11.4 degrees (range: 10.1-12.4 degrees), which was significantly larger than that in AM (average 5.0 degrees (range: 4.5-5.5 degrees) ($P = 0.048$) and PM (average 7.9 (range: 6.7-9.9 degrees) types ($P = 0.013$) (Figure 3J). The posterior slope in PM type was also significantly larger than that in AM type ($P = 0.048$). While, there were no differences between three fracture types about the medial slope.

DISCUSSION

Harolds^[2] posited that the location of medial tibial plateau fatigue fractures are medial and posterior because it is here that weight-bearing stress is greatest. In agreement, the more frequent site of these stress fractures was medial and posterior in our study. But, we found that it occurred antero-medially in some cases. As a result, localization of the medial tibial plateau stress fracture was classified into the following three patterns based on MRI findings: AM, PM, and P types. Furthermore, fracture classification was correlated with

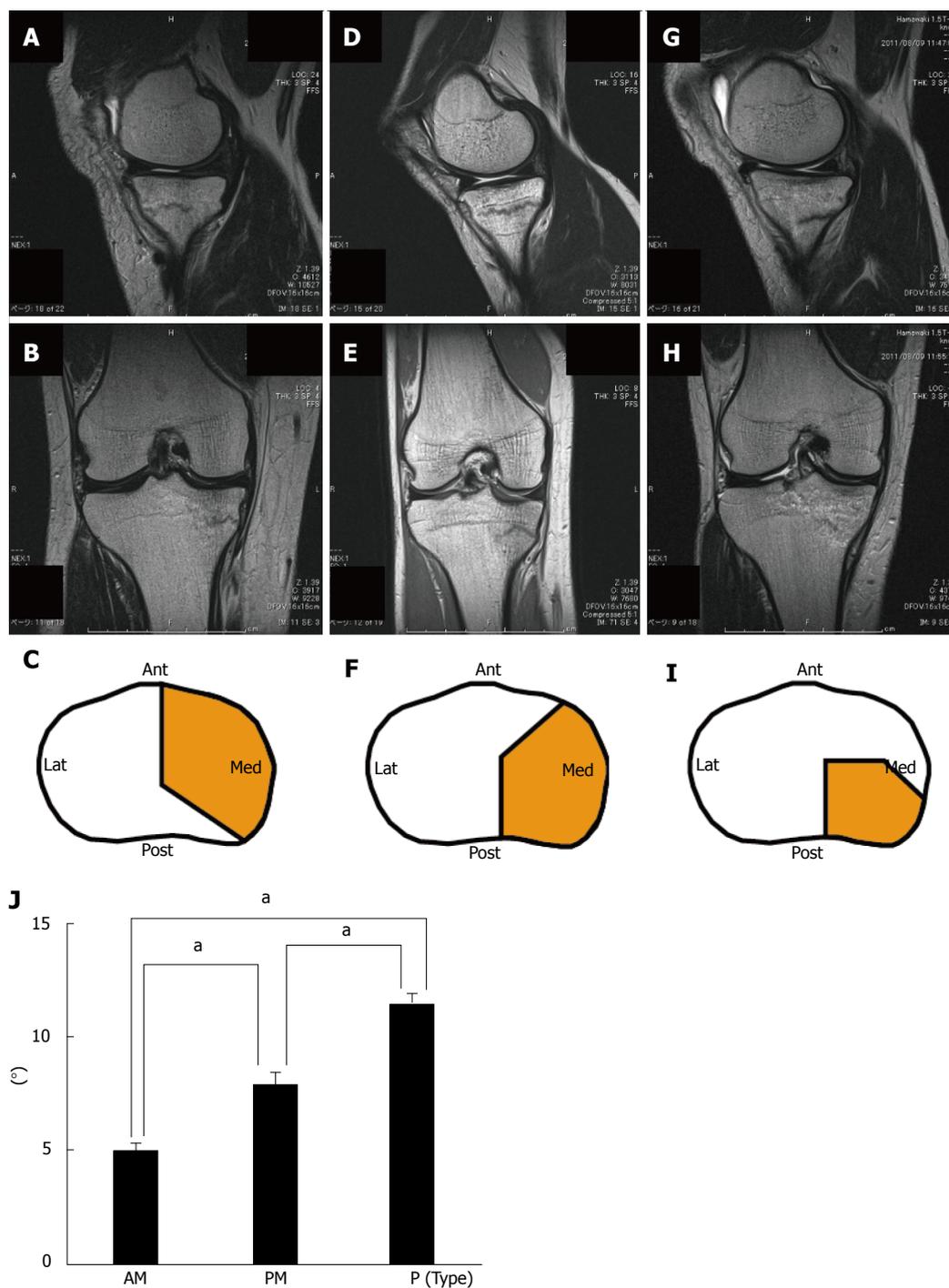


Figure 3 Representative magnetic resonance imaging of T2-weighted sagittal (A, D, and G) and coronal (B, E, and H) views in the anteromedial (AM), posteromedial (PM), posterior (P) types of medial tibial plateau stress fractures. Illustrative diagrams of the fracture area (orange) of AM (C), PM (F), and P (I) types at the tibial plateau. Ant: Anterior; Lat: Lateral; Med: Medial; Post: Posterior. J: Relationship between fracture location and posterior tibial slope of the medial tibial plateau. Error bar indicates standard error, ^a $P < 0.05$.

the posterior slope of the medial tibial plateau.

Dynamic contact mechanics of the tibial plateau during running have not been elucidated, but cadaver studies have described the pressure distribution pattern of the knee during a simulated gait^[9,10]. Bedi *et al*^[9] demonstrated that the posterior portion of the plateau had higher peak contact pressures than the anterior portion in the stance phase of gait at 14% of the gait cycle, which correspond to 15° knee flexion with axial

loads of 2280N. Wang *et al*^[10] also reported that one of the most prominent contact stress patterns was observed at the posterior aspect of the medial tibial plateau in nine of 12 cadaveric knees with a single peak stress that occurred at 14%-18% of the gait cycle during the early stance phase. These results are consistent with the fact that more frequent location of medial tibial plateau stress fractures is posterior, although tibial posterior slope was not taken into consideration in their studies.

The tibial posterior slope is originally defined by the angle perpendicular to the longitudinal axis of the bone and tangent to the plateaus on the lateral radiographs. But, it is difficult to discriminate between the medial and lateral plateaus^[11,12]. Recent studies have recommended separate assessment of tibial posterior slopes of the medial and lateral plateaus^[8,13,14]. Matsuda *et al.*^[14] reported that the mean tibial posterior slope in the medial plateau on MRI examination was 10.7° (range, 5°-15.5°) in the normal knees of Japanese populations. This average value was similar to that of the present Japanese patients group. The present study indicated that increased the posterior slope caused the plateau to fracture more posteriorly. Giffin *et al.*^[15] reported that an increase in tibial posterior slope shifted the resting position of the tibia anteriorly relative to the femur. These data suggest that loading of the medial tibial plateau from the femoral condyle may shift from anterior to posterior due to the increased posterior tilt of the tibial plateau. However, the relationship between dynamic contact stress pattern on the tibial plateau and tibial posterior slope during gait and running still remains unclear.

In general, medial tibial plateau stress fractures are more common than stress fractures of the lateral tibial plateau^[16,17]. Mizuta *et al.*^[16] reported a case of the lateral tibial plateau stress fracture, which was associated with knee valgus angulation with 92 degrees of medial tibial slope on radiographs. Hashemi *et al.*^[8] described that the lateral-to-medial slope of the tibial plateau, which they used the term "coronal tibial slope", ranged between -1° and 6°, whereas the only one subject had a coronal tibial slope of 91° in normal subjects. In our cases of medial tibial plateau stress fractures, medial tibial slope ranged between -0.2° and 6.1°. These data suggest that the patient, who has medial tibial slope within normal limits, is subjected to medial tibial plateau stress fracture, but not lateral.

This fracture type most frequently occurs in soldiers and marathon runners^[1,2]. In our series, thirteen of 14 cases were recreational runners. Running has positive effects on physical fitness including reduction in the incidence of obesity, cardiovascular disease, and the other chronic health problems. On the other hand, more people may sustain a running-related injury of the lower extremity. Physicians should be aware of a stress fracture at the medial tibial plateau when patients, particularly runners, present with medial knee pain. Tibial plateau stress fractures in athletes or soldiers are usually self-limiting disease without any persistent deformities because they are comparatively young and they do not have osteoporosis. In fact, all of the present cases did not have any changes of tibial plateau morphology in the follow-up X-rays. On the other hand, insufficiency fractures of the tibial plateau caused by osteoporosis, steroid-use, and rheumatoid arthritis occur in elderly patients^[17,18]. We believe that BMD should be evaluated for older runners because delayed diagnosis and treatment can lead to

deformity of the knee if osteoporosis is more severe.

One of the limitations of the present study is a small number of the patients because of its rarity. The second limitation is an insufficient length of the tibia on MRI because we used the knee MRI to measure the tibial and medial slopes, which includes only proximal one-third of the whole tibia. MR images of whole tibia might result in more precise slope measurements.

In conclusion, we found three distinct location types of isolated stress fractures of the medial tibial plateau based on MRI. MRI is the preferred technique to correctly diagnose these fracture types because X-rays might not detect the fracture for two week after the onset. Other modalities, such as ultrasound or CT, may be considered as alternatives to diagnose to tibial plateau stress fractures^[4]. At that time, tibial posterior slope could serve as an indicator to find out the fracture location at the medial tibial plateau.

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COMMENTS

Background

Stress fractures of the lower extremity commonly occur in athletes and military personnel. The tibial shaft is the most common location for stress fractures during running and marching activities, whereas the medial tibial plateau is a relatively uncommon site. This fracture type is difficult to detect on initial roentgenograms at the onset of symptoms. This injury is easily misdiagnosed because the location of pain and tenderness is very similar to the meniscal injury and pes anserinus bursitis, which are common problems in running activities.

Research frontiers

Bone scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) are widely used for early detection of stress fractures. Among them, MRI has been found to be more sensitive than CT and more specific than scintigraphy. T2- and STIR-MR images are useful for detecting edema of the cancellous bone that usually presents as a linear fracture line at the medial tibial plateau. No studies have investigated more detailed MRI features of medial tibial plateau stress fractures.

Innovations and breakthroughs

The authors found three different types of location in stress fracture of the medial tibial plateau. The geometry of the tibial plateau in patients with stress fractures of medial tibial plateau and the relationship with the fracture location were also evaluated.

Applications

The authors found three distinct location types of isolated stress fractures of the medial tibial plateau based on MRI. Other modalities may be considered as alternatives to diagnose to tibial plateau stress fractures. Tibial posterior slope could serve as an indicator to find out the fracture location at the medial tibial plateau.

Peer-review

It is a very interesting study. The authors present a series of patients with imaging regarding stress fractures of the tibial plateau.

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Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at algianakos@gmail.com, who will provide a permanent, citable and open-access home for the dataset.

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Abstract

AIM

To examine the evidence behind the use of concentrated bone marrow aspirate (cBMA) in cartilage, bone, and tendon repair; establish proof of concept for the use of cBMA in these biologic environments; and provide the level and quality of evidence substantiating the use of cBMA in the clinical setting.

METHODS

We conducted a systematic review according to PRISMA guidelines. EMBASE, MEDLINE, and Web of Knowledge databases were screened for the use of cBMA in the repair of cartilage, bone, and tendon repair. We extracted data on tissue type, cBMA preparation, cBMA concentration, study methods, outcomes, and level of evidence and reported the results in tables and text.

RESULTS

A total of 36 studies met inclusion/exclusion criteria and were included in this review. Thirty-one of 36 (86%) studies reported the method of centrifugation and preparation of cBMA with 15 (42%) studies reporting either a cell concentration or an increase from baseline. Variation of cBMA application was seen amongst the studies evaluated. Twenty-one of 36 (58%) were level of evidence IV, 12/36 (33%) were level of evidence III, and 3/36 (8%) were level of evidence II. Studies evaluated full thickness chondral lesions (7 studies), osteochondral lesions (10 studies), osteoarthritis (5 studies), nonunion or fracture (9 studies), or tendon injuries (5 studies). Significant clinical improvement with the presence of hyaline-like values and lower incidence of fibrocartilage on T2 mapping was found in patients receiving cBMA in the treatment of cartilaginous lesions. Bone consolidation and time to bone union was improved in patients receiving cBMA. Enhanced healing

rates, improved quality of the repair surface on ultrasound and magnetic resonance imaging, and a decreased risk of re-rupture was demonstrated in patients receiving cBMA as an adjunctive treatment in tendon repair.

CONCLUSION

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. This study also demonstrates discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, and lack of standardized outcome measures. Future studies should attempt to examine the integral factors necessary for tissue regeneration and renewal including stem cells, growth factors and a biologic scaffold.

Key words: Concentrated bone marrow aspirate; Bone; Cartilage; Osteochondral lesion; Osteoarthritis; Tendon

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Core tip: With the widespread use of orthobiologics in everyday practice, attention must be directed to substantiate the evidence for their current use and to direct future practice guidelines. The use of concentrated bone marrow aspirate (cBMA) has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries. This systematic review demonstrates the potential benefits of utilizing cBMA for the repair of different tissue types in the clinical setting. This systematic review also highlights discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, variable methods of application of cBMA, and the lack of standardized outcome measures.

Gianakos AL, Sun L, Patel JN, Adams DM, Liporace FA. Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review. *World J Orthop* 2017; 8(6): 491-506 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i6/491.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i6.491>

INTRODUCTION

With the widespread use of orthobiologics in everyday practice, attention must be directed to substantiate the evidence for their current use and to direct future practice guidelines. In any bioengineered environment, three components are required to provide the necessary biologic milieu for cell regeneration and renewal. The presence of stem cells, growth factors, and a biologic scaffold are integral to this process. Bone marrow aspirate (BMA) has been utilized as a source of bone marrow-derived mesenchymal stem cells (BM-MSC) with its relative ease of harvest, low morbidity, and feasible

cost. BMA alone has a relatively low percentage of MSCs with only 0.001% to 0.01% of all nucleated cells in BMA being MSCs^[1]. Therefore, the aspirate is typically concentrated by centrifugation in order to increase the ratio of MSCs. Concentrated bone marrow aspirate (cBMA) provides both stem cells and growth factors and relies on the host tissue to provide scaffold. The use of cBMA has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries. Despite both basic science and clinical evidence of its efficacy, recent literature suggests that cBMA has different functions and roles in each biologic environment. Evidence suggests that stem cells act to direct local cells to stimulate regeneration and repair that is specific to each tissue. This process is mediated by secretomes from the stem cells, which allow their adaptation in each environment and therefore provides the appropriate growth factors and cytokines necessary to stimulate each tissue in a different fashion^[2]. Growth factors derived from cBMA may be required for cell lineage differentiation although the exact growth factors have not to date been fully elucidated. The available literature regarding the use of cBMA in different tissue repair is highly heterogeneous with regards to indications, concentrations and overall functional outcomes.

This review attempts to examine the evidence behind the use of cBMA in cartilage, bone, and tendon regeneration and repair and to establish proof of concept for the use of cBMA in these biologic environments. In addition our systematic review will provide the reader with a reference of the level and quality of evidence of the current available literature evaluating the uses of cBMA in the treatment of lesions in cartilage, tendon, and bone.

MATERIALS AND METHODS

A systematic review was conducted according to PRISMA guidelines^[3]. The following search terms were used in MEDLINE, EMBASE, and Web of Science databases on November 22, 2016: "cBMA OR concentrated bone marrow aspirate OR BMC OR bone marrow concentrate OR bone marrow derived mesenchymal stem cells". This was paired with one of the following search strategies: (1) "cartilage OR chondrocytes OR chondrogenesis OR arthritis OR osteoarthritis OR osteochondral OR chondral"; (2) "tenocytes OR tendon OR tendinitis OR tendinosis OR tendinopathy"; or (3) "bone OR bone healing OR malunion OR delayed union OR osteocyte OR osteogenesis". Inclusion criteria were: (1) clinical studies demonstrating the effect of cBMA in cartilage, bone; or tendon (2) published in peer-reviewed journal; and (3) written in English. Exclusion criteria included review articles, case reports, basic science studies, and studies evaluating additional pathologic processes. Two independent reviewers performed the literature search screening both title and abstract for all results. Potentially

eligible studies received a full text review. The reference list of the identified articles in the results were manually screened for additional articles. A senior author was consulted if a consensus could not be reached. The following information was extracted and recorded from the included studies: Number of patients, preparation method of cBMA, cell count, treatment groups, adjunctive therapies/scaffolds, follow-up, objective and subjective outcomes, and level of evidence.

RESULTS

The initial literature search resulted in 1202 total studies. Once duplicates were removed and articles were screened for inclusion/exclusion criteria, 135 were included and full texts were assessed for eligibility. A total of 36 studies met inclusion/exclusion criteria and were included in this review.

Study characteristics

Thirty-one of 36 (86%) studies reported the method of centrifugation and preparation of cBMA. Fifteen of 36 (42%) studies reported either a cell concentration or an increase from baseline. There were no studies that reported on the minimal number of colony forming units in which below that number, cBMA did not provide significant benefit. Twenty-one of 36 (58%) were level of evidence IV, 12/36 (33%) were level of evidence III, and 3/36 (8%) were level of evidence II. Two studies were industry funded while 37 declared no conflict of interest.

cBMA in full thickness cartilage lesions

Seven studies evaluated the effect of cBMA in the treatment of full thickness cartilage defects in the knee and all reported significant clinical improvement post-operatively summarized in Table 1^[4-10]. Three studies evaluated the effect of cBMA combined with microfracture and demonstrated improved clinical outcomes with reconstitution of original cartilage on magnetic resonance imaging (MRI). All three studies reported bone marrow edema and/or subchondral irregularities^[4-6]. One study evaluated the effects of cBMA when compared with matrix-induced autologous chondrocyte implantation (MACI) and found that patients receiving cBMA had a significantly improved IKDC subjective score ($P = 0.015$) with 81% complete cartilage filling on MRI^[7]. One study compared the effects of cBMA to PRP and reported that patients who received cBMA had T2 values closer to that of superficial hyaline cartilage ($P = 0.01$)^[10]. Variation of cBMA application was seen amongst the studies evaluated. Several studies used cBMA in isolation, while other studies combined cBMA with either a collagen or hyaluronic acid scaffold. Many of these studies prepared the defect site and implanted cBMA through arthroscopic techniques.

cBMA in osteochondral lesions

Ten studies evaluated the effect of cBMA in the treatment of osteochondral defects in the talus (7/10) and the

knee (3/10) summarized in Table 2^[2,11-19]. All ten studies reported both clinical and radiologic improvements post-operatively after receiving cBMA. Six studies evaluated the effects of cBMA with no concomitant procedure and reported good clinical outcome scores including AOFAS, IDKS, and KOOS. For studies that utilized either a collagen or a hyaluronic acid scaffold, no significant difference was reported between the two groups. Buda^[11] evaluated cBMA compared to autologous chondrocyte implantation (ACI) and reported no clinical difference between the two treatment strategies but found a higher presence of hyaline like values and lower incidence of fibrocartilage on T2 mapping in the cBMA group. One study favored treatment with cBMA when comparing cBMA to microfracture reporting 100% and 28% normal IDKC values at 5-year follow up, respectively^[18]. Lastly, one study reported higher MOCART scores and T2 relaxation values with measurements resembling those of native cartilage in groups that received both microfracture with cBMA compared to groups that received microfracture alone^[19]. cBMA had also been used as an adjunctive treatment to autologous osteochondral transplantation and resulted in overall improved FAOS scores post-operatively^[2]. Variation of cBMA application was seen amongst the studies evaluated. These included the use of either a collagen powder or hyaluronic acid scaffold, with the majority of studies using arthroscopic techniques for cBMA implantation.

cBMA in osteoarthritis

Five studies evaluated cBMA in the treatment of knee osteoarthritis (OA) summarized in Table 3^[20-24]. Only two studies evaluated the efficacy of cBMA without an adjunctive procedure. One reported better clinical outcomes at one week and three months in patients who received cBMA but found no difference in these scores after six months^[24]. One study reported significant clinical improvements but found that 76% of patients had abnormal International Cartilage Repair Society repair scores^[23]. Three studies evaluated cBMA combined with either PRP or PRF and found functional and clinical improvements in the cBMA groups with improvement in cartilage repair, although not significant^[20-22]. Variation of cBMA application was seen amongst the studies evaluated, which utilized ultrasound or fluoroscopy for needle placement or was performed under arthroscopic guidance.

cBMA in bone healing

Nine studies evaluated the use of cBMA in bone healing summarized in Table 4^[25-33]. Eight of nine studies reported on the use of cBMA in either non-union or delayed union. One study demonstrated initial radiographic and functional improvements in the cBMA group, but reported similar outcomes after one year post-operatively^[31]. All studies reported either lower or similar complication rates post-operatively in groups that received cBMA compared to groups receiving no additional treatment. Bone

Table 1 Studies evaluating concentrated bone marrow aspirate in the treatment of full thickness chondral lesions

Ref.	Tissue	BMAC preparation	Concentration	Study design/methods/follow up	Outcomes measured	Results	LOE
Enea <i>et al</i> ^[4]	Knee	60 mL BMA from iliac crest processed with MarrowStim Concentration Kit (Biomet) resulting in 3-4 mL of BMAC. Chondral lesion debrided and microfracture performed. Biocollagen MeRE collagen membrane (Biotech) cut to match shape and immersed in BMAC until implantation. 10:1 mixture of 1-2 mL fibrin glue and BMAC laid on lesion. Membrane inserted and placed. 2-3 mL of fibrin glue-BMAC injected over and left to solidify	NS	<i>n</i> = 9. Arthroscopic microfracture covered with collagen membrane immersed in autologous BMAC from iliac crest. Follow up: 29 mo	Biopsy cartilage evaluated by surgeon using criteria of international cartilage repair society. The following items were utilized: Cartilage repair assessment, MRI, IKDC, Lysholm, VAS (pre and post op), Tegner (pre and post op). Four patients had second look arthroscopy and biopsy	Significant clinical improvement (<i>P</i> < 0.005). Cartilage macroscopic assessment at 12 mo revealed all repairs appeared almost normal. Histo-analysis showed hyaline-like cartilage repair in 1 lesion, fibrocartilaginous repair in 2 lesions and a mixture of both in 1 lesion. Post op MRIs (6-9 mo out) all showed reconstitution of original cartilage. Bone marrow edema and/or subchondral irregularities observed in all cases. Non-homogeneous cartilage signal and fissuring observed in 2 of 3 cases	IV
Enea <i>et al</i> ^[5]	Knee	60 mL of BMA from the iliac crest was obtained and processed with MarrowStim Concentration Kit (Biomet) to obtain 3-4 mL of BMAC. Cartilage was treated with arthroscopic microfracture and the defect was covered with PGA-HA scaffold matrix (Chondrotissue) seeded with autologous BMAC. 10:1 mixture of 1-2 mL of fibrin glue and BMAC was then applied to lesion bed. PGA-HA soaked in BMAC was then applied with 2-3 mL additional fibrin glue-BMAC mixture dispersed over the matrix until solidification at 2-3 min	NS	<i>n</i> = 9 (Outerbridge type III/IV) Consecutively treated with arthroscopic Polyglycolic acid/hyaluronan - covered microfracture and BMAC. Follow up: 22 mo	Clinical scoring, IKDC, Lysholm, VAS, Tegner, cartilage microscopic examination at 12 mo, MRI at 8-12 mo post op. 5 patients underwent second look and 2 had biopsy	All patients but one showed improvement in clinical scoring from pre-op to last follow-up (22 mo). All other variables increased from baseline to latest follow-up. Nineteen cartilage exams appeared normal, three almost normal, and one abnormal at 12 mo. Histo showed hyaline-like cartilage repair tissue formation in one case. MRI showed complete defect filling	IV
Gigante <i>et al</i> ^[6]	Knee	NA	NA	<i>n</i> = 5. MACI augmented with BMAC	Second look arthroscopy biopsy, CRA, ICRS II Visual Histological Assessment Scale	Normal ICRS/CRA at arthroscopic evaluation and had mean overall histological ICRS II of 59.8 ± 14.5. Hyaline-like matrix only found in one case. Mixture of hyaline/fibrocartilage was found in one case and fibrocartilage was found three cases	IV
Gobbi <i>et al</i> ^[7]	Patello-femoral	60 mL of BMA from ipsilateral iliac crest concentrated by BMAC Harvest Smart PreP2 system to obtain concentration of BMC 4-6 times baseline value	4-6 × baseline	(1) MACI <i>n</i> = 19; (2) BMAC <i>n</i> = 18. Both with HYAFF1 scaffold. Follow up: 3 yr	XR, MRI, IKDC score, KIOOS score, VAS, Tegner	Both groups showed significant improvements in all scores from preop to final follow up (<i>P</i> = 0.002). There was no difference between the two groups except in the IKDC subjective scores which favored BMAC group (<i>P</i> = 0.015). MRI showed complete filling of defect in 76% of MACI and in 81% of BMAC	III
Gobbi <i>et al</i> ^[8]	Knee	60 mL of BMA from ipsilateral iliac crest concentrated by BMAC Harvest Smart PreP2 system to obtain concentration of BMC 4-6 times baseline value. Activated using batroxobin enzyme to form sticky clot. Implanted and covered with collagen-based membrane scaffold (ChondroGide) and sealed with fibrin glue (Tissucol)	4-6 × baseline	<i>n</i> = 25. Cartilage transplantation with multipotent stem cells and collagen type I / III matrix	XR, MRI, VAS, IKDC, KOOS, Lysholm, Marx, Tegner	Significant improvement at follow up across all measures. < 45-year-old and smaller lesions = better results. MRI = good stability of implant, hyaline-like cartilage found is histo analysis of biopsied tissue	IV

Gobbi <i>et al</i> ^[9]	Knee	60mL BMA from ipsilateral iliac crest (PreP2) and concentrated to 4-6 times baseline value, after activation with batroxobin enzyme (Plateltex Act) and pasted into lesion Covered with collagen type I / III matrix (Chondro-Gide) and sealed with fibrin glue (Tissucol)	4-6 × baseline	<i>n</i> = 15. One step surgery with BMAC and Collagen I / III matrix (chondro-gide)	XR, MRI at 1 and 2 yr. VAS, IKDC, KOOS, Lysholm, Marx, SF-36, Tegner at 6, 12, 24 mo. 3 had second look biopsy	Significant improvement at follow up across all measures (<i>P</i> < 0.0005). Single lesion and smaller lesions had better improvement. MRI showed greater hyaline-like tissue in all patients. Hyaline-like cartilage on histology in 3 biopsies	IV
Krych <i>et al</i> ^[10]	Distal femur	NS	NS	(1) <i>n</i> = 11 control scaffold; (2) <i>n</i> = 23 scaffold + PRP; (3) <i>n</i> = 12 scaffold + BMAC. Follow up: 12 mo	MRI, T2 mapping	BMAC and PRP groups had superior cartilage infill (<i>P</i> = 0.002, <i>P</i> = 0.03). BMAC demonstrated mean T2 value closer to that of superficial hyaline cartilage (<i>P</i> = 0.01)	III

BMA: Bone marrow aspirate; NS: Not significant; CRA: Cartilage repair assessment; MRI: Magnetic resonance imaging; MACI: Matrix-induced autologous chondrocyte implantation; PRP: Platelet-rich plasma.

Table 2 Studies evaluating concentrated bone marrow aspirate in the treatment of osteochondral defects

Ref.	Tissue	BMAC preparation	Concentration	Study design/ methods/follow up	Outcomes measured	Results	LOE
Buda <i>et al</i> ^[11]	OCL of talus	Scaffold was a hyaluronic acid membrane loaded with previously cultured chondrocytes (ACI) or with BMAC. Platelet rich fibrin gel was produced the day before surgery using Vivostat System 1 (vivolution A/S). Harvested and processed 120 mL of the patient's venous blood to obtain 6 mL of platelet rich fibrin gel. 60 mL BMA was harvested from posterior iliac crest using Smart PRePl to obtain 6 mL of BMAC. 1 g powder mixed with 2 mL BMAC and 1 mL platelet rich fibrin gel. The hyaluronic acid membrane was cut and loaded with 2 mL BMAC and 1 mL platelet rich fibrin gel. A layer of platelet rich fibrin gel was placed over the implant once in place to provide additional stability	NS	<i>n</i> (total) = 80: (1) <i>n</i> = 40 - autologous chondrocytes implantation; (2) <i>n</i> = 40 with BMAC. Follow up: 48 mo	Clinical scores, XR, MRI MOCart score, T2 mapping	Groups had similar results at 48 mo. No statistically significant difference in clinical outcomes. Return to sport was slightly better with BMAC. MRI MOCART score was similar in both groups. T2 mapping highlighted a higher presence of hyaline like values and lower incidence of fibrocartilage in BMAC group	IV
Buda <i>et al</i> ^[12]	OCL of knee	Combined with either MAST or HA matrix	NS	<i>n</i> = 30. One step arthroscopic BMAC transplant with scaffold. Follow up: 29 mo	Clinical inspection, MRI, IKDC, KOOS	Good clinical outcome and osteochondral regeneration on MRI and biopsies in both groups	IV
Buda <i>et al</i> ^[13]	OCL of talus	Scaffolds either: (1) porcine collagen powder SpongostanI Powder (J and J) mixed with autologous cell concentrate and platelet gel; or (2) hyaluronic acid membrane (fidia advanced biopolymers) with addition of platelet gel. Platelet rich fibrin gel was produced the day before surgery using Vivostat System 1 (vivolution A/S). Harvested and processed 120 mL of the patient's venous blood to obtain 6 mL of platelet rich fibrin gel. 60 mL BMA was harvested from posterior iliac crest using Smart PRePl to obtain 6mL of BMAC. 1 g powder mixed with 2 mL BMAC and 1mL platelet rich fibrin gel. The hyaluronic acid membrane was cut and loaded with 2 mL BMAC and 1 mL platelet rich fibrin gel. A layer of platelet rich fibrin gel was placed over implant once in place to provide additional stability	NS	<i>n</i> = 64. One step arthroscopic BMAC transplant with scaffold (collagen powder of hyaluronic acid membrane) and platelet gel. Follow up: 53 mo	AOFAS scale score, radiographic, scaffold type, lesion area, previous surgery, lesion depth	Mean preop AOFAS was 65.2. Regardless of scaffolding type all patients showed similar pattern of clinical improvement at each follow-up. No correlation between area of lesion and pre-op AOFAS score but did observe relationship between area and AOFAS at each follow up post-operatively. No relationship between AOFAS score and depth of lesion	IV

Buda <i>et al</i> ^[14]	OCL of knee	Scaffold either MAST or HA matrix + PRF	NS	<i>n</i> = 20. Follow up: 24 mo	Clinical, MRI	Significant improvement at 12 and 24 mo, satisfactory MRI	IV
Giannini <i>et al</i> ^[15]	OCL of talus	Porcine collagen powder (J and J) or hyaluronic membrane scaffold. 60 mL of bone marrow harvested from posterior iliac crest and concentrated by SmartPrep to 6 mL of BMC. One step delivery system	NS	<i>n</i> = 49 received either BMA with collagen scaffold or BMA with HA membrane scaffold. Follow up: 48 ± 6 mo	AOFAS, radiograph, MRI	AOFAS improved <i>P</i> < 0.0005. T2 mapping analysis showed regenerated tissue with T2 values similar to hyaline cartilage in a mean of 78% of the repaired lesion area	IV
Giannini <i>et al</i> ^[16]	OCL of talus	One step arthroscopic transplantation. Platelet gel using Vivostat system. 60 mL BMA harvested from posterior iliac crest. Concentrated using SmartPreP in order to obtain 6 mL of concentrate. Scaffold: Either collagen powder (Spongostan1 Powder) or hyaluronic acid membrane. Scaffold was loaded with 2 mL BMAC and 1 mL PRF	NS	<i>n</i> = 25 in BMAC group. Study also compared to ACI	AOFAS, histology	Statistically significant improvement in mean AOFAS scores post-operatively (<i>P</i> < 0.0005). Only 1 superficial infection noted. Nearly homogeneous regenerated tissue on MOCART MRI in 82% of cases. Hypertrophy found in 2 cases on histology	IV
Giannini <i>et al</i> ^[17]	OCL of talus	Porcine collagen powder (J and J) or hyaluronic membrane scaffold. 60 mL of bone marrow harvested from posterior iliac crest and concentrated by SmartPrep to 6 mL of BMC. One step delivery system	NS	(1) <i>n</i> = 23 - Collagen scaffold + BMA; (2) <i>n</i> = 25 HA membrane scaffold + BMA. Follow up: 29 mo (24-35)	AOFAS, histology	AOFAS improved, Histology showed regenerated tissue in various degrees of remodeling	IV
Gobbi <i>et al</i> ^[18]	OCL of knee	Hyaluronic acid-based scaffold was used with BMAC 60 cc of BMA from Iliac Crest spun to 6 × normal concentration. Batroxobin enzyme used to activate BMAC	6 × baseline	<i>n</i> = 25 HA-BMAC, <i>n</i> = 25 microfracture. Observed prospectively for 5 yr	Patient-reported scoring tools: IKDC Subjective Knee Evaluation, KOOS, Lysholm Knee Questionnaire, and Tegner activity scale	Microfracture - 64% normal/nearly normal according to IKDC objective score at 2 yr and declined to 28% at 5 yr HA-BMAC - 100% normal/nearly normal objective IKDC at 2 yr, 100% at 5 yr for ALL outcomes measured	II
Hannon <i>et al</i> ^[19]	OCL of talus	60 mL of BMA from ipsilateral iliac crest, concentrated by Arterocyte Magellan Autologous Platelet Separator System to obtain 3 mL of BMAC	NS	(1) <i>n</i> = 12 BMS; (2) <i>n</i> = 22 BMAC+BMS. Follow up: 48.3 mo for BMAC + BMS, 78.3 mo for BMS	AOFAS, FAOS, SF-12, MOCART	Mean FAOS and SF-12 PCS scores improved pre to post operatively (<i>P</i> < 0.01) for both groups. MOCART score significantly higher in cBMA + BMS (<i>P</i> = 0.023). T2 relaxation values in cBMA + BMS group significantly higher with measurements of adjacent cartilage	III
Kennedy <i>et al</i> ^[2]	OCL of talus	60 mL of BMA from ipsilateral iliac crest, concentrated by commercially available BMAC centrifuge system to obtain 4 mL of pluripotent cells	NS	<i>n</i> = 72. AOT with BMAC. Follow up: 28 mo	FAOS, SF-12	FAOS, SF-12 significantly improved from pre to post-op	III

KOOS: Knee injury and Osteoarthritis Outcome Score; NS: Not significant; OCL: Osteochondral lesions; BMA: Bone marrow aspirate; MRI: Magnetic resonance imaging.

consolidation and time to bone union was improved in patients receiving cBMA, with faster healing rates when

Table 3 Studies evaluating concentrated bone marrow aspirate in the treatment of osteoarthritis

Ref.	Tissue	BMAC preparation	Concentration	Study design/methods/follow up	Outcomes measured	Results	LOE
Centeno <i>et al</i> ^[20]	Knee	60 mL of BMA from iliac crest was obtained to produce 1-3 mL of BMAC. 60 cc of heparinized IV venous blood drawn to be used for isolating PRP and platelet lysate. Lipoaspirate - miniliposuction of the posterior superior buttocks or lateral thigh was performed under ultrasound and minimally processed (centrifuged) adipose tissue was injected into the articular space. Preparations were injected into the articular space of the knee together (5-10 cc) between the meniscus on the most painful side and over lying collateral ligament	NS	Data from registry. (1) <i>n</i> = 616 - BMAC+ PRP vs (2) BMAC + PRP + adipose graft. Outcomes and complication questionnaires at 1, 3, 6, 12 mo completed. 2 groups (A-BMAC and PRP protocol, B BMAC and PRP plus adipose fate graft (lipoaspirate))	LEFS, NPS, subjective percentage improvement rating, frequency and type of adverse events	Mean LEFS score increased in both groups and mean NPS decreased in both groups. AE rates were 6% without graft and 8.9% with graft. No difference between groups. Addition of adipose graft did not provide a detectable benefit over BMAC alone	IV
Centeno <i>et al</i> ^[21]	Knee	10-15 cc whole bone marrow aspirate harvested from 6-8 sites on posterior iliac crest (3-4 each side). Centrifuged and cells isolated. Patient heparinized blood for PRP and PL. Aspirates mixed together and injected into joint. Cell counts were counted four times and average was taken under microscope for total nucleated cell count	Lower and higher cell count groups defined using threshold of 4×10^4 cells	Data from registry. <i>n</i> = 373 patients that received BMAC combined with PRP and PL injections for 424 OA knees	Clinical scales assessed at baseline, 1, 3, 6, 12 and annually thereafter. NPS, LEFS, pain and functional outcome measures	Significant positive results with treatment for all pain and functional metrics. Higher cell group reported lower post treatment numeric pain scale values ($P < 0.001$). No significant difference detected for other metrics	IV
Haleem <i>et al</i> ^[22]	Femoral condyle	20 mL BMA from iliac crest isolated with density gradient (Ficoll-Paque), supplemented with 10% fetal bovine serum and penicillin streptomycin. Microfracture performed and sclerotic bone curetted. Autologous periosteal flap harvested from anteromedial ipsilateral proximal tibia to fit defect size and stuffed into place. 1 mL platelet concentrate and 1 mL fibrinogen and 1 mL thrombin placed with BMAC PR fibrin glue	NS	<i>n</i> = 5, treated with BMAC + PRF	At 6 and 12 mo: Lysholm and Revised HHS Knee Score, XR and MRI. 2 patients had follow up arthroscopy at 12 mo rated by ICRS	All patients had statistically significant improvement at 6 and 12 mo ($P < 0.005$). No statistically significant difference between 6 and 12 mo post op in clinical scores. ICRS were near normal for 2 patients who consented to arthroscopy. MRI of 3 patients at 12 mo showed complete defect filling and complete surface congruity with native cartilage. Two patients showed incomplete congruity. BMAC on platelet rich fibrin gel as a scaffold may be effective to promote repair of articular cartilage defects	IV
Koh <i>et al</i> ^[23]	Knee	60 mL BMA from Iliac crest processed with MarrowStim Concentration Kit (Biomet) to obtain 3-4 mL of BMAC. Adipose tissue harvested from buttocks through liposuction. All fluid removed from knee arthroscopically. Lesion filled with cell suspension and held stationary for 10 minutes with defect facing upwards. Adherence of MSC confirmed. No marrow stimulation procedures were performed	Average of 3.8×10^6 ($2.5-6.1 \times 10^6$)	<i>n</i> = 37 knees using second-look arthroscopy after mesenchymal stem cell implantation for cartilage lesions done 12 mo post op	IKDC, Tegner, cartilage repair assessed using ICRS grading	IKDC and Tegner scores significantly improved ($P < 0.001$). ICRS overall repair grades 2/37 were normal, 7/37 were near normal, 20/37 abnormal, 8/37 severely abnormal. Patient satisfaction: 33/34 reported good to excellent satisfaction. High BMI (> 27.5) and large lesion ($> 5.4 \text{ cm}^2$) had significant prediction of poor clinical and arthroscopic outcomes ($P < 0.05$)	IV

Shapiro <i>et al</i> ^[24]	Knee	52 mL BMA from iliac crest concentrated in Arterocyte Magellan Autologous Platelet Separator System centrifuge to yield 6 mL of cellular product	NS	<i>n</i> = 25 BMAC, <i>n</i> = 25 saline (patients had bilateral knee pain)	OARSI measure, VAS score, safety outcomes, pain relief, function	OARSI and VAS decreased significantly from baseline at 1wk, 3 mo, 6 mo (<i>P</i> < 0.019), no difference in pain relief	II
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BMA: Bone marrow aspirate; MRI: Magnetic resonance imaging; NS: Not significant; OA: Osteoarthritis; BMI: Body mass index; VAS: Visual analogue scale; OARSI: Osteoarthritis Research Society International.

Table 4 Studies evaluating concentrated bone marrow aspirate in bone healing

Ref.	Tissue	BMAC preparation	Concentration	Study design/methods/follow up	Outcomes measured	Results	LOE
Bastos Filho <i>et al</i> ^[25]	Tibia/femur nonunion	11G × 10 cm bone marrow aspiration needle into posterior iliac crest to obtain a total of 100 to 110 mL for each patient - concentrated to 20 mL with Sepax system	NS	<i>n</i> = 6 patients with nonunion of tibia or femur. Four received percutaneous infusion of autologous bone marrow aspirated without Sepax processing. Two received with processing. Follow up to 6 mo	Clinical examination and radiographic evaluation at 2, 4, 6 mo. Clinical criteria included full weight bearing tolerance and absence of pain upon palpation at the fracture site. Radiographic healing checked with AP, lateral and oblique films to look for bone callus. Patient satisfaction questionnaire scale from 0-10	Bone consolidation obtained in all the patients. Bone callus observed in the radiographic between 3 and 24 wk, average 13.8 wk in group without processing. Mean satisfaction increased in all patients	II
Desai <i>et al</i> ^[26]	Nonunion/delayed union of tibia	Total of 60 cc bone marrow aspirated from iliac crest with 16 gauge Jamshidi needle (Harvest system). Concentrated to 10 cc for injection	101.48 ± 64.13/cc	<i>n</i> = 49 patients with tibial nonunion had BMAC injection with DBM and/or rhBMP-2. Follow up until radiographic union or another procedure was performed	Radiographic healing (bridging of 3 out of 4 cortices on AP and lateral films)	No difference in healing rate between patients with fracture gaps less than and greater than 5 mm	III
Garnavos <i>et al</i> ^[27]	Humeral shaft delayed union	With the use of a 10 cm long and 3 mm wide biopsy needle, 60 mL of bone marrow was aspirated from each patient's iliac wing and was centrifuged to provide 10 mL of concentrated mesenchymal stem cells. The concentrated bone marrow mixed with 10 cc of DBM putty	NS	<i>n</i> = 5. Intramedullary nailing with antegrade/unreamed technique was performed for 4 patients. One patient was treated previously with retrograde/unreamed nailing left in situ. The concentrated mixture was infused percutaneously in the area of nonunion with a biopsy needle under fluoroscopy. Patients were followed up every 4-6 wk for 12 mo	Patients were assessed for union process, discomfort, level of activities and functional improvement	There were no peri- or postoperative complications. Sound union was obtained in all cases from 12 to 20 wk after the operation. At final followup, all patients had regained a satisfactory range of shoulder and elbow motion. They had also returned to pre-injury level of activities and were happy with their treatment and outcome	IV
Guimaraes <i>et al</i> ^[28]	Femoral shaft nonunion	11G × 10 cm needle used for aspiration from iliac crest. The marrow samples were harvested in small amount (2 mL) and the contents of each syringe were pooled in the container of the bone-marrow-collection kit containing anticoagulant solution. The final volume of bone marrow aspirate (200 mL) was then filtered through a sequence of successively	9.8 ± 4.3 × 10 ⁶ vs 20.2 ± 8.6 × 10 ⁶	<i>n</i> = 16 patients with aseptic nonunion of femur were treated with injection of BM-MSCs who had locked IMN. Follow up: 3-8 mo	Radiographic RUST scores	Bone union occurred in 8 of 16 patients according to RUST. The grafts used in patients whom treatment failed contained significantly lower number of total nucleated cells (9.8 ± 4.3 × 10 ⁶ vs 20.2 ± 8.6 × 10 ⁶)	IV

Hernigou <i>et al</i> ^[29]	Ankle nonunion	smaller-diameter mesh filters. The cells were finally collected in a blood transfer pack unit. The aspirated material was reduced to a final volume of 40 mL by removing most of the RBC the plasma by centrifugation 150 mL of bone marrow aspirate obtained from anterior portion of the ipsilateral iliac crest then treated with a cell separator	27.3 ± 14.6 × 10 ⁶	<i>n</i> = 86 ankle nonunion in diabetic patients treated with BM- MSCs <i>vs n</i> = 86 diabetic matched nonunion treated with a standard bone iliac crest autograft	Time of union, callus volume, complication, morbidity of graft harvesting <i>vs</i> bone marrow aspiration in diabetic patients	70 out of 86 patients (82.1%) III treated with BMC achieved healing with a low number of complications; 53 (62.3%) of patients treated with iliac bone graft had healing and major complications were observed: Amputations, osteonecrosis of fracture wound edge, infections
Hernigou <i>et al</i> ^[30]	Tibial shaft nonunion	Bone marrow aspirated from anterior iliac crest total of 300 mL then concentrated to 50 mL	18 ± 7 million	BMAC injected into 60 noninfected atrophic nonunion of tibia. Follow up until union	Radiographic union; healing time; volume of callus	Patients who did not achieve IV union had significantly lower number of progenitor cells comparing to the 53 patients who achieved union. There was positive correlation between the volume of mineralized callus at 4 mo and the number and concentration of fibroblast colony-forming units in the graft; there was a negative correlation between the time needed to obtain union and the concentration of CFU in the graft
Ismail <i>et al</i> ^[31]	Long bone nonunion	40 mL of bone marrow was aspirated from posterior iliac crest and transferred into a container prefilled with 5000 U/mL of heparin. Aspirate was diluted with phosphate-buffered saline at a ratio of 1:1 and centrifuged at room temperature at 3000 rpm for 30 min. The collected buffy coat was washed and transferred into a culture flask containing Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum. Cells were incubated at 37 °C at 5% CO ₂ with a routine culture medium change every two to three days. Subculture was performed between	14-18 million BMSCs	<i>n</i> (total) = 10. <i>n</i> = 5, treated with combination of 15 million BM-MSCs, 5 g/cm ³ (HA) granules and internal fixation. <i>n</i> = 5, control subjects were treated with iliac crest autograft, 5 g/cm ³ HA granules with internal fixation. Follow up = 12 mo	VAS, LEFS, DASH score. Radiological assessments for union were conducted by a blinded radiologist using two radiological scoring systems: The Lane-Sandhu and Tiedeman radiological scores	No significant differences III in post-op pain between the two groups. The treatment group demonstrated initial radiographic and functional improvements. Statistically significant differences in functional scores were present during the first (<i>P</i> = 0.002), second (<i>P</i> = 0.005) and third (<i>P</i> = 0.01) month. Both groups achieved similar outcomes by the end of one year follow up

Le Nail <i>et al</i> ^[32]	Open tibia fracture	<p>days 7 and 10. Mixed with 5 g/cm³ defect of HA granules</p> <p>Hernigou's technique. Bone marrow from posterior iliac crest by needle aspiration. Around 500 mL concentrated by centrifugation to obtain 50 mL</p>	171 ± 107 × 10 ⁶ vs 118 ± 28 × 10 ⁶	<p>n = 43 cases of open tibial fractures with initial surgical treatment that developed nonunion or delayed union, subsequently treated with injection of BMAC</p>	<p>Clinical success (consolidation without any subsequent procedure): Non painful callus palpation and a full weight bearing without any contention system. Radiographic bone healing 3 out of 4 cortices</p>	23 successes (53.5%) within 17 wk after BMAC	IV
Thua <i>et al</i> ^[33]	Long bone nonunion	<p>BMA (300-350 mL) were obtained by Jamshidi vacuum. Both posterior iliac crests of patients were harvested under loco-regional anaesthesia. BMAC was produced <i>via</i> density gradient centrifugation using the Sorvall centrifuge at 3670 rpm for 7 min. Afterwards, a total volume of 8 mL BMAC was mixed with freeze-dried allograft cancellous bone chips. BMAC was incubated for 15 min with bone chips as a composite of BMAC-ACB prior to transplantation</p>	2.43 ± 1.03 (× 10 ⁶) CD34 cells/mL (staining)	<p>n (total) = 27. n = 9 control treated with autologous cancellous bone graft from iliac crest. n = 18 clinical trial group treated with BMSCs and allograft cancellous bone chips. Correction and optimization of fixation device were done for previously failed procedures. Patients were followed up in outpatient clinic for 1, 3, 6, 9 12, 18, 24 mo</p>	<p>Functional outcomes, radiographic outcomes based on modified Lane and Sandhu radiological scoring system</p>	<p>Bone consolidation was obtained in 88.9% and mean interval between cell transplantation and union was 4.6 ± 1.5 months in autograft group. Bone union rate was 94.4% in group of composite BMAC-ACB implantation. The time to union in BMAC-ACB grafting group was 3.3 ± 0.9 mo, and led to faster healing when compared to the autograft</p>	III

NS: Not significant; BM-MSC: Bone marrow-derived mesenchymal stem cell; BMA: Bone marrow aspirate; RBC: Red blood cell; CFU: Colony-forming units; BMSC: Bone marrow derived stroma cell.

compared to patients in the autograft group^[33]. One study found a significantly lower number of progenitor cells in patients who did not achieve union as well as a negative correlation between the time needed to obtain union and the concentration of colony forming units in the graft^[30]. Lastly, one study evaluated the efficacy of cBMA in the treatment of open tibia fractures and found adequate bone consolidation and bone callus formation in all patients^[25]. Variation of cBMA application was seen amongst the studies evaluated. These methods utilized cBMA in isolation or in combination with DBM/rhBMP-2, freeze-dried allograft, or cancellous bone chips. Application of cBMA to the site of nonunion was accomplished by either fluoroscopic visualization or percutaneous injection.

cBMA in tendon repair

Five studies evaluating cBMA in tendon repair were included and summarized in Table 5^[34-38]. One study evaluated open Achilles tendon repair augmented with cBMA and reported excellent functional outcomes, early mobilization, normal range of motion, and no re-ruptures at a mean follow up of 29.7 mo^[38]. One study evaluated the use of cBMA during rotator cuff repair and reported enhanced healing rates, improved quality of the repair

surface on ultrasound and MRI, and a decreased risk of re-rupture when compared to the control group^[34]. The MSC content in rotator cuff tears was evaluated in one study, which demonstrated a moderate-to-severe reduction in content at the tendon-bone interface tuberosity relative to the control^[35]. Lastly, one study showed that MSCs treated with insulin had an increase in tendon-specific markers, content of tendon specific proteins, and receptors on the cell surface compared with control cells^[36]. None of the studies specifically described the method of cBMA injection.

DISCUSSION

cBMA in cartilage repair

Articular cartilage injury presents orthopedic surgeons with a difficult challenge as its inherent avascularity and poor healing potential can hinder its self-regenerative capacity. This poor repair capacity has been implicated in the development of post-traumatic osteoarthritis (PTOA) and osteochondral lesions (OCL). Traditional techniques for surgical stimulation of cartilage repair include microfracture and micropicking. These techniques penetrate the subchondral bone in order to stimulate blood flow and allow MSCs access to the cartilage defect. In addition,

Table 5 Studies evaluating concentrated bone marrow aspirate in tendon repair

Ref.	Tissue	BMAC preparation	Concentration	Study design/methods/follow up	Outcomes measured	Results	Level of evidence
Hernigou <i>et al</i> ^[34]	Rotator cuff	150 mL BMA from iliac crest mixed with an anticoagulant solution (citric acid, sodium citrate, dextrose). MSCs were injected in the tendon at the junction between the bone and tendon (4 mL), and in the bone at the site of the footprint (8 mL). Each patient in the MSC-treated group received a total of 12 mL of bone marrow concentrate	51000 ± 25000 cells in 12 mL of injected BMC	<i>n</i> = 45 received MSCs during repair. <i>n</i> = 45 matched control group of 45 patients who did not receive MSCs. Follow up: 3, 6, 12, 24 mo and 10 yr	RTC healing and re-tear rate confirmed by ultrasound and MRI	45/45 repairs with MSC augmentation had healed by six months <i>vs</i> 30/45 repairs without MSC treatment by 6 mo. Intact rotator cuffs were found in 39/45 patients in the MSC-treated group, but just 20/45 patients in the control group. Patients with a loss of tendon integrity at any time up to the ten-year follow-up milestone received fewer MSCs as compared with those who had maintained a successful repair during the same interval	III
Hernigou <i>et al</i> ^[35]	Tendon-bone interface rotator cuff	NS	NS	<i>n</i> = 125 symptomatic patients. <i>n</i> = 75 control patients. Assessed the level of MSCs in the tuberosity of the shoulder of patients undergoing a rotator cuff repair	Mesenchymal stem cell content at the tendon-bone interface tuberosity was evaluated by bone marrow aspiration collected in the humeral tuberosities of patients at the beginning of surgery	A significant reduction in MSC content (from moderate, 30%-50%, to severe > 70%) at the tendon-bone interface tuberosity relative to the MSC content of the control was seen in all rotator cuff repair study patients. Severity of the decrease was statistically correlated to the delay between onset of symptoms and surgery, number of involved tendons, fatty infiltration stage and increasing patient age	III
Mazzocca <i>et al</i> ^[36]	Rotator cuff	MSCs were exposed to either insulin or tendon-inducing growth factors or were left untreated to serve as a control. The BMA was overlaid onto a 17.5% sucrose gradient and centrifuged for 5 min at 1500 rpm (205 g), and the resulting pink middle layer was obtained. After the isolation of bone marrow, MSCs were exposed to a 1-time dose of 10-9-mol/L, 10-10-mol/L, 10-12-mol/L, or 10-13-mol/L insulin from bovine pancreas or were left untreated to serve as a control	NS	<i>n</i> = 11 patients undergoing arthroscopic RCR. After the determination of the optimal dose of insulin, MSCs were (1) exposed to the hormone insulin; (2) exposed to the growth factors IGF-1, bFGF, and GDF-5, which served as a positive control for MSCs' differentiation into a tendon; or (3) left untreated to serve as a negative control. In the growth factor group, MSCs were treated with a 1-time dose, 10 ng/L, of IGF-1, bFGF, and GDF-5 or 10-10-mol/L insulin	Cell count, gene expression, protein analysis, and immunocytochemical analysis. Confirmation of protein levels was verified on immunocytochemistry analysis by 4 independent evaluators blinded to group assignment	MSCs treated with insulin showed increased gene expression of tendon-specific markers (<i>P</i> > 0.05), increased content of tendon-specific proteins (<i>P</i> > 0.05), and increased receptors on the cell surface (<i>P</i> > 0.05) compared with control cells. Histologic analysis showed a tendon-like appearance compared with the control cells	III
Mazzocca <i>et al</i> ^[37]	Rotator cuff	Isolation 1: one 5 min centrifugation at 1500 rpm in which BMA was overlaid onto a 17.5% sucrose gradient in a 50-mL conical tube followed by extraction of CIPs in the fractional layer. Isolation 2:30 min	Nucleated cells harvested from fractionated layer were counted and plated	<i>n</i> = 23 BMAC harvested through the anchor tunnel of the humeral head during arthroscopy. <i>n</i> = 23 matched controls. Mean time to follow-up was	Reverse transcription polymerase chain reaction analysis, Single Assessment Numeric Evaluation score	Reverse transcription polymerase chain reaction analysis and cellular staining confirmed the osteogenic potential of the connective tissue progenitor cells. There was no statistically	III

		centrifugation at 1500 rpm followed by fractionated layer extraction of CTPs using a Histopaque gradient	on 100 mm Primaria dishes at a concentration of 0.5×10^6 cells/9.6 cm ² then incubated	10.6 ± 6.7 mo in the aspirate group and 10.0 ± 6.2 mo in the control group		significant difference in the Single Assessment Numeric Evaluation score, range of motion measures or post-operative strength measures between groups
Stein <i>et al</i> ^[38]	Achilles	30 to 60 mL of BMA, combined with a standardized mixture of anticoagulant citrate dextrose solution A and separated by centrifugation at 3200 rpm for 15 min. The aspirate was concentrated to yield a volume of 6-9 mL of BMAC	NS	<i>n</i> = 28 open repairs with BMAC. Mean follow up: 29.7 mo. Patients were followed postoperatively at two weeks, six weeks, three months, six months, one year and annually thereafter	Calf atrophy, maximum dorsi- and plantarflexion, and fatigue limit during single-limb heel raise. Functional and activity status was measured in terms of time to walking, light activity (such as cycling or jogging) and return to sport, as with the validated Achilles Total Rupture Score. Self-reported functional status, activity level and ATRS	All patients achieved good or excellent outcomes postoperatively by attaining functional use or return to sport. At final follow-up of 29.7 ± 6.1 mo, mean calf circumference for paired operative and nonoperative extremities was 37.7 ± 2.0 and 38.2 ± 2.0 (difference - 0.5 ± 1.3) cm, respectively, for the 26 patients with single Achilles tendon repair. Walking without a boot was at 1.8 ± 0.7 mo, and participation in light activity was at 3.4 ± 1.8 mo. Overall, 92% (25 of 27) patients returned to their preferred sport successfully at 5.9 ± 1.8 mo. Mean ATRS at final follow-up was 91 (range 72-100) points, with no single mean item score below 8 points. All patients were able to achieve a ROM of neutral dorsiflexion or greater and were able to successfully perform a single-limb heel raise at final follow-up

NS: Not significant; MSC: Mesenchymal stem cell; BMA: Bone marrow aspirate.

mosaicplasty and autologous chondrocyte implantation (ACI) have been utilized to repair chondral damage. First and second-generation ACI procedures, as well as mosaicplasty, have several concerns including donor site morbidity, cost, and lack of availability to all surgeons due to FDA restrictions. The inability of chondrocytes to self-regenerate and self-renew has directed surgeons to investigate alternative biologic augments in the traditional surgical treatment for cartilage defects. cBMA is a rich source of mesenchymal stem cells and has emerged as a treatment strategy to regenerate cartilage defects in OCL and PTOA.

Several *in vivo* models have demonstrated production of type II collagen and hyaline-like repair tissue when introducing MSCs to a cartilage defect, therefore the use of cBMA may provide further stimulation of chondrogenesis when addressing cartilaginous lesions^[19]. There have been a number of studies evaluating the use of cBMA in cartilage regeneration and repair in the animal model. Saw *et al*^[39] investigated the use of cBMA combined with hyaluronic acid in the treatment of full-thickness chondral defects in a goat model and reported hyaline regeneration after 24 wk. Fortier *et al*^[40] evaluated the treatment of

full-thickness cartilage defects with cBMA combined with microfracture in the equine model. Improvements in both macroscopic and histologic scores in tissue treated with cBMA were reported with MRI demonstrating an increase in defect filling and improved repair tissue integration with normal surrounding cartilage^[40].

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilage injury in the clinical setting. Significant clinical improvement in functional scores was demonstrated with the use of cBMA in the treatment of full thickness cartilage injury, post-traumatic osteoarthritis, and osteochondral lesions. Improved clinical and histologic results were reported when cBMA was used as an adjunctive procedure with either microfracture or MACI in the treatment of full thickness chondral lesions^[4,6,7]. On MRI, groups treated with cBMA demonstrated superior cartilage ingrowth with T2 values closer to that of superficial hyaline cartilage when compared to either a control scaffold or MACI alone^[7,10]. These positive results were also demonstrated when utilizing cBMA in the treatment of OCLs. Gobbi *et al*^[18] compared with microfracture with cBMA in the treatment of OCLs and found that microfracture resulted

in 65% normal IKDC at 2 years with decline to 27% at 5 years vs 100% normal at 2 years and no decline at 5 years for patients treated with cBMA. Buda *et al*^[11] reported a higher presence of hyaline like values and lower incidence of fibrocartilage on T2 mapping in patients who received cBMA when compared to those who received ACI. Hannon *et al*^[19] also demonstrated better T2 relaxation values with higher measurements of adjacent cartilage in patients treated with bone marrow stimulation (BMS) with cBMA than those treated with BMS alone. Surprisingly, these positive results were not translated as effectively when evaluating cBMA in the treatment of knee OA. Overall, studies demonstrated positive results with improved pain and clinical scores initially but after one-year follow-up, there was no significant difference between groups receiving cBMA and those that did not.

cBMA in bone regeneration

Nonunion is a catastrophic failure of bone healing, which has gained increased attention over the last two decades. It is estimated that 5% to 10% of fractures will result in delayed union or nonunion resulting in prolonged treatment and repeated hospitalizations, longer rehabilitation protocols, and increased overall morbidity^[41]. The financial burden posed by nonunion remains a challenge for orthopedic surgeons with a total estimated cost of these complications ranging between \$23000 and \$60000 per patient^[42]. Numerous techniques of treating nonunion have been described in the literature including invasive interventions such as open reduction internal fixation with the use of bone graft or bone graft substitutes. Autologous cancellous bone graft derived from the iliac crest is still considered the gold standard graft option due to its high potentials of osteoconduction, osteoinduction, and osteogenesis. However, there is a limit to the amount of bone graft from iliac crest donor site that can be harvested in the reconstruction of large osseous defects. In addition, there are disadvantages of chronic donor site pain, cosmetic concern, and nerve injury, which have been documented in the literature^[33].

The use of cBMA as an adjunctive procedure has gained attention in the treatment of nonunions^[30]. The current literature demonstrates faster healing with greater than 94% union rate when using cBMA combined with allograft compared with conventional autologous cancellous bone graft^[33]. Ismail *et al*^[31] reported similar union rates and outcomes when comparing cBMA and iliac crest autograft. The benefits of cBMA as an adjunctive therapy has also been demonstrated in the treatment of upper extremity long bone nonunion. Garnavos *et al*^[27] described successfully using a minimal invasive approach by injecting cBMA to address humeral diaphyseal fractures, thereby avoiding potential complications associated with the conventional compression plating technique for treating humeral nonunions. Hernigou *et al*^[29] utilized the same minimally invasive technique to treat diabetic ankle fractures nonunion. The diabetic population poses a challenge for orthopedic surgeons with well-documented increased complications and increased time to bony union.

Hernigou *et al*^[29] also reported a union rate of 82.1% with minimal complications in patients who received cBMA compared to a union rate of 62.3% with major complications in patients who received iliac bone graft alone.

Several studies evaluated the effect of BMA concentration on functional outcomes when treating long bone nonunions. Hernigou *et al*^[30] demonstrated that improved time to union with the use of cBMA was potentially related to the number of progenitors in the graft. The amount of bone healing may be directly related to the concentration of cells and the time to union may be indirectly related to the number of cells^[30]. This finding was also supported by Guimaraes *et al*^[28] demonstrating that grafts used in patients whom treatment failed contained significantly lower number of total nucleated cells. Bastos Filho *et al*^[25] compared using cBMA vs whole volume BMA reporting no significant difference in time to union and patient satisfaction score. Although no significant difference was reported, this may be attributed to the small sample size in the cBMA group ($n = 2$) and minimal follow up. In addition, this study highlighted that unprocessed cBMA contains larger volume and fatty content in the graft increasing the risk of pulmonary embolism, therefore the smaller volume of cBMA may in fact be a safer alternative.

cBMA in tendon repair

Tendon injuries typically result from repetitive motions or overuse and can be difficult to treat as many patients either present late or after a prolonged period of non-operative management making treatment challenging due to the chronicity of the injury. It has been well documented that delayed presentation of rotator cuff tears decreases the MSC content and healing potential in patients^[35]. A study by Hernigou *et al*^[35] reported a significant reduction in the number of MSCs at the tendon-bone interface of the greater tuberosity in patients with a rotator cuff injury. In addition, they found that the severity of the decrease in MSC content correlated to increasing patient age, delay between onset of symptoms and surgery, fatty infiltration stage of muscle, and the number of involved tendons^[35]. It has been demonstrated that MSCs have the potential to develop into tenocytes and can be a source of growth factors to establish an environment conducive to tendon tissue regeneration. MSCs in the form of cBMA have been shown to improve the strength and quality of tissue formed when used in tendon repair^[34,35,38].

The current literature has demonstrated that the addition of cBMA can help to heal tendon injuries and at times may decrease the healing time and rate of re-rupture. Hernigou *et al*^[35] reported enhanced healing and improved quality of the repair surface on ultrasound and MRI in patients receiving cBMA during rotator cuff repair. They reported that 100% of the rotator cuff repairs healed by six months compared to 67% in the control group. Furthermore, 87% of the study group had an intact rotator cuff repair compared to 44% of the control at ten year follow up indicating superior outcomes in the longer term^[34]. The benefits of cBMA in tendon repair

have also been demonstrated in the Achilles tendon model. Stein *et al.*^[38] reported excellent results with no re-ruptures, decreased calf atrophy, early mobilization, a 92% return to sport, and better ankle range of motion in patients receiving adjunctive cBMA during Achilles tendon repair compared to those who received no additional treatment.

One of the difficulties in analyzing BMA literature is the variable methods of harvesting, preparing, and concentrating cBMA. Mazzocca *et al.*^[37] devised a novel technique for harvesting BMA in patients undergoing rotator cuff repair with no donor site morbidity. BMA was harvested through the anchor tunnel of the humeral head during routine arthroscopic rotator cuff repair. No additional complications during the procedure, no significant delay in the procedure, and no difference in functional patient outcomes were reported when using this harvest technique^[37]. Lee *et al.*^[43] studied the use of two different concentrations of allogenic cBMA in patients with lateral epicondylitis. They found no significant differences in the changes of elbow pain and performance between the two groups on follow up visits but they did note faster pain improvement and an earlier plateau of performance scores in the group that received a higher concentration of MSCs^[43]. Lastly, Mazzocca *et al.*^[36] showed that MSCs treated with insulin showed statistically significant increase in gene expression of tendon-specific markers, increase in content of tendon-specific proteins, and increase in receptors on the cell surface. Therefore, these studies demonstrate that there are many factors that can increase the potential for tenocyte differentiation and enhanced tendon repair and regeneration.

Level of evidence

Although the literature highlights the potential benefit of cBMA as either a primary or adjunctive treatment strategy in the treatment of cartilaginous lesions, bony defects, and tendon injury, the majority of these studies were of clinical level of evidence III or IV. This review demonstrates the need for future randomized clinical trials with larger numbers of subjects and standardization of harvesting and application. Although several studies evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for each tissue environment.

Summary of MSC mechanism

Adult BMSCs have two primary functions: (1) to differentiate into distinctive end-stage cell types such as bone, cartilage, and tendon; and (2) to secrete bioactive macromolecules that are both immunoregulatory and regenerative^[44]. Every cell has a half-life with a turnover sequence mechanism that gives rise to the phenotypes in complex tissues. This allows for both replacement of cells, as well as, the capacity for differentiation into bone, cartilage, and tendon. BMSCs also have characteristic markers of pericytes, which are smooth muscle vascular

support cells that may play an important role in stem cell differentiation^[44,45]. MSCs also demonstrate trophic activity through secretion of both cytokines and growth factors^[46]. The intrinsic secretory activity of MSCs affords a regenerative environment for the repair of injured or damaged tissues^[44]. Tissue-specific scaffolds have also been utilized in tissue engineering to reform tissues when MSCs are implanted into different tissue sites. The capacity for cell regeneration and repair relies on several additional factors including patient age, extent of injury/damage, and the functional ability of MSCs to grow and repair. Tissue engineering allows for the manipulation of both the delivery of MSCs to targeted tissue sites and the microenvironment for which cells grow in order to enhance differentiation^[44]. Future investigations will continue to focus on harnessing the therapeutic potential of MSCs in tissue specific environments to enhance regeneration and repair of cartilage, bone, and tendon.

Conclusion

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. The studies have demonstrated using cBMA as an adjunctive procedure can result in cartilage healing similar to that of native hyaline tissue, faster time to bony union, and a lower rate of tendon re-rupture. This systematic review also demonstrates discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, and lack of standardized outcome measures. Although several studies evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for each tissue environment. Future studies should attempt to examine the integral factors necessary for tissue regeneration and renewal including stem cells, growth factors and a biologic scaffold.

COMMENTS

Background

Bone marrow aspirate (BMA) has been utilized as a source of bone marrow-derived mesenchymal stem cells (BM-MSC) with its relative ease of harvest, low morbidity, and feasible cost. BMA alone has a relatively low percentage of MSCs and therefore concentrated bone marrow aspirate (cBMA) has gained increased attention. cBMA stimulates tissue regeneration and repair and has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries.

Research frontiers

Current research has focused on the use of cBMA in cartilage, bone, and tendon regeneration and repair. The available literature regarding the use of cBMA in different tissue environments is highly heterogeneous with regards to indications, concentrations and overall functional outcomes. This systematic review attempts to establish proof of concept for the use of cBMA in these biologic environments.

Innovations and breakthroughs

This systematic review demonstrates the potential benefits of utilizing cBMA for the repair of different tissue types in the clinical setting based on the most up-to-date published clinical studies. This systematic review also highlights

discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, variable methods of application of cBMA, and the lack of standardized outcome measures.

Applications

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. The studies have demonstrated using cBMA as an adjunctive procedure can result in cartilage healing similar to that of native hyaline tissue, faster time to bony union, and a lower rate of tendon re-rupture.

Terminology

cBMA: Concentrated bone marrow aspirate; BMA: Bone marrow aspirate concentrated by centrifugation in order to increase the ratio of MSCs.

Peer-review

The authors present a well written systematic review examining the use of BMA in the management of cartilage, bone, and tendon injuries. Overall, the paper is very well organized and reads well.

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Distal triceps injuries (including snapping triceps): A systematic review of the literature

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Abstract

AIM

To review current literature on types of distal triceps injury

and determine diagnosis and appropriate management.

METHODS

We performed a systematic review in PubMed, Cochrane and EMBASE using the terms distal triceps tears and snapping triceps on the 10th January 2017. We excluded all animal, review, foreign language and repeat papers. We reviewed all papers for relevance and of the papers left we were able to establish the types of distal triceps injury, how these injuries are diagnosed and investigated and the types of management of these injuries including surgical. The results are then presented in a review paper format.

RESULTS

Three hundred and seventy-nine papers were identified of which 65 were relevant to distal triceps injuries. After exclusion we had 47 appropriate papers. The papers highlighted 2 main distal triceps injuries: Distal triceps tears and snapping triceps. Triceps tear are more common in males than females occurring in the 4th-5th decade of life and often due to a direct trauma but are also strongly associated with weightlifting and American football. The tears are diagnosed by history and clinically with a palpable gap. Diagnosis can be confirmed with the use of ultrasound (US) and magnetic resonance imaging. Treatment depends on type of tear. Partial tears can be treated conservatively with bracing and physio whereas acute tears need repair either open or arthroscopic using suture anchor or bone tunnel techniques with similar success. Chronic tears often need augmenting with tendon allograft or autograft. Snapping triceps are also seen more in men than women but at a mean age of 32 years. They are characterized by a snapping sensation mostly medially and can be associated with ulna nerve subluxation and ulna nerve symptoms. US is the diagnostic modality of choice due to its dynamic nature and to differentiate between snapping triceps tendon or ulna nerve. Treatment is conservative initially with activity avoidance and if that fails surgical management includes resection of triceps edge or transposition of the tendon plus or minus

ulna nerve transposition.

CONCLUSION

Distal triceps injuries are uncommon. This systematic review examines the evidence base behind diagnosis, imaging and treatment options of distal triceps injuries including tears and snapping triceps.

Key words: Triceps; Distal; Tear; Rupture; Snapping; Partial thickness; Biomechanical; Anatomy

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Core tip: The anatomy, demographics, associations and mechanisms of triceps injuries are presented from the evidence base in the literature. Partial thickness tears and snapping triceps can be difficult to diagnose and appropriate assessment and imaging is essential. The surgical management available in the literature is presented for these uncommon injuries.

Shuttlewood K, Beazley J, Smith CD. Distal triceps injuries (including snapping triceps): A systematic review of the literature. *World J Orthop* 2017; 8(6): 507-513 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i6/507.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i6.507>

INTRODUCTION

Triceps injuries are relatively rare in comparison to other tendons around the elbow and found to be present on 3.8% of elbow magnetic resonance imaging (MRI) studies following elbow injury^[1]. Lateral and medial epicondylitis being the most commonly encountered pathology and distal biceps ruptures presenting more frequently^[2]. However, triceps pathology can cause significant symptoms and due to its less common nature can cause problems with diagnosis and treatment. The aim of this study was to review all current literature and present the best evidence for the management of distal triceps injuries.

MATERIALS AND METHODS

A systematic review was conducted using three search strategies (distal [All Fields] AND triceps [All Fields] AND ("1996/12/31" [PDAT]: "2017/01/10" [PDAT]), (triceps [All Fields] AND tear [All Fields] AND ("1996/12/31" [PDAT]: "2017/01/10" [PDAT]) and (snapping [All Fields] AND triceps [All Fields] AND ("1996/12/31" [PDAT]: "2017/01/10" [PDAT]) in PubMed on January 10th 2017. EMBASE and Cochrane databases were also searched with the same strategy. Additional references were looked for in the citations of the selected studies.

Inclusion criteria

Clinical studies investigating distal triceps injuries in

English.

Exclusion criteria

Review articles; studies in foreign languages; animal studies; double publication of data; letters to authors.

Forty-seven studies were eligible for review and a further three studies were found from citations within the selected studies (Figure 1).

RESULTS

Appraisal of literature

All studies identified by the above search were case series and case reports. Inclusion criteria in the series was generally poorly described. Study number were small with the largest series being only 37 patients^[3]. The tears were assessed by a number of modalities with no standard assessment utilised. Patient reported outcome measures were inconsistently used. As a consequence of this heterogeneity of patient groups, imaging and outcomes reported, reliable synthesis of data is not possible. As such the data is reported in a descriptive manner. Four distinct entities were identified. Acute tears, chronic tears, partial tears (either acute or chronic) and snapping triceps.

Anatomy

The triceps brachii is composed of three muscle bellies. The long head arises off the infraglenoid tubercle of the scapula, the medial head off the posterior aspect of the distal to the spiral groove and the lateral head off the lateral intermuscular septum and the posterolateral aspect of the humerus above the spiral groove. The triceps inserts as a bilaminar tendon over a wide area onto the tip of the olecranon. The average triceps width at its distal insertion, including the tendon and lateral expansion, has been reported as 40.6 mm^[4]. With the tendon being a mean width of 30.6 mm and the distance from its medial edge to the ulna nerve at 10.2 mm^[4]. Its footprint has a mean length of 22.5 mm and a width of 22.7 mm, giving the footprint an area of 466.2 mm²^[4]. In around half of specimens a discrete tendinous portion of the medial triceps deep to the long and lateral head has been reported in cadaveric dissection, with the long and lateral portion forming a tendon superficial to it^[5]. The mean dimensions of this medial head insertion were 16 mm × 4 mm, with a mean area of insertion of 44 mm²^[5]. This study also demonstrated a second variant in the other half of specimens. This had a common combined tendon insertion, but still with the medial fibres deep to the long and lateral head.

Partial tears can be located on the superficial tendon only (combined lateral or long head)^[6-8] but have also been described for the deep portion of the tendon in isolation (medial head)^[5,9,10] the central one third of the tendon in isolation^[10], the lateral portion in isolation^[10], the lateral and central portion combined^[10] or involving the medial and long head insertions with the lateral portion intact^[10,11].

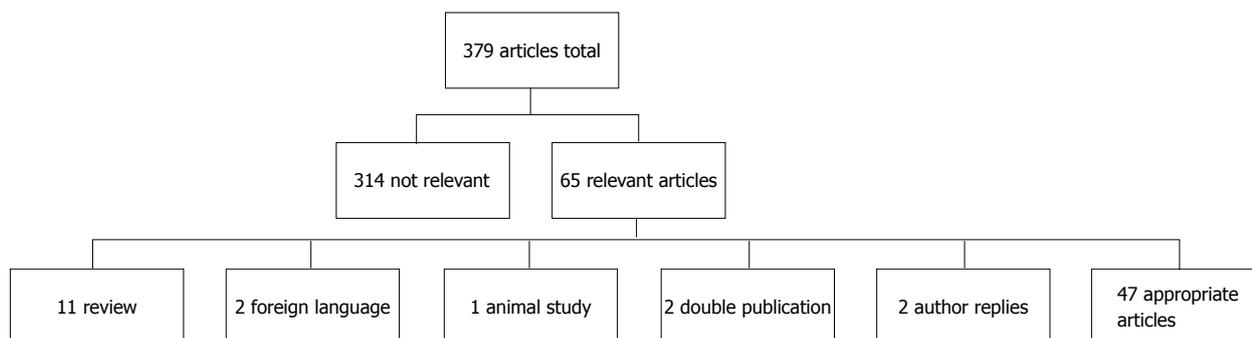


Figure 1 Flow diagram of systematic review process.

Demographics

Triceps tendon ruptures most commonly affect men in the 4th and 5th decades of life. From our pooled results we observed the mean age at rupture to be 47.5 years with a range from 12 to 75 years^[1,3,5,8-28]. There was an 11:1 ratio of males to females ($n = 170$)^[1,3,5,8-29]. Three paediatric cases have been reported in the literature in 12 and 16 year olds^[11,22,26].

Associations

Triceps tendon ruptures are reported to be more common in systemic disease or entities such as chronic renal failure with secondary hypo-parathyroidism, rheumatoid arthritis and diabetes^[8]. Localised infection has also been reported as a cause of rupture^[1]. Interestingly chronic pre-existing posterior elbow pain may be present in up to a third of the patients^[25] and with histology demonstrating chronic tendinopathy features in patients with pre-existing pain^[17]. In traumatic ruptures, one study observed intra-articular fractures or collateral ligament ruptures in 3 of 6 patients (50%) and advised arthroscopic assessment of the joint at the same time as repair^[12]. Concurrent olecranon fractures^[16] and ulna neuropathy secondary to haematoma^[23] have also been observed with traumatic ruptures. Bilateral tears have been reported in patients with a history of anabolic steroid use^[26-28].

Mechanism of injury

The two described mechanisms for acute tears of the triceps are direct contact trauma, such as a fall or hitting fixed resistance with the posterior elbow^[5,14,19,21,25]. Weightlifting^[1,5,17,19,23-25,27,30] was the most common sport associated with acute tears and was often associated with a history of steroid use^[1,23,30]. American football^[3,29] and general sports injuries^[8], as well as direct lacerations^[10] have all also been reported as mechanisms.

Investigation

History and examination form the mainstay of diagnosis. Patients typically present with ecchymosis, pain, swelling, extension lag and a decreased active range of motion^[10,19,21,22,31]. Palpable defects are commonly found and present in up to 80% of patients^[10,21,22,31]. Partial tears may be easily missed as patients may have a good range of active motion, but do typically present with reduced

power on extension of the elbow^[5,6,9,15,18,20,31].

A bony fleck proximal to the olecranon is commonly identified on lateral radiographs^[10,12,17,23,25,27] and is strongly suggestive of a triceps avulsion injury. The bony fleck may also be demonstrated on ultrasound (US)^[7,8]. This radiological sign reflects the intra-operative observation that 33%-73% of patients have avulsion fractures off the olecranon. The remainder of patients have a rupture at the bone tendon junction^[19,25]. Triceps ruptures can be missed on X-ray^[22,25] and both US and magnetic resonance imaging (MRI) have been used to diagnosis complete tears and partial tears^[7,17,19,25,27]. US has been reported to be as accurate as MRI for both complete and partial ruptures, including identifying the location of partial rupture^[8,22].

Treatment

Partial tears: Good results of non-operative treatment even in patients with high functional demands have been reported for the treatment of partial tears. Treatment involves physiotherapy, bracing and avoidance of heavy lifting, pushing or resisted extension for a period of up to 12 wk^[27,31]. Harris *et al.*^[27] reported good results in a single high demand patient with bilateral tears treated with a conservative regime. Platelet rich plasma (PRP) injection has also been advocated for the treatment of partial tears^[18,29]. Cheatham *et al.*^[18] reported the results of a single patient treated with PRP with resolution of pain and return to gym 4 mo after a PRP and physiotherapy regime.

Complete tears

Acute tears: Early primary repair is indicated for complete acute ruptures. Surgery is preferably performed within the first three weeks of injury. Numerous surgical techniques have been reported. These include suture anchors in the triceps footprint^[5,6,21,25,32], bone tunnels^[10,14,20,22,31,33] or a combination of both tunnels and anchors^[15,19,33]. Suture anchors repairs have also been performed arthroscopically^[5,6,32].

Bava *et al.*^[21] reported the results of 5 male patients treated with an open suture anchor technique. They reported a mean American Shoulder and Elbow Surgeons elbow score of 99.2 at an average of 32 mo follow-up^[21]. Lempainen *et al.*^[25] also reported excellent

results in three athletes treated with an open suture anchor technique for acute tendon rupture. van Reit and Neuman^[10] report on the largest series of open bone tunnel repairs. van Reit *et al*^[10] reported the results of 14 patients treated for acute tendon rupture with a bone tunnel technique. Triceps strength was noted to be 4/5 or 5/5 on manual testing in all examined subjects post operatively. Isokinetic testing of ten patients showed that peak strength was, on the average, 82% of that of the untreated extremity. Three re-ruptures were reported in their series^[10]. van Riet *et al*^[10] reported the results of six patients treated with a bone tunnel technique and reported good to excellent results at 12 mo post op with no cases of re-rupture. Kokkalis *et al*^[19], Paniago *et al*^[15] and Paci *et al*^[33], all report good results utilising a combined bone tunnel and suture anchor technique in three separate case reports with no adverse advents reported.

Techniques utilising arthroscopic repairs for acute injuries have been reported by Athwal *et al*^[5] and Ng *et al*^[32]. Athwal *et al*^[5] reported good results for the arthroscopic repair of two acute tears treated with an arthroscopic technique at 2 years' follow-up with respect DASH and Mayo elbow scores. Ng *et al*^[32] did not report outcomes for their technique.

Because of the heterogeneity of types of tear, repair techniques, and outcome measures it is impossible to determine superiority of one technique over another. Generally surgery has been reported to give good improvement in the Morrey score, Mayo, ASES, Oxford elbow scores and DASH^[6,9,14,21,29]. It is reported to significantly reduce pain and improve muscle strength^[6,10,19]. Our pooled results have demonstrated that in three studies, all patients achieved full extension in some studies with flexion to at least 110 degrees^[10,14,15], whereas others achieve an average loss of 7-10 degrees of extension^[10,19]. Three of 14 (21%) re-ruptures were reported in van Reit^[10]'s study, one suture anchor pullout was been reported and needed revision^[14], and one asymptomatic partial re-rupture was detected on post-operative MRI^[6]. Otherwise no re-ruptures were reported or commented on.

Chronic tears: The management of chronic tendon ruptures is a challenge. Occasionally it is possible to repair the tendon using one of the techniques described above. For chronic ruptures with significant tendon retraction, reconstruction with a graft may be required. Grafts include achilles allograft^[11,13] or ipsilateral semitendinous tendon^[10,15], aconeus^[10,11], Latisimus Dorsi^[10], plantaris^[10] and palmaris longus^[10]. Aconeus^[26] and palmaris longus have also been used in augmentation of primary repairs^[20]. Sanchez-Sotelo *et al*^[11] reports the largest case series of chronic rupture reconstruction from the Mayo clinic. They utilised an achilles tendon allograft in three cases or an anconeus muscle flap in four cases. One rotation flap failed six months after operation. At an average of 33 mo follow-up the remaining six patients had no or slight pain, restoration of a functional arc of

movement and normal or slightly decreased power of extension^[11].

Biomechanical studies

Petre *et al*^[34] reported the intact triceps tendon has a peak load to failure of 1741N, in comparison to peak load to failure of 317N, and 593N for a direct repair, and augmented repair tendons respectively. Comparison made between peak load to failure for a trans-osseous cruciate suture technique^[10] and a two bone tunnel and knotless sutures technique^[33], showed a significant difference of 510N for the knotless technique and 283N for the cruciate technique^[35]. A similar peak load to failure of 317N was found for the same trans-osseous cruciate suture technique^[10], but found to be less than the peak load of 593N when the repair was augmented with interwoven flexor carpi radialis^[34]. Interestingly Yeh *et al*^[4] observed no significant difference in the peak load to failure for an "anatomic" double row trans-osseous repair^[4], the trans-osseous cruciate suture technique^[10] and a 2 suture anchor with Krakow-type whip-stitch technique^[4].

Snapping triceps

The snapping triceps occurs in a younger population than triceps tendon rupture with a mean age of 32 years ($n = 30$), ranging from 14-65 years^[36-42] and slightly reduced male to female ratio of 6.5:1^[36-42].

Snapping triceps is a dynamic condition occurring during flexion or extension^[43] of the elbow and is characterised by a snap on both active and passive movement^[43]. The triceps can dislocate on either the medial or lateral side, but is much more common medially^[41]. It can be asymptomatic, cause snapping, elbow pain or ulna neuropathy if dislocating medially^[42-44]. Snapping triceps has been demonstrated to be bilateral in some patients, but is not necessarily symptomatic on both sides^[42]. On the medial side, the snapping can be attributed to the ulna nerve, but snapping may still occur despite ulna nerve transposition^[36]. Snapping triceps may be associated with dislocation of the ulna nerve^[43]. Spinner *et al*^[42] reported all 17 patients in his series (100%) having concurrent dislocation of the ulna nerve with the snapping triceps. Spinner postulated that a snapping ulna nerve and snapping triceps could be differentiated by the angle at which the snapping occurred. The ulna nerve is thought to snap at 70-90 degrees of flexion, whereas the triceps is thought to snap at around 115 degrees of flexion^[43].

Aetiology

Snapping triceps is thought to be due to the medial vector placed on triceps that can occur in cubitus varus and is not thought to be associated with rotational deformities^[44] or muscle activation patterns^[40]. This medial vector is a function of the T angle where the T angle is the angle between the subtended line of pull of triceps (humeral shaft with extended elbow) and the longitudinal line of proximal ulna^[44].

On the medial side snapping triceps can be a com-

plication of displaced supracondylar fractures^[36,45], inherited as an accessory medial triceps or abnormal insertion^[43,46], due to hypertrophy of the medial triceps in athletes^[43,47], associated with hypermobility of the ulna nerve^[42], associated with osseous abnormalities^[42] and as a complication of ulna nerve transposition^[48,49]. On the lateral side it has been associated with a widened triceps tendon inserting more laterally and is treated with resection of the lateral edge^[41].

Diagnosis

US, MRI, CT and sonoelastography have been used for diagnosis^[37-39,43,50]. Ultrasound is the imaging modality of choice of some as can be used as a dynamically to differentiate between a snapping medial triceps and a subluxing medial nerve^[37].

Treatment

Initially conservative treatment can be attempted with NSAIDs and avoidance of provoking activities for 3-6 mo^[43]. If this is unsuccessful surgery can be considered^[36]. Surgery can include resection of the triceps edge, transposition of the tendon, transposing an associated ulnar nerve and correction of cubitus varus^[43,45]. Transposition involves transferring the medial third of the tendon to the lateral position^[36,47].

DISCUSSION

The distal insertion of the triceps anatomy is presented and relates to the different types of tears seen in clinical practice. Distal triceps tears can present in a wide age group, but are much more common in males. They can be associated with a history of steroid use and sports injuries, especially weightlifting. Full thickness tears are usually easily diagnosed on clinical examination, but partial thickness tears can be missed and require imaging with either MRI or US. They can be associated with intra-articular fractures and collateral ligament injuries around the elbow. Some partial thickness tears can be managed with nonsurgical treatment, and full thickness tears can be treated with reattachment *via* anchors or transosseous sutures. Chronic tears may require augmentation with tendinous allograft or autograft. Snapping triceps presents in a younger age group, but still with predominance in males. It is much more common on the medial side and can present with an array of symptoms apart from snapping. It can be misdiagnosed as an ulnar nerve subluxation and can be a cause of persistent symptoms after surgery for this. Treatment initially is non-surgical, but can involve resection of the thickened edge of the tendon, transposition of the tendon and management of the ulnar nerve.

COMMENTS

Background

Distal triceps injuries are rare and therefore can be misdiagnosed and poorly managed. The purpose of the systematic review of distal triceps injuries was

to identify the main injuries that occur and how to diagnose these as well as to identify if there was a consensus or how to manage these.

Research frontiers

The main hotspot identified in this review is the best type of fixation for distal triceps ruptures and if these injuries are being better diagnosed then hopefully there will be larger numbers of cases to investigate clinically with regards to superiority of fixation.

Innovations and breakthroughs

The systematic review has shown that magnetic resonance imaging is superior at confirming the diagnosis of distal triceps tears when there is clinical doubt whereas snapping triceps are better diagnosed using ultrasound due to its dynamic nature. Partial tears of the distal triceps can be initially treated conservatively but full tears need to be treated surgically. Snapping triceps can also be treated conservatively initially but failure to resolve symptoms can be treated surgically with resection of the snapping edge of triceps and/or transposition.

Applications

The systematic review will hopefully make readers more aware of distal triceps injuries and the differential diagnosis of snapping triceps when faced with a subluxing ulna nerve. The authors hope that as there is no gold standard for distal triceps tear fixation that future research can investigate these in the clinical setting as opposed to the cadaveric setting to identify which fixation is superior.

Peer-review

This is a review article on the topic of distal triceps lesions. The authors perform a systematic review of the literature and present their conclusions based only in original data from the search. This is a well written paper that is interesting to read and will be of help to the readers of the journal.

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Worldwide orthopaedic research activity 2010-2014: Publication rates in the top 15 orthopaedic journals related to population size and gross domestic product

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Abstract

AIM

To perform a bibliometric analysis of publications rates in orthopedics in the top 15 orthopaedic journals.

METHODS

Based on their 2015 impact factor, the fifteen highest ranked orthopaedic journals between January 2010 and December 2014 were used to establish the total number of publications; cumulative impact factor points (IF) per country were determined, and normalized to population size, GDP, and GDP/capita, comparison to the median country output and the global leader.

RESULTS

Twenty-three thousand and twenty-one orthopaedic articles were published, with 66 countries publishing. The United States had 8149 publications, followed by the United Kingdom (1644) and Japan (1467). The highest IF was achieved by the United States (24744), United Kingdom (4776), and Japan (4053). Normalized by population size Switzerland lead. Normalized by GDP, Croatia was the top achiever. Adjusting GDP/capita, for publications and IF, China, India, and the United States

were the leaders. Adjusting for population size and GDP, 28 countries achieved numbers of publications to be considered at least equivalent with the median academic output. Adjusting GDP/capita only China and India reached the number of publications to be considered equivalent to the current global leader, the United States.

CONCLUSION

Five countries were responsible for 60% of the orthopaedic research output over this 5-year period. After correcting for GDP/capita, only 28 of 66 countries achieved a publication rate equivalent to the median country. The United States, United Kingdom, South Korea, Japan, and Germany were the top five countries for both publication totals and cumulative impact factor points.

Key words: Bibliometrics; Orthopedic surgery; Impact factor; Publication productivity

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Core tip: The total number of publications by a country is one of the best indicators of research output and productivity, and is an important aspect of clinical excellence. Our results demonstrate that the United States collectively published more articles and accumulated the highest number of impact factors during the study period, and confirms its overwhelming dominance of publications in the fifteen highest ranked journals in orthopaedics. However, after adjusting for population size, Switzerland was the most academically productive nation. Similarly, after adjusting the number of publications with respect to GDP, Croatia was the most productive, and "cost effective" country.

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INTRODUCTION

The total number of publications by a country is one of the best indicators of research output and productivity^[1], and is an important aspect of clinical excellence^[2,3]. Prior bibliographic analyses of orthopaedic academic output have concentrated on the total number of publications per country over various periods ranging from five to ten years^[4-6]. The United States, United Kingdom, Germany, Japan, and South Korea have all consistently ranked among the five most productive countries.

The availability of funding has been shown to result in higher publication output, favoring those countries with a larger population size and more powerful economies^[6,7].

However, no prior bibliographic analysis of orthopaedic research and publications has accounted for population size or economic discrepancies. To adjust for these inconsistencies, the use of the gross domestic product (GDP) and gross domestic product per capita (GDP/capita) may provide a more meaningful result, and allow for a better comparison between countries^[8]. Although the number of publications per capita is one simple way to minimize this inherent bias, it is not the only approach that can be used to determine how academically productive various nations have been. The reciprocal, population size per publication for example, is an equally valid metric that perhaps better expresses this relationship. This reciprocal approach has been employed instead in various iterations throughout this study, to more directly investigate how academically active each nation has been in the field of orthopaedics over the past five years.

Using the fifteen highest rated orthopaedic journals over a five year period, based on the 2015 impact factor, the purpose of this study was threefold: First, to investigate the number of publications and total impact factor from each country, and to then relate these variables to population size, GDP, and GDP per capita. Second, to determine the minimum number of publications required to be comparable to the country producing the median number of publications, when normalized for GDP per capita. Finally, to establish the number of publications that would be required from each country to be equivalent to the country having the highest research output, when normalized for GDP per capita.

MATERIALS AND METHODS

The 2015 Journal Citation report was accessed on the Web of Science (Thomson Reuters, New York, United States)^[9], and the fifteen highest ranked journals based on their 2015 impact factor were selected from the category "orthopedics". Journals were excluded from this list if they were not directly related to the field of orthopedics, or if their main purpose was to provide narrative review articles (Table 1). The abstracts of all articles published in these 15 journals between January 2010 and December 2014 were screened *via* the journals' websites. Letters to the editor, editorials, editorial comments, historical articles, errata, proceeding papers, meeting abstracts, and notes were excluded. Only research articles (levels 1-4), systematic reviews, meta-analyses, non-solicited review articles, and case reports were included. The level of evidence was recorded for each published article; if the journal did not assign the level of evidence, the levels of evidence chart published by the Journal of Bone and Joint Surgery was used^[10]. Each publication was assigned a country of origin defined by the location of the the authors' principal institution, or defined by the country of origin of the corresponding author if the manuscript did not provide details about study location. Any discrepancies were resolved by agreement between the two senior authors.

Table 1 Impact factors (2015 Journal Citation Reports - Thomson Reuters) and number of included publications from 2010-2014

	Journal	Impact points	Publications 2010-2014
1	Journal of Bone and Joint - American Volume	5.280	1833
2	American Journal of Sports Medicine	4.362	1561
3	The Bone and Joint Journal	3.309	1379
4	Arthroscopy - The Journal of Arthroscopic and Related Surgery	3.206	1072
5	Knee Surgery Sports Traumatology Arthroscopy	3.053	1747
6	Journal of Orthopaedic Research	2.986	1301
7	Acta Orthopaedica	2.771	565
8	Clinical Orthopaedics and Related Research	2.765	2027
9	Journal of Arthroplasty	2.666	1873
10	Spine Journal	2.426	1029
11	Spine	2.297	2848
12	Journal of Shoulder and Elbow Surgery	2.289	1324
13	Injury - International Journal of the Care of the Injured	2.137	1133
14	International Orthopaedics	2.110	1477
15	European Spine Journal	2.066	1852
	Total number of publications		23021

Excluded journals: Osteoarthritis Cartilage (No. 3 - IF: 4.165); Journal of Physiotherapy (No.4 - IF: 3.708); Journal of Orthopaedic Sports Physiotherapy (No. 8 - IF: 3.011); Gait Posture (No. 12 - IF: 2.752); Journal of the American Academy of Orthopaedic Surgeons (No. 14 - IF: 2.527); Physical Therapy (No 15 - IF: 2.526); Clinical Journal Sports Medicine (No 19 - IF: 2.268)

The total number of publications and the total number of impact factor points per country were collated.

GDP and GDP per capita were sourced from the World Bank website^[11], and population size was extracted from the CIA World Factbook^[12]. To describe the relationship between population size and the number of publications from a given nation, the population size of that country was divided by their total number of publications. The resulting value describes the population size per publication (PSPP) for that nation; in other words, the calculated value defines the population size per published article, allowing for a better and more direct comparison accounting for population size. Likewise, to define the population size per impact factor point (PSIP) from a given nation the population of that country was divided by their total impact factor points.

Extending this analysis, the gross domestic product was also divided by the total number of publications and impact factor points. These values provide an overview of the gross cost associated with producing a manuscript (GDPP), as well as the gross cost associated with producing one impact factor point (GDPI) for each country. Finally, to simultaneously adjust for population size and economic strength, the GDP per capita was divided by either the total number of publications or by cumulative impact factor points. These values then provide information regarding the gross cost per capita associated with producing a manuscript (GDPCP), or the gross cost per capita associated with producing one impact factor point (GDPCI) for each country.

The list for GDPCP was next ranked lowest to highest to identify the median country. This median country then served as the benchmark, and a correction coefficient was calculated that was normalized to this median country. In this way the number of publications of the median country could then be used to calculate the number of publications every country would need

to produce to be considered equivalent to that median country. Dividing the GDPCP of each country by this normalizing coefficient, (NC_{med}) determined the number of publications that would be necessary for each country to produce to be considered equivalent to the median country. This provides an excellent measure, corrected for economic power (GDP/capita) and population size, of the expected academic output of different countries, normalized to the output of the median nation.

Finally, a very similar process was followed where a correction coefficient was determined that was instead normalized to the publication output of the current global leader in orthopaedic research. The most active country then served as the benchmark, and a coefficient was calculated that was normalized to the academic activity of that country (NC_{top}). This value was then used to calculate the number of publications every country would need to produce to be considered equivalent to the global leader. Dividing the GDPCP of each country by this NC_{top} thus determines the number of publications that would be necessary for each country to produce to be considered equivalent to the global leader. This provides an excellent measure, corrected for economic power (GDP/capita) and population size, of the expected academic output of different countries, normalized to the output of the leading nation.

RESULTS

A total of 23021 orthopaedic articles were published in the 15 highest ranked orthopaedic surgery journals during the study period, between January 2010 and December 2014 (Table 1). Table 2 demonstrates the top ten countries for each of the fifteen journals, in terms of number of publications. The United States was consistently the leading country in ten of the fifteen journals, and was also the most productive country with a total of

Table 2 Top 10 Number of publications per country for each of the 15 selected journals

Journal	1	2	3	4	5	6	7	8	9	10
JBJS-Am	USA-1124	CAN-107	KOR-84	UK-75	JAP-52	HOL-46	GER-45	FRA-39	SWIS-37	AUS-27
Am J Sports Med	USA-819	KOR-117	JAP-84	GER-82	UK-49	AUS-40	ITA-25	CAN-34	SWE-32	SWIS-31
Bjj	UK-545	USA-115	KOR-76	JAP-75	HOL-50	CAN-46	AUS-43	GER-41	CHINA-35	SWIS-31
Arthroscopy	USA-513	KOR-105	JAP-63	GER-55	CHINA-40	CAN-34	ITA-27	UK-22	FRA-18	SPAIN-18
KSSTA	USA-242	GER-195	KOR-157	ITA-149	JAP-144	UK-85	HOL-76	TURK-70	SWE-64	CHINA-62
J Orthopaedic Research	USA-535	JAP-107	GER-96	CAN-69	CHINA-67	UK-48	TAIW-45	AUS-37	KOR-31	HOL-31
Acta Orthopaedica	SWE-125	DEN-76	NOR-69	HOL-59	FIN-40	GER-34	UK-34	USA-21	JAP-17	AUS-13
CORR	USA-1155	CAN-110	KOR-98	JAP-71	UK-60	SWIS-60	GER-59	FRA-49	ITA-45	HOL-33
J Arthroplasty	USA-934	JAP-136	CAN-124	UK-117	KOR-114	AUS-72	CHINA-64	GER-37	SPAIN-29	HOL-26
Spine Journal	USA-491	KOR-78	CHINA-62	JAP-56	CAN-48	HOL-29	UK-24	SWIS-23	INDIA-21	ITA-21
Spine	USA-1168	JAP-307	CHINA-255	CAN-166	KOR-163	UK-73	GER-65	AUS-59	HOL-57	TAIW-49
J Shoulder Elbow Surg	USA-659	JAP-79	UK-72	KOR-65	CAN-60	SWIS-49	FRA-42	GER-36	ITA-35	BELG-34
Injury	UK-215	USA-126	GER-114	ITA-89	CHINA-78	HOL-57	GREEC-48	SPAIN-37	SWIS-34	AUS-34
International Orthopaedics	GER-232	CHINA-198	UK-101	USA-97	FRA-97	JAP-81	ITA-76	A-76	CRO-54	SWIS-49
European Spine Journal	CHINA-251	JAP-182	GER-161	USA-150	ITA-133	UK-124	FRA-104	KOR-90	SWIS-84	HOL-81

Excluded journals: Osteoarthritis Cartilage (No. 3 - IF: 4.165); Journal of Physiotherapy (No.4 - IF: 3.708); Journal of Orthopaedic Sports Physiotherapy (No. 8 - IF: 3.011); Gait Posture (No. 12 - IF: 2.752); Journal of the American Academy of Orthopaedic Surgeons (No. 14 - IF: 2.527); Physical Therapy (No 15 - IF: 2.526); Clinical Journal Sports Medicine (No 19 - IF: 2.268). USA: United States; UK: United Kingdom; SWE: Sweden; GER: Germany; Can: Canada; Kor: Korea; JAP: Japan.

8149 publications; they were followed by the United Kingdom and Japan, having 1644 and 1467 publications, respectively. A total of 66 countries had published at least one article (Table 3) during the study period. Similar to the number of publications, the United States also accumulated the largest number of impact factor points (24744) followed by the United Kingdom (4776) and Japan (4053) (Table 3). Overall, the top five countries were the United States, United Kingdom, Japan, South Korea, and Germany, and these countries were together responsible for 60.4% of all publications, and 61.4% of all impact factor points.

However, when adjusted for population size (PSPP), Switzerland was the leading country with one publication per 15300 people, followed by Norway with one publication per 21100, and Denmark with one publication per 22300. Switzerland was also the leader in the category of impact factor (PSPI), accumulating one impact factor point per 5400 people, followed by Norway with one impact factor point per 6700, and Holland with one impact factor point per 7800 (Table 4).

The number of publications, when normalized with respect to economic activity (GDPP), was highest for Croatia, with one publication per \$772000, followed by Korea with \$1042000, and Greece with \$1294000. For impact factor (GDPI) Croatia was again the leader, and produced one impact factor point per \$359000, followed by South Korea with \$375000, and Holland with \$408000 (Table 5). When adjusting for both GDP and population simultaneously (GDPCP) China was the leader, producing one publication per \$6200, followed by India with \$6400, and the USA with \$6700. The United States was the leader in the impact factor category (GDPCI), producing one impact factor point per \$2200, followed by India with \$2400 and China \$2500 (Table 6). However, these results need to be interpreted carefully, and it is probable that the extremely large population

size of both China and India resulted in data distortion.

When ranked with respect to GDPCP Poland was the median country, publishing 61 articles, and served as the median academic output benchmark. The results showed that 28 countries were able to achieve this academic output (Table 7). As an example, for the United States to achieve this benchmark a minimum of 235 publications were required; however, a total of 8149 publications were recorded, which was 3,468% greater than the requisite number. For Norway, to achieve this benchmark a minimum of 414 publications were required, but only 240 publications were recorded; this was only 58% of the number of publications necessary to have achieved an academic output equivalent to the median activity (Table 7).

The United States was the leader when ranked with respect to GDPCP, publishing 8,149 articles, and served as the leading academic output nation. Using the NC_{top} to calculate the required number of publications to be equivalent with the global research leader (United States), only two other countries, China and India, were considered equivalent or superior (Table 8). For example, for Korea 4174 publications would have been needed to have an academic output equivalent to that of the United States, but only 1354 articles (32%) were published. Again, these results need to be interpreted carefully, and it is highly probable that the large population size of both China and India resulted in data distortion.

DISCUSSION

These results demonstrate that the United States collectively published more articles and accumulated the highest number of impact factor points during the study period from 2010 through 2014, and confirms its overwhelming dominance of publications in the fifteen highest ranked journals in the field of orthopaedics.

Table 3 Highest number of publications and impact points for each country

Rank	Country	Publications	Rank	Country	Impact points
1	United States	8149	1	United States	24744
2	United Kingdom	1644	2	United Kingdom	4776
3	Japan	1467	3	Japan	4053
4	South Korea	1354	4	South Korea	3765
5	Germany	1272	5	Germany	3491
6	China	1222	6	China	3034
7	Canada	930	7	Canada	2774
8	Italy	737	8	Holland	2155
9	Holland	663	9	Italy	1982
10	France	548	10	Switzerland	1507
11	Switzerland	527	11	Australia	1412
12	Australia	485	12	France	1382
13	Sweden	403	13	Sweden	1187
14	Spain	311	14	Spain	833
15	Austria	295	15	Austria	801
16	Taiwan	264	16	Norway	755
17	Denmark	254	17	Taiwan	729
18	India	246	18	Denmark	710
19	Norway	240	19	India	646
20	Turkey	235	20	Turkey	630
21	Belgium	219	21	Belgium	614
22	Greece	182	22	Greece	508
23	Finland	167	23	Brazil	408
24	Brazil	147	24	Finland	402
25	Hong Kong	130	25	Hong Kong	371
26	Israel	119	26	Israel	315
27	Ireland	98	27	Singapore	295
28	Singapore	84	28	Ireland	262
29	New Zealand	78	29	New Zealand	227
30	Croatia	74	30	Iran	174
31	Egypt	68	31	Egypt	168
32	Iran	65	32	Croatia	159
33	Poland	61	33	Poland	141
34	Thailand	52	34	Thailand	128
35	Czech Republic	39		Slovenia	128
36	Slovenia	32	35	Czech Republic	84
37	Hungary	29	36	Hungary	71
38	Portugal	25	37	Portugal	71
39	Chile	24	38	Chile	66
40	Malaysia	23	39	Malaysia	63
41	South Africa	21	40	South Africa	59
42	Argentina	20	41	Argentina	55
43	Serbia	19	42	Serbia	43
44	Luxemburg	14	43	Luxemburg	43
45	Saudi Arabia	12	44	Saudi Arabia	29
46	Mexico	10	45	Mexico	26
47	Lebanon	9	46	Lebanon	23
	Lithuania	9		Lithuania	23
	Russia	9	47	Russia	21
48	Estonia	7	48	Estonia	17
48	Nigeria	7	49	Nigeria	15
49	Pakistan	6	50	Romania	13
	Romania	6		Philippines	13
50	Columbia	5	51	Pakistan	12
	Kuwait	5	52	Columbia	11
	Philippines	5		Tunisia	11
	Tunisia	5	53	Kuwait	9
51	Bulgaria	3	54	Iceland	7
	Iceland	3	55	Bulgaria	6
	Iraq	3		Iraq	6
52	Malawi	2	56	Malawi	5
	Morocco	2		Nepal	5
	Nepal	2		Uganda	5
53	Ethiopia	1	57	Morocco	4
	Sudan	1	58	Ethiopia	3
	Uganda	1		Sudan	3

Table 4 Number of publications (PSPP) and impact (PSPI) normalized for population size (publication/impact point per in thousand populations)

Rank	Country	PSPP	Rank	Country	PSIP
1	Switzerland	15.3	1	Switzerland	5.4
2	Norway	21.1	2	Norway	6.7
3	Denmark	22.3	3	Holland	7.8
4	Sweden	24.1	4	Denmark	7.9
5	Holland	25.4	5	Sweden	8.2
6	Austria	28.7	6	Austria	10.6
7	Finland	32.3	7	Canada	12.1
8	Canada	35.9	8	Luxemburg	12.6
9	Luxemburg	38.9	9	United States	12.9
10	South Korea	38.9	10	United Kingdom	13.4
11	United Kingdom	38.9	11	Finland	13.4
12	United States	39.3	12	South Korea	13.6
13	Australia	44.3	13	Australia	15.2
14	Belgium	51.1	14	Belgium	18.2
15	Hong Kong	55.3	15	Singapore	18.3
16	New Zealand	57.3	16	Hong Kong	19.4
17	Croatia	57.8	17	New Zealand	19.7
18	Greece	60.4	18	Greece	21.6
19	Germany	63.1	19	Germany	23
20	Singapore	64.3	20	Slovenia	24
21	Slovenia	64.3	21	Ireland	24.3
22	Ireland	65.1	22	Israel	25.6
23	Israel	67.7	23	Croatia	27
24	Italy	82.4	24	Italy	30.7
25	Japan	86.8	25	Japan	31.4
26	Taiwan	88.4	26	Taiwan	32
27	Iceland	107.7	27	Iceland	46.1
28	France	121.5	28	France	48.1
29	Spain	151.9	29	Spain	56.7
30	Estonia	185.7	30	Estonia	76.5
31	Czech Republic	269.2	31	Turkey	121.7
32	Turkey	326.2	32	Czech Republic	125
33	Lithuania	333.3	33	Lithuania	130.4
34	Hungary	341.4	34	Hungary	139.4
35	Serbia	379.5	35	Portugal	147.3
36	Portugal	418.4	36	Serbia	167.7
37	Lebanon	551.8	37	Lebanon	215.9
38	Poland	631.6	38	Chile	247.6
39	Kuwait	673.8	39	Poland	272
40	Chile	680.8	40	Kuwait	374.3
41	China	1110.5	41	Iran	443.5
42	Egypt	1176.5	42	China	447.3
43	Iran	1187.3	43	Malaysia	471.7
44	Thailand	1283.1	44	Egypt	476.2
45	Malaysia	1292.1	45	Brazil	491.2
46	Brazil	1363.2	46	Thailand	521.2
47	Argentina	2072.5	47	Argentina	753.6
48	Tunisia	2178.0	48	South Africa	915.2
49	Saudi Arabia	2402.5	49	Tunisia	990
50	Bulgaria	2421.7	50	Saudi Arabia	12108.3
51	South Africa	2571.4	51	Bulgaria	15353.8
52	Romania	3326.7	52	Romania	15353.9
53	India	5089.4	53	India	19380.8
54	Malawi	8180.0	54	Malawi	32720
55	Ethiopia	9410.0	55	Columbia	43649
56	Columbia	9602.8	56	Mexico	45536.5
57	Iraq	11140	57	Nepal	55600
58	Mexico	11839.5	58	Iraq	55700
59	Nepal	13900	59	Russia	68333.3
60	Russia	15944.4	60	Uganda	75160.0
61	Morocco	16505	61	Philippines	75684.6
62	Philippines	19678	62	Morocco	82525.0
63	Nigeria	24800	63	Nigeria	115733.3
64	Pakistan	32695.7	64	Sudan	126533.3
65	Uganda	37580	65	Pakistan	163478.3
66	Sudan	37976	66	Ethiopia	313666.7

Table 5 Number of publications (GDPP) and impact points (GDPI) related to GDP (in thousand dollars)

Rank	Country	GDPP	Rank	Country	GDPI
1	Croatia	772	1	Croatia	359
2	South Korea	1042	2	South Korea	375
3	Greece	1294	3	Holland	408
4	Holland	1326	4	Greece	464
5	Switzerland	1330	5	Switzerland	465
6	Denmark	1348	6	Sweden	481
7	Sweden	1417	7	Denmark	482
8	Slovenia	1417	8	Slovenia	576
9	Austria	1547	9	Austria	579
10	Finland	1630	10	United Kingdom	626
11	United Kingdom	1818	11	Canada	644
12	Taiwan	1852	12	Norway	662
13	Canada	1920	13	Taiwan	671
14	Norway	2083	14	Finland	677
15	Malawi	2129	15	United States	704
16	United States	2138	16	Hong Kong	784
17	Hong Kong	2237	17	New Zealand	829
18	Serbia	2309	18	Malawi	852
19	New Zealand	2412	19	Belgium	866
20	Belgium	2427	20	Israel	970
21	Ireland	2559	21	Ireland	975
22	Israel	2569	22	Serbia	1020
23	Italy	2905	23	Australia	1032
24	Australia	3003	24	Singapore	1044
25	Germany	3041	25	Italy	1080
26	Japan	3137	26	Germany	1108
27	Turkey	3398	27	Japan	1135
28	Singapore	3665	28	Turkey	1267
29	Estonia	3784	29	Luxemburg	1509
30	Egypt	4213	30	Estonia	1558
31	Spain	4442	31	Spain	1658
32	Hungary	4471	32	Egypt	1706
33	Luxemburg	4634	33	Hungary	1949
34	Lebanon	5081	34	Lebanon	1988
35	France	5163	35	France	2047
36	Czech Republic	5263	36	Lithuania	2102
37	Lithuania	5372	37	Iceland	2434
38	Iceland	5679	38	Czech Republic	2444
39	Iran	6543		Iran	2444
40	Thailand	7785	39	Thailand	3163
41	India	8327	40	India	3171
42	China	8474	41	Portugal	3241
43	Poland	8933	42	China	3413
44	Portugal	9204	43	Poland	3865
45	Tunisia	9722	44	Chile	3910
46	Nepal	9884	45	Nepal	3954
47	Chile	10752	46	Tunisia	4419
48	Malaysia	14700	47	Malaysia	5367
49	Brazil	15960	48	Uganda	5400
50	South Africa	16671	49	Brazil	5750
51	Bulgaria	18906	50	South Africa	5934
52	Argentina	26833	51	Bulgaria	9452
53	Uganda	26998	52	Argentina	9757
54	Kuwait	32722	53	Romania	15311
55	Romania	33174	54	Kuwait	18179
56	Pakistan	40605	55	Ethiopia	18540
57	Morocco	55004	56	Pakistan	20303
58	Ethiopia	55621	57	Philippines	21906
59	Philippines	56955	58	Sudan	24734
60	Saudi Arabia	62187	59	Saudi Arabia	25733
61	Sudan	74202	60	Morocco	27502
62	Iraq	74503	61	Columbia	34340
63	Columbia	75448	62	Iraq	37251
64	Nigeria	81215	63	Nigeria	37901
65	Mexico	129469	64	Mexico	49796
66	Russia	206733	65	Russia	88600

Table 6 Number of publications (GDPCP) and impact points (GDPCI) related to GDP per capita (in thousand dollars)

Rank	Country	GDP Rank	Country	GDPI
1	China	6.2	United States	2.2
2	India	6.4	India	2.4
3	United States	6.7	China	2.5
4	South Korea	20.7	South Korea	7.4
5	Japan	24.7	Japan	8.9
6	United Kingdom	28.2	United Kingdom	9.7
7	Germany	37.6	Germany	13.7
8	Turkey	44.7	Turkey	16.7
9	Egypt	47	Italy	17.6
10	Italy	47.4	Canada	18.1
11	Canada	54	Egypt	19
12	Brazil	77.4	Holland	24.2
13	France	78	Brazil	27.9
14	Holland	78.7	France	30.9
15	Iran	83.7	Iran	31.3
16	Spain	95.4	Spain	35.6
17	Thailand	114.9	Greece	42.3
18	Greece	118.1	Taiwan	43.8
19	Taiwan	120.8	Australia	43.9
20	Malawi	127.5	Thailand	46.7
21	Australia	127.7	Sweden	49.6
22	Sweden	146.2	Malawi	51
23	Switzerland	162.4	Switzerland	56.8
24	Austria	173.5	Austria	63.9
25	Croatia	182.1	Belgium	77.1
26	Belgium	216.2	Croatia	84.7
27	Pakistan	219.5	Denmark	85.5
28	Poland	235.1	Poland	101.7
29	Denmark	239	Hong Kong	108.3
30	Finland	298.3	Pakistan	109.7
31	South Africa	308.7	South Africa	109.9
32	Hong Kong	309	Israel	118.1
33	Israel	312.7	Finland	123.9
34	Serbia	323.8	Norway	128.9
35	Nepal	351	Nepal	140.4
36	Norway	405.4	Uganda	
37	Nigeria	457.6	Serbia	143.1
38	Hungary	483.7	New Zealand	166.9
39	New Zealand	485.8	Malaysia	179.5
40	Malaysia	491.6	Singapore	190.8
41	Czech Republic	500.8	Ethiopia	191.3
42	Ireland	554.8	Hungary	197.6
43	Ethiopia	574	Ireland	207.5
44	Philippines	574.4	Nigeria	213.5
45	Chile	605.3	Chile	220.1
46	Argentina	625.4	Philippines	220.9
47	Singapore	670	Argentina	227.4
48	Uganda	715	Czech Republic	232.5
49	Slovenia	750	Slovenia	279.1
50	Tunisia	884.2	Portugal	311.7
51	Portugal	885.3	Sudan	371.7
52	Mexico	1032.6	Mexico	397.1
53	Sudan	1115	Tunisia	401.9
54	Lebanon	1117.6	Lebanon	437.3
55	Russia	1415.1	Russia	606.5
56	Columbia	1580.8	Lithuania	717.8
57	Morocco	1595	Columbia	718.5
58	Romania	1666.2	Romania	769
59	Lithuania	1834.1	Morocco	797.5
60	Saudi Arabia	2013.4	Saudi Arabia	833.1
61	Iraq	2140	Iraq	1070
62	Bulgaria	2617	Estonia	1186
63	Estonia	2880.3	Bulgaria	1308.5
64	Luxemburg	8333.1	Luxemburg	2713.3
65	Kuwait	8718.8	Kuwait	4843.8
66	Iceland	17334.5	Iceland	7429.1

Table 7 Number of publications required to equivalent with the median (Poland *n* = 61) using the benchmark measure

Rank	Country	Published publications 2010-2014	Papers to be published	% of published papers
1	China	1222	32	3783
2	India	246	7	3656
3	United States	8149	235	3505
4	South Korea	1354	119	1137
5	Japan	1467	235	952
6	United Kingdom	1644	197	833
7	Germany	1272	203	625
8	Turkey	235	45	525
9	Egypt	68	14	499
10	Italy	737	148	496
11	Canada	930	214	435
12	Brazil	147	48	303
13	France	548	182	301
14	Holland	663	222	298
15	Iran	65	23	280
16	Spain	311	126	246
17	Thailand	52	25	204
18	Greece	182	91	198
19	Taiwan	264	136	194
20	Malawi	2	1	184
21	Australia	485	263	183
22	Sweden	403	251	160
23	Switzerland	527	364	145
24	Austria	295	218	135
25	Croatia	74	57	129
26	Belgium	219	201	109
27	Pakistan	6	6	100
28	Poland	61	61	100
29	Denmark	254	258	98
30	Finland	167	212	79
31	South Africa	21	28	76
32	Hong Kong	130	171	76
33	Israel	119	158	75
34	Serbia	19	26	72
35	Nepal	2	3	67
36	Norway	240	414	58
37	Nigeria	7	14	50
38	Hungary	29	60	49
39	New Zealand	78	161	48
40	Malaysia	23	48	47
41	Czech Republic	39	83	47
42	Ireland	98	231	42
43	Ethiopia	1	2	50
44	Philippines	5	12	41
45	Chile	24	62	39
46	Argentina	20	53	38
47	Singapore	84	239	35
48	Uganda	1	3	33
49	Slovenia	32	102	31
50	Tunisia	5	19	26
51	Portugal	25	94	26
52	Mexico	10	44	23
53	Sudan	1	5	20
54	Lebanon	9	43	21
55	Russia	9	54	17
56	Columbia	5	34	15
57	Morocco	2	14	15
58	Romania	6	42	14
59	Lithuania	9	70	13
60	Saudi Arabia	12	103	12
61	Iraq	3	27	11
62	Bulgaria	3	33	9
63	Estonia	7	86	8.1
64	Luxemburg	14	496	2.8
65	Kuwait	5	185	2.7
66	Iceland	3	221	1.4

Table 8 Number of publications required to equivalent with the leader (United States) the benchmark measure

Rank	Country	Published publications 2010-2014	Papers to be published	% of published papers
1	China	1222	1132	108
2	India	246	236	104
3	United States	8149	8149	100
4	South Korea	1354	4174	32
5	Japan	1467	5402	27
6	United Kingdom	1644	6915	24
7	Germany	1272	7138	18
8	Turkey	235	1569	15
9	Egypt	68	477	14
10	Italy	737	5210	14
11	Canada	930	7498	12
12	Brazil	147	1699	8.6
13	France	548	6378	8.6
14	Holland	663	7787	8.5
15	Iran	65	812	8
16	Spain	311	4429	7
17	Thailand	52	892	5.8
18	Greece	182	3208	5.6
19	Taiwan	264	892	5.5
20	Malawi	2	38	5.2
21	Australia	485	9243	5.1
22	Sweden	403	8797	4.6
23	Switzerland	527	12775	4.1
24	Austria	295	7640	3.9
25	Croatia	74	2011	3.7
26	Belgium	219	7068	3.1
27	Pakistan	6	197	3
28	Poland	61	2141	2.8
29	Denmark	254	9091	2.7
30	Finland	167	7436	2.2
31	South Africa	21	968	2.1
	Hong Kong	130	5995	2.1
	Israel	119	5553	2.1
	Serbia	19	918	2.1
32	Nepal	2	105	1.9
33	Norway	240	14523	1.6
34	Nigeria	7	487	1.5
35	Hungary	29	2094	1.4
	New Zealand	78	5656	1.4
	Malaysia	23	1688	1.4
36	Czech Republic	39	2915	1.3
	Ireland	98	8115	1.2
	Ethiopia	1	86	1.2
	Philippines	5	429	1.2
37	Chile	24	2168	1.1
	Argentina	20	1867	1.1
38	Singapore	84	8401	1
39	Uganda	1	107	0.94
40	Slovenia	32	3582	0.89
41	Tunisia	5	660	0.76
42	Portugal	25	3303	0.75
43	Mexico	10	1541	0.65
44	Sudan	1	166	0.6
	Lebanon	9	1502	0.6
45	Russia	9	1901	0.47
46	Columbia	5	1180	0.42
47	Morocco	2	476	0.42
48	Romania	6	1492	0.4
49	Lithuania	9	2464	0.36
50	Saudi Arabia	12	3606	0.33
51	Iraq	3	958	0.31
52	Bulgaria	3	1172	0.26
53	Estonia	7	3009	0.23
54	Luxemburg	14	17412	0.08
	Kuwait	5	6507	0.08
55	Iceland	3	7762	0.04

However, after adjusting for population size, Switzerland was the most academically productive nation. Similarly, after adjusting the number of publications with respect to GDP, Croatia was the most productive, and "cost effective" country.

Over the last 30 years, English has become the international language of medical science^[13]. Of the current top 50 highest impact journals in orthopaedics, 45 are based in English speaking countries; all 50 of these journals publish their manuscripts in English only^[9]. The majority of those countries where English is the primary language also enjoy a high standard of living, and would appear to have advantages in terms of research funding and academic opportunity. Although this suggests an inherent bias towards authors from those countries where English is the principal language, over this 5-year period articles were published by a total of 66 different countries; in many of those countries English is not the main language. Strategies were employed here to attempt to eliminate or minimize any of these potential socio-economic advantages, and therefore obtain a better measure of the relative academic activity and orthopedic research output from various nations around the world. This study has revealed superior academic activity outcomes has been achieved by several of these countries, when adjusted for population size and GDP.

Both GDP and GDP per capita are indicators of economic strength, representing the value of all goods and services produced over a specified time period^[7]. The cost of producing a research paper per GDP/capita is theoretically a better indicator of a country's research productivity, one that takes into consideration some of the socio-economic conditions that might favor more populous or prosperous nations. After adjusting for GDP per capita both India and China were the leading countries, but due to their inordinately large population size the calculated figures are most likely biased. After eliminating these two countries, the United States, South Korea, Japan, Germany, and the United Kingdom ranked among the top five countries with the highest number of both publications and impact factor points. One possible explanation could be that the research output of these countries is directly related to economic vitality, although none of these five leading countries had the highest GDP per capita. For example, the United States, ranked 8th, Germany 15th, the United Kingdom 17th, Japan 23rd and South Korea 27th. Earlier research by Meo *et al*^[7] and Halpenny *et al*^[8] also failed to demonstrate a correlation between GDP per capita, total number of publications, and h-index in different science fields and social science disciplines. However, they were able to confirm a strong and positive correlation between the number of publications and the percentage of GDP spent on research.

This study introduced a new metric to bibliographic analysis, normalizing the collective publications and impact factor points of individual nations to that of the output of the median nation, after first correcting for both population size and economic activity. Although

this measure has not been validated yet and may lack the robustness of standard citation and content analysis, it is nevertheless similar to other accepted bibliometric measures. In our opinion it facilitates a better comparison between countries, by defining the number of publications that would be necessary for a particular country to produce to have an output equivalent to that of the median nation.

After normalizing research output, 28 countries exceeded this benchmark, whereas 38 were below the level of the median nation. These findings unequivocally demonstrated the dominance of the United States compared to all other countries. To have an output equivalent to the median nation, Poland, it was necessary for the United States to publish 235 articles: However, they collectively published 8149 and were the global leader by an overwhelming margin. China and India were ranked even higher by this metric, but this might demonstrate an inherent limitation of this methodology related to population size. Those countries with a very low GDP per capita, a large population size, and a relatively large number of publications will most likely result in a ceiling effect, and normalizing research output to that of the median nation would thus be unreliable. Therefore, further research is required to better define the extent of this problem and to validate this approach.

Research output is an important determinant of economic growth, and an increase in service delivery, education, and innovation is often an indicator of a society's shift from a producing economy to a knowledge-based economy^[14]. In fact, publications of scientific literature can indicate a nation's growth and progress in science and technology^[5]. Moir *et al.*^[15] observed a 21% increase in orthopaedic publications from 1980 to 1994 in six selected journals. More recently, Bosker and Verheyen^[4] also reported an increased number of orthopaedic publications in the 15 major clinical orthopaedic journals from 2000-2004, with a total of 13311 articles. The present bibliometric analysis counted over 23000 articles, representing a 73% increase over a 10 years interval. Several authors have previously performed subspecialty analyses^[1,16]. Luo *et al.*^[1] showed that high income countries published 90% of all articles in foot and ankle research, with the United States publishing the highest number; however, Switzerland took the lead when it was normalized to population size and GDP. Liang *et al.*^[16] reported that the United States published the largest number of publications in the subspecialty of arthroscopy, but when adjusted for population size Switzerland was again the country with the highest number of publications. Similar findings were reflected in our results, although in their study Korea ranked first when academic output was adjusted for GDP.

Bibliometric analysis has also been performed by other disciplines. In emergency medicine, the United States was the most productive country followed by the United Kingdom and Australia. When normalized to population size, Australia had the highest number of articles per million persons, but Germany had the highest mean impact factor and citations^[17,18]. In the specialty of

critical care medicine, the United States has published the most articles, followed by the United Kingdom, Germany, France, and Australia. The United States also had the highest number of randomized controlled trial publications, the highest total impact factor points, and the highest total citations^[17,18]. Halpenny *et al.*^[8] performed a bibliographic analysis in radiology. In their study, the United States published 42% of the 10,925 papers, followed by Germany and Japan. When corrected for GDP, Switzerland (0.925), Austria (0.694), and Belgium (0.648) produced the most publications per billion of GDP. Robert *et al.*^[19] evaluated the pain medicine literature over a period of 30 years and reported that the United States, the United Kingdom and Germany were the highest ranking countries. The pattern of publication rates are comparable to orthopaedics and these findings can possibly be generalized to other disciplines of medicine.

This study has recognized limitations. While the total number of articles and cumulative impact factor points was determined for each nation, the value of individual articles was not assessed; it is possible that there was a significant discrepancy in the manuscript quality between countries, potentially introducing selection bias. Even the selection of impact factor as an outcome measure to evaluate publication quality has been criticized, as it is determined by technicalities that are not related to the scientific value of the research studies themselves^[20,21]. Citation analysis was also not performed, and it is acknowledged that the number of citations are a proxy measure of influence reflecting the recognition and quality of the published research by its peers^[22]. However, using the impact factor reflects citation counts indirectly, as article citation rates ultimately determine the journal's impact factor^[20]. Nevertheless, overcitation, biased citing, audience size, biased data, and ignorance of the literature are additional common criticisms of bibliometric studies^[23]. Another potential limitation of this method is that the research output of the median nation was based on data collected over a specific five-year period from the fifteen currently highest ranked orthopaedic journals. These results will almost certainly change if more journals are included, or the time interval is either extended or shortened.

In conclusion, the results of this study demonstrate that five countries were responsible for 60% of the research output in orthopaedic surgery over a 5-year period, when restricted to the 15 highest ranked journals specific to the field. Only 28 of 66 countries were able to achieve a publication rate equivalent to that of the median nation, after first correcting for GDP per capita. The United States was unequivocally the global leader when judged by this measure, and exceeded the median production by more than 34 times. Although China and India ranked the highest after correcting for both GDP and population size, this probably reflects the inordinately large populations of both countries. The United States, United Kingdom, South Korea, Japan, and Germany placed in the top five countries with respect to both publication totals and cumulative impact factor points.

COMMENTS

Background

Bibliographic analysis of academic output has been performed for many indications and can be an indicator for academic excellence. However most studies have focussed on the total number of publications without accounting for gross domestic product or economic discrepancies between countries. The primary aim of this study was therefore to investigate the number of publications and total impact factor from each country, and to then relate these variables to population size, gross domestic product (GDP), and GDP per capita. Secondly they determined the minimum number of publications required to be comparable to the country producing the median number of publications, when normalized for GDP per capita. The final aim was to establish the number of publications that would be required from each country to be equivalent to the country having the highest research output, when normalized for GDP per capita.

Research frontiers

Over the last 30 years English has become the international language of medical science. In Orthopedics 45 of the 50 highest impact orthopaedic journals are based in English countries. Based on these facts the majority of publications in these journals should come from primary English speaking countries.

Innovations and breakthroughs

Based on the total number of publications and impact points the United States was the undebated leader for both the total number of publications and impact points. However when adjusting for publication size and GDP per capita, it was Switzerland respectively Croatia which were the most productive nations. When using a newly introduced benchmark to adjust for both population size and GDP, 28 countries exceeded and 38 nations were below the median nation.

Applications

This review suggests that the total number of publications and impact points are not representative of true research output and other factors should be included into bibliometric analysis.

Terminology

Bibliometric analysis is based on quantitative variables such as number of publications, impact points and citation rates. Analysis can be performed at the macro-level comparing countries performances, at the middle level analyzing Universities or other institutional output or at the microlevel investigating research output of departments or individuals.

Peer-review

The authors present a very interesting paper on the worldwide orthopaedic research activity. They relate the scientific production with the GDP, and per capita GDP. This sort of information, although known for general science, was unknown in the orthopaedic field. The relevance of this paper is not only related to science but also to politics.

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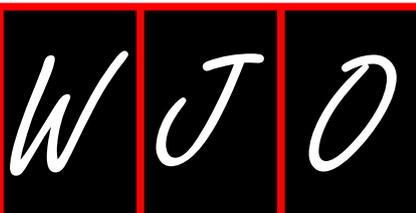
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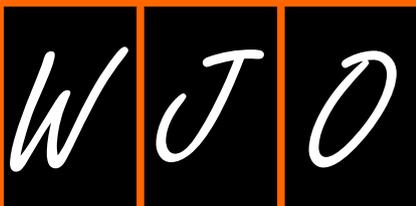
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Radiation exposure and reduction in the operating room: Perspectives and future directions in spine surgery

Ankur S Narain, Fady Y Hijji, Kelly H Yom, Krishna T Kudaravalli, Brittany E Haws, Kern Singh

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Abstract

Intraoperative imaging is vital for accurate placement of instrumentation in spine surgery. However, the use of biplanar fluoroscopy and other intraoperative imaging modalities is associated with the risk of significant radiation exposure in the patient, surgeon, and surgical staff. Radiation exposure in the form of ionizing radiation can lead to cellular damage *via* the induction of DNA lesions and the production of reactive oxygen species. These effects often result in cell death or genomic instability, leading to various radiation-associated pathologies including an increased risk of malignancy. In attempts to reduce radiation-associated health risks, radiation safety has become an important topic in the medical field. All practitioners, regardless of practice setting, can practice radiation safety techniques including shielding and distance to reduce radiation exposure. Additionally, optimization of fluoroscopic settings and techniques can be used as an effective method of radiation dose reduction. New imaging modalities and spinal navigation systems have also been developed in an effort to replace conventional fluoroscopy and reduce radiation doses. These modalities include Isocentric Three-Dimensional C-Arms, O-Arms, and intraoperative magnetic resonance imaging. While this influx of new technology has advanced radiation safety within the field of spine surgery, more work is still required to overcome specific limitations involving increased costs and inadequate training.

Key words: Intraoperative imaging; Ionizing radiation; DNA damage; Genomic instability; Shielding; Distance; Dose reduction; Spinal navigation

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Core tip: Intraoperative radiation exposure is a significant concern for patients, surgeons, and operative

room staff during spine surgery. All surgeons should practice general radiation safety techniques including shielding, distance, and fluoroscopic dose reduction. New imaging modalities and spinal navigation systems have also been developed to mitigate radiation exposure risk. These modalities include CT-based techniques such as Isocentric Three-Dimensional C-arms and O-Arms. Intraoperative magnetic resonance imaging has also been adapted from the neurosurgical field and is another developing imaging technique. Further research is required to overcome the limitations of these novel technologies in regards to costs and training requirements.

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INTRODUCTION

The use of instrumentation and other implants is often necessary for orthopaedic surgical intervention. This is especially true in the field of spine surgery, where anterior and posterior instrumentation is frequently utilized to treat degenerative, traumatic, and neoplastic pathologies. Posterior pedicle screws are the most widely used instruments within spine surgery; however, inaccurate positioning of such constructs can lead to significant intraoperative and postoperative adverse events^[1-5]. Specifically, injury to nearby neurovascular structures can occur, which often results in significant patient morbidity and financial burden on the healthcare system.

In order to ensure accurate placement of spinal instrumentation, intraoperative radiographic images are used to guide and confirm implant location. The use of intraoperative imaging is especially important in minimally-invasive procedures, where instrumentation is inserted percutaneously without the direct anatomic visualization afforded in open procedures. Biplanar fluoroscopy was one of the first real-time intraoperative imaging modalities, and remains the dominant technique amongst orthopaedic and spinal practitioners^[6-8]. However, radiation exposure from intraoperative imaging remains a significant concern for patients, surgeons, and other operative room personnel^[9-13]. In order to mitigate the risk associated with intraoperative radiation exposure, new imaging technologies and personal protective equipment have been developed.

The purpose of this review is to summarize the pathophysiology of intraoperative radiation exposure, discuss effective strategies for intraoperative radiation safety, and to introduce new intraoperative imaging and navigation modalities within the field of spine

surgery.

PATHOPHYSIOLOGY AND EFFECTS OF RADIATION EXPOSURE

During the use of intraoperative imaging, surgical staff and patients are exposed to both direct and scatter radiation. Direct radiation is the radiation absorbed from the beam as it projects from the source. Direct radiation is the predominant source of radiation exposure for the patient and surgeon. Scatter radiation is radiation from the source that is deflected off of a surface, typically the patient in an operative setting. Scatter radiation exposure is the primary form of exposure for operative staff who stand further away from the surgical table. While many different types of radiation exist, the most concerning in regards to the development of pathology is ionizing radiation. Ionizing radiation from intraoperative imaging leads to cellular damage through the induction of direct or indirect DNA lesions and production of reactive oxygen species^[14,15]. The ensuing cellular stress response can lead to cell death *via* replicative or apoptotic mechanisms^[14]. Conversely, if cell death does not occur, the risk of neoplastic proliferation may be increased due to the persistence and replication of cells with DNA lesions and subsequent genomic instability^[15].

The pathologic effects of ionizing radiation exposure can further be described as either deterministic or stochastic. Deterministic effects are short-term responses observed only after a certain threshold radiation exposure has been reached. These effects are subsequently worsened with any additional exposure past that threshold^[16]. Examples of pathology associated with deterministic effects includes hair loss, skin erythema, skin burns, and cataract formation^[17-19]. As the thresholds for deterministic effects are known in many cases, they can be prevented *via* careful monitoring of radiation exposure levels over short time-periods. More worrisome are stochastic effects, in which incidence increases with exposure without any definitive time period or threshold exposure level^[16]. Stochastic effects are most commonly associated with carcinogenesis and teratogenesis^[17,20-23]. For example, Mastrangelo *et al.*^[21] determined that working as an orthopaedic surgeon was a significant risk factor for tumor development in a survey of cancer incidence amongst 316 hospital employees. The authors cautioned that this increased risk was possibly a result of orthopaedic surgeon radiation exposure along with poor work safety practices.

In order to protect against the dangers of excessive radiation exposure, guidelines are available regarding dosage limits both for those exposed in occupational settings and the general public. The primary international organization producing these guidelines is the International Commission on Radiological Protection (ICRP). The dosage limits are expressed in the units of joules per kilogram, otherwise known as a Sievert

(Sv)^[24]. The Sievert is a measure of the stochastic effects of ionizing radiation, and an exposure of 1 Sv is associated with a 5.5% risk of developing cancer^[24]. Under ICRP guidelines, occupational exposure should be limited to a maximum average of 20 mSv per year over a five-year period, with no exposure greater than 50 mSv in a single year^[24]. For the general public, exposure should be limited strictly to a maximum average of 1 mSv per year over a 5-year period^[24]. These limits can be used as reference points for the evaluation of the safety and efficacy of new imaging technologies and radioprotective techniques.

GENERAL STRATEGIES FOR REDUCING RADIATION EXPOSURE IN SPINAL PROCEDURES

Shielding

In attempting to reduce intraoperative radiation exposure, a variety of simple methods should be employed by all practitioners. One of these methods is shielding, which involves the use of physical barriers to absorb a portion of scatter radiation and prevent it from reaching soft tissues. Shielding for operative room personnel is primarily accomplished by the wearing of lead aprons and thyroid shields, which protect radiosensitive areas from the upper body to the gonads^[18,19,23,25-27]. Other less commonly utilized methods of shielding include lead gloves to reduce hand exposure, lead skirts for operative tables, and mobile shielding screens to provide additional protection to operative room personnel^[28-30]. The literature is overwhelmingly supportive of the utility of shielding, with reported reductions in radiation exposure between 42%-96.9%^[19,27,28,30]. For example, Ahn *et al.*^[27], in a study of three surgeons performing percutaneous endoscopic lumbar discectomies, determined that lead aprons and collars reduced radiation exposure to the upper body and thyroid by 94.2% and 96.9%, respectively. Furthermore, the use of lead aprons was estimated to increase the number of total operations before reaching occupational exposure limits by 5088 procedures.

Distance

An additional method to reduce intraoperative radiation exposure is to feasibly maximize the distance between the patient surface and the surgeon or operative room personnel^[18,30]. This principle derives from the fact that radiation intensity follows an inverse square law, decreasing substantially with increasing distance from the radiation or scatter source. As such, with appropriate shielding, scatter radiation may be reduced to 0.1% and 0.025% of the primary radiation at a distance of 3 feet and 6 feet, respectively^[11]. This principle is further illustrated by Lee *et al.*^[18], in an investigation of scatter radiation doses measured during intraoperative C-arm fluoroscopy. In this study, a chest

phantom on a surgical table was exposed to fluoroscopy while a whole-body phantom was placed in varying positions in the operating room to simulate the surgeon and operative room staff. Measured scatter doses to the whole-body phantom decreased with increasing distance up to 100 cm from the chest phantom device. Kruger *et al.*^[30] provided further recommendations for operative room setup, noting that the image intensifier should be placed on the same side of the operative table as the surgeon so as to increase the distance between the radiation source and operative room personnel.

Fluoroscopic dose reduction techniques

Dose reduction techniques are also an important strategy both in reducing radiation exposure and following the "as low as reasonably achievable" (ALARA) principle. One such technique is the use of fluoroscopy in pulsed and low dose modes^[26,29-31]. Pulsed mode refers to a method where power to the radiation source is applied intermittently producing short pulses of radiation, while low-dose mode reduces the peak kilovolts and miliamperes necessary to create the radiation beam^[26]. Goodman *et al.*^[26], in a study of 316 patients undergoing spinal interventional procedures, determined that the combination of pulsed and low-dose modes decreased average radiation exposure time by 56.7%. The authors also suggested that pulsed modes are most effective in reducing radiation exposure when the surgeon is required to be in closest proximity to the patient. Plastaras *et al.*^[29] examined the effect of pulsed fluoroscopy in conjunction with shielding in patients undergoing interventional spine procedures. The combination of the two methods resulted in a 97.3% reduction in effective dose to all operative room staff. Despite the benefit of radiation exposure reduction, pulsed and low-dose modes exhibit potential disadvantages. Of primary concern is reduced image quality, and as such, the adoption of these fluoroscopy modes is dependent on surgeon acumen and comfort^[26].

Other dose reduction techniques include intermittent fluoroscopy and last image hold^[30,32]. Intermittent fluoroscopy refers to applying fluoroscopy only for short time periods, while last image hold displays the last collected image even when fluoroscopy is not being applied^[32]. These methods allow for both reduced total fluoroscopy time and the ability to better plan surgical approaches through image review. Finally, collimation can be utilized to reduce radiation dose. Collimation refers to narrowing the radiation beam over the area of anatomic interest, thus reducing radiation exposure by subjecting less total body area to interaction with radiation^[26,31].

INTRAOPERATIVE THREE-DIMENSIONAL IMAGING AND SPINAL NAVIGATION SYSTEMS

Spinal navigation systems have been developed with

the goals of increasing the accuracy of instrumentation placement and reducing operative radiation exposure. Navigation technologies are comprised of many different components that must act in concert. Typically, an imaging mechanism is used to collect radiographic images that are then imported into a computer workstation that creates a three-dimensional (3D) reconstruction of the anatomy of interest^[33]. This computer system interacts with a specialized optical camera and surgical tools to guide real-time insertion of instrumentation without the need for repetitive collection of fluoroscopic images^[33].

Since its inception, navigation has shifted from utilizing preoperative images to using intraoperative 3D imaging modalities^[34]. These imaging modalities are more frequently used because, unlike with preoperative imaging, they do not require as significant a degree of the time-consuming process of anatomic registration^[17]. Furthermore, intraoperative imaging is a better representation of surgical anatomy than preoperative studies, as preoperative images do not reflect anatomic shifts and variations due to surgical positioning^[35-40]. Multiple intraoperative imaging modalities can be used in conjunction with navigation systems, including computed tomography (CT) and magnetic resonance imaging (MRI) based approaches.

Isocentric 3D C-arm

Isocentric 3D C-arms are CT based systems that collect images from a 190° screening arc^[36,41,42]. Up to 200 fluoroscopic images are collected at equidistant angles which are then utilized by navigation systems to create a 3D reconstruction of the relevant spinal anatomy^[41,43]. In one pass, these modified C-arms can collect images from a 12 cm³ anatomical space^[44]. Furthermore, the surgeon and surgical staff can step outside of the operating room during image acquisition, possibly reducing unnecessary radiation exposure^[45,46].

In regards to radiation exposure, prior investigations have exhibited reduced fluoroscopy time and radiation doses with the use of Isocentric 3D C-arms compared to standard fluoroscopy^[41,45,46]. Kim *et al.*^[45] performed one such study in 18 cadaveric spines undergoing minimally invasive transforaminal lumbar interbody fusion (MIS TLIF). The authors demonstrated that while the navigation group had greater setup time (9.67 min vs 4.78 min), the overall fluoroscopy time was lower compared to the standard fluoroscopy group (28.7 s vs 41.9 s). Radiation exposure, measured in millirems (mREM), was also lower in the navigation group (undetectable vs 12.4 mREM). Furthermore, in a subsequent series of 18 patients undergoing MIS TLIF, the navigation group had lower overall fluoroscopy time (57.1 vs 147.2 s). Smith *et al.*^[46] noted similar findings in an investigation of 4 cadavers in which lumbar pedicle screw placement was attempted. Compared to standard fluoroscopy, isocentric C-arm use was associated with lower total mean radiation exposure to the surgeon's torso (0.33 mREM vs 4.33 mREM). The

advantages of isocentric 3D C-arm use also extend past limiting radiation exposure, as multiple studies have indicated equivalent or superior accuracy of pedicle screw placement when compared to standard fluoroscopic methods^[36,44,46,47].

O-arm

The O-arm (Medtronic, Fridley, Minnesota) is a cone-beam, CT-based intraoperative imaging modality that can produce a 360° scanning arc^[8]. O-arm devices can acquire up to 750 images in a single scan, and these images can be utilized with navigation systems to create 3D anatomical reconstructions^[7,48,49]. The O-arm also is programmed with preset modes that optimize kilovoltage and milliamperage settings for various patient sizes and anatomical regions^[25,48,49]. Similar to the isocentric 3D C-arm, the O-arm can possibly reduce radiation exposure by allowing the surgical staff to exit the operating theatre during image acquisition^[49].

The literature regarding the use of O-arm imaging is mixed in terms of its efficacy in radiation dose reduction. Multiple studies have determined that while O-arm imaging reduces radiation exposure to operative room personnel, it increases the radiation exposure to the patient^[7,17,25,48-50]. Tabaraee *et al.*^[50] demonstrated such findings in a cadaveric study investigating the insertion of 160 pedicle screws under either C-arm or O-arm imaging. In the operative room staff, O-arm imaging led to undetectable levels of radiation exposure while C-arm imaging was associated with an exposure of 60.75 mREM. The opposite correlation was seen in cadavers, where the use of the O-arm modality was associated with higher mean radiation doses compared to the use of conventional C-arm fluoroscopy. Mendelsohn *et al.*^[17] confirmed this association in a matched cohort analysis of 146 patients undergoing posterior pedicle screw insertion. In the 73 patients undergoing a procedure with O-arm imaging, the observed radiation dose in patients was 8.74 times greater than that of the OR staff. Those patients also experienced a higher mean effective dose of radiation (1.09 mSv) compared to published radiation dosages for patients undergoing pedicle screw insertion using standard C-arm fluoroscopy following MIS (0.611 mSv) or open (0.393 mSv) techniques. The results of these studies indicate that any practitioner considering the use of O-arm imaging must weigh the benefit of reduced radiation exposure to operative staff with the limitation of increased radiation exposure to patients.

Intraoperative MRI

Intraoperative MRI is a developing technology in the field of spine surgery that has the potential for significant reductions in intraoperative radiation exposure both for patients and surgical personnel. Intraoperative MRI has been adapted from the field of neurosurgery, and it involves the use of ultra-high field 3T MRI scanners^[51]. Within the spine literature, few studies exist regarding the safety and efficacy of intraoperative MRI. Woodard

et al.^[52], in a case series consisting of both cervical and lumbar procedures, demonstrated that intraoperative MRI could feasibly be used for localization and confirmation of neural decompression. Similarly, Choi *et al.*^[53] conducted a study utilizing intraoperative MRI for surgical site localization and confirmation of decompression in 89 patients undergoing percutaneous endoscopic lumbar discectomy. The authors concluded that intraoperative MRI was successful in detecting inadequate intraoperative decompression, especially in cases of highly migrated or segmented discs. While this initial data is promising, further work is required to definitively determine the efficacy of procedures utilizing intraoperative MRI.

Limitations to the adoption of intraoperative 3D imaging

While the data supporting the use of intraoperative 3D imaging modalities and navigation systems is promising, these techniques have not yet achieved widespread adoption. Estimates of the percentage of spine surgeons who routinely utilize navigation systems are in some instances as low as 11%^[54]. In attempting to identify impediments to adoption, multiple studies have been undertaken to survey the opinions of practitioners in the field of spine surgery^[54,55]. These investigations consistently identify increased cost, lack of adequate training, and increased associated operative times as factors precluding the use of navigation systems^[54,55]. Costs associated with buying and implementing new imaging and guidance technologies can be burdensome, especially to single-physician and small-group practices. Furthermore, concerns regarding inadequate training extend not only to the surgeon, but to members of the entire operative staff who must adjust to an unfamiliar operative workflow with the introduction of new imaging systems. Worries about increased operative time are also logical, especially during the initial phase of navigation system adoption when surgical teams are at the beginning of their learning curve. However, recent studies have noted no significant differences in operative time in navigated and non-navigated procedures^[44,50]. Nonetheless, manufacturers and proponents of new imaging and navigation systems must still work to overcome the disadvantages of cost, training, and the learning curve to ensure greater adoption of this technology within the field of spine surgery.

CONCLUSION

Radiation exposure is a significant concern for patients, surgeons, and operative room staff. Exposure to ionizing radiation from conventional fluoroscopy is associated with a number of pathologies, the most worrisome being the development of malignancy. As such, radiation safety must be a priority in the operative setting. All practitioners, irrespective of their practice setting, can and should employ the safety principles of

shielding, distance, and dose reduction. Furthermore, practitioners should also consider the use of new navigation systems with alternative imaging modalities such as isocentric-3D C-arm, O-arm, or intraoperative MRI. While these systems may be associated with reductions in radiation exposure to operative staff, they also have significant limitations pertaining to cost, training requirements, and operative times. Further work is still required within the field of spine surgery to improve radiation safety and to further increase the adoption of new imaging modalities.

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Use of recombinant human bone morphogenetic protein-2 in spine surgery

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Abstract

Bone morphogenetic proteins are osteoinductive factors which have gained popularity in orthopaedic

surgery and especially in spine surgery. The use of recombinant human bone morphogenetic protein-2 has been officially approved by the United States Food and Drug Administration only for single level anterior lumbar interbody fusion, nevertheless it is widely used by many surgeons with off-label indications. Despite advantages in bone formation, its use still remains a controversial issue and several complications have been described by authors who oppose their wide use.

Key words: Recombinant human bone morphogenetic protein-2; Spine; Fusion; Bone graft; Yale University Open Data project

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Core tip: The use of recombinant human bone morphogenetic protein-2 is widely used in spine surgery not only in approved indications but also in off-label indications. Despite its ability to promote fusion there are many reported disadvantages. That's why the Yale University Open Data project aims to serve both the patients but also the companies which fund the vast majority of research in medical products.

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INTRODUCTION

During the last 10 years, the use of bone morphogenetic proteins (BMPs) has become very popular in orthopaedic surgery. BMPs are osteoinductive factors which are capable of inhibiting chondrocyte differentiation independently and they are recognized

as important regulators of growth, differentiation, and morphogenesis during embryology^[1,2]. They are members of the superfamily of transforming growth factor- β (TGF- β) and play an important role in the development and regeneration of various tissues including bone, cartilage, and tendons^[3,4]. Urist^[5] in 1965 described first these factors with the term "bone autoinduction principle". During the last two decades BMPs gradually gained popularity in bone healing and especially in spinal fusion enhancement. BMPs are released by platelets and osteogenic cells and their main role is to stimulate cellular proliferation, angiogenesis, osteoblast differentiation, and direct bone matrix formation^[6]. More than 20 different types of BMPs have been identified since Urist^[7] described their properties and all of them have significant osteogenic properties. From all types of BMPs, BMP-2 has been found to be the most osteoinductive and its efficacy to generate an osseous fusion mass has been well established in several preclinical spine models^[8].

In spine surgery, autogenous bone grafting is often used to stimulate fusion. Due to the insufficiency of traditional techniques of bone grafting in long spinal fusions or spinal fusions in adverse metabolic conditions, bone graft substitutes, such as recombinant human bone morphogenetic protein-2 (rhBMP-2), have been introduced in the clinical practice^[9].

INDICATIONS

RhBMP-2 in spinal surgery was first studied clinically in anterior lumbar interbody fusion (ALIF) and was compared with iliac crest bone graft^[10]. The fusion rate of rhBMP-2 group was 94.5% whereas the fusion rate in the group where iliac crest bone graft was used was 88.7%. More studies supporting the effectiveness of rhBMP-2 in spine fusion followed, which resulted in the approval of rhBMP-2 by the United States Food and Drug Administration (FDA) for single-level ALIF within specific threaded cages in skeletally mature patients. In a meta-analysis in 2014 the authors report that rhBMP-2 in lumbar spine fusion can increase the fusion rate^[11], while reduce the reoperation rate and operating time. Additionally, it does not increase the complication rate, the amount of blood loss, and the hospital stay.

OFF-LABEL USE

Although rhBMP-2 has been approved by the FDA for a single narrow method of spinal fusion, over the last 10 years, numerous articles on BMP-2 have documented its use for a far wider range of spinal applications. Since its approval, rhBMP-2 has gained popularity as an effective bone-graft substitute as it obviates the need for autologous bone graft harvesting and eliminates associated complications and donor site morbidity^[12,13]. Many surgeons, began the off-label use of the product in all spinal regions^[14-17], after which new complications associated with the use of rhBMP-2

emerged, including among others severe soft-tissue swelling following anterior cervical discectomy and fusion, heterotopic bone formation, and vertebral body osteolysis in the thoracic and lumbar spine^[18-20]. Ong *et al*^[21] reported that the 85% of all surgeries in which rhBMP-2 was used were for "off-label" applications. These off-label indications included posterior lumbar interbody infusion, transforaminal lumbar interbody infusion, posterior lumbar fusion, anterior cervical discectomy and fusion (ACDF), and more recently, lateral lumbar interbody fusion^[22].

Rihn *et al*^[23], in 2009 published their study about the use of rhBMP-2 in single-level transforaminal lumbar interbody fusion. They showed high rate of fusion and improvement of symptoms. Nevertheless, its use was associated with complications that raise concern including a high rate of postoperative radiculitis. One year later, Oliveira *et al*^[24] presented their results using rhBMP-2 in standalone lateral lumbar interbody fusion. Following a 24-mo follow-up, the authors concluded that single level disc degenerative disease can be successfully treated with standalone lateral lumbar interbody fusion using rhBMP-2 providing except of pain relief significant cost reduction. Complications included cage subsidence, heterotopic bone formation, persistent stenosis, and adjacent level degeneration.

According to a current retrospective cohort study^[25], during the last years a decrease in the off-label use of BMP-2 in spinal fusions and particularly in cervical spine fusions was noticed. The authors noted that although there was a tendency of decreased odds from 2009 to 2012, a higher resource utilization and odds for complications remained in patients in whom BMP-2 was used.

ADVANTAGES

One of the main advantages of the use of rhBMP-2 in spinal fusion is the elimination of adverse events that have been associated with iliac crest bone graft harvesting despite the improvement of bone-harvesting techniques. These complications include pain, hematoma formation, sacral fracture, and infection^[8].

In spine surgery, the rhBMP-2 fusion rate is usually compared with the iliac crest bone graft fusion rate. In the first prospective randomized controlled trial in 2000 Boden *et al*^[26] supported that arthrodesis occurred more reliably in patients treated with rhBMP-2 filled cages than in controls treated with autogenous bone graft. In general, the fusion rate with the use of rhBMP-2 ranges from 94.5% to 100%, whereas with the use of iliac crest bone graft the fusion rate ranges from 88.7% to 100%. The main complaint in the group of patients treated with iliac crest bone graft was the pain at the donor site. It was also suggested that there is more blood loss with the use of iliac crest bone graft, as well as more operating time. Moreover, in some specific cases, such as in women with osteoporosis, it was speculated that the osteoinductive ability of

rhBMP-2 was more efficient when compared to iliac crest bone graft^[10,17].

In 2009, Dawson *et al*^[27] combined rhBMP-2 on an absorbable collagen sponge with a ceramic-granule bulking agent in patients undergoing single level posterolateral lumbar fusion. The group of patients who received this combination was compared with a control group of patients who were treated with autogenous iliac crest bone graft. The authors concluded that the combination of the absorbable collagen sponge soaked with rhBMP-2 and ceramic granules provided not only improved clinical results, but also higher radiographic fusion rates when compared to the control group of patients.

The cost should also be taken seriously into consideration. In 2008, Glassman *et al*^[28] compared the perioperative costs for patients treated with rhBMP-2 or iliac crest bone graft. Surprisingly, the mean cost for the 3 mo perioperative period was \$ 33860 in the rhBMP-2 group and \$ 37227 in the iliac crest bone graft group. A decreased physician fee was also noticed in the rhBMP-2 group (\$ 5082 and \$ 5316, respectively).

Taking all these into consideration, someone can assume that there is no difference between the rhBMP-2 and the iliac crest bone graft in terms of obtaining a solid spinal fusion. Nevertheless, it seems that the rhBMP-2 can achieve an "easier" and faster fusion with no donor site morbidity.

COMPLICATIONS

The first studies presenting the results of rhBMP-2 in spine surgery, reported no adverse events directly related to BMP-2 usage^[7]. It has to be mentioned though that all these studies were industry supported.

More recently, authors started to present disadvantages for the use of BMPs especially in its off-label indications. Epstein^[29] in 2013 presented several complications associated with the off-label use of rhBMP-2 including heterotopic ossification, postoperative seroma/hematoma formation, increased infection rate, arachnoiditis, dysphagia following ACDF, retrograde ejaculation after ALIF, increased neurologic deficits, and cancer. Neurologic deficits following lateral lumbar interbody fusion with the supplementary use of rhBMP-2 were also recorded in another study where 919 treated levels were reviewed^[30]. Immediately after surgery, sensory and motor deficits were identified in 38% of the patients treated with rhBMP-2 and in 23.9% of the patients fused with cancellous allograft or iliac crest bone autograft. At the last follow-up, the percentage of sensory and motor deficits was decreased to 24.1% and 17.3%, respectively. A potential deleterious effect of rhBMP-2 on the lumbosacral plexus was suggested^[22]. Mitchell *et al*^[31] in an experimental study in 2016, modeled the clinical use of BMP-2 for posterior lumbar fusion. They concluded that the implantation of rhBMP-2 on the lumbar spine may trigger neuroinflammatory responses in the dorsal

root ganglia.

Certain cancer cell lines have been shown to have BMPs receptors and local administration of these growth factors has led to stimulation of cell growth of cancer lines *in vitro*^[32]. In a comparative study of 463 patients, Carragee *et al*^[33] concluded that a high dose of 40 mg of rhBMP-2 in lumbar spinal arthrodesis is associated with an increased risk of new cancer. On the other hand, in a current study of Beachler *et al*^[34] in a large population of elderly United States adults who underwent lumbar arthrodesis, rhBMP-2 was not associated with cancer risk or increased mortality.

The mechanism of rhBMP-2 action that may have led to complications described above has been investigated. Hsu *et al*^[35] in an experimental study of posterolateral intertransverse lumbar spinal fusion demonstrated that the *in vivo* host response to rhBMP-2 may be associated with circulating proinflammatory and osteoclastic cytokines, such as tumor necrosis factor- α , macrophage inflammatory protein 1-alpha, and interleukin1- β . Additionally, angiogenesis was found to be stimulated through the induction of vascular endothelial growth factors secretion^[36].

FURTHER RESEARCH

Increased use of rhBMP-2 in spine surgery has raised several controversial conflicts among investigators. During the last years a new promising project has been established, which aims to cope with the issue of unpublished or selectively published clinical evidence^[37,38]. The Yale University Open Data Access (YODA) project aims to serve patients and produce benefits for the companies that fund the vast majority of research in medical products. Lately two systematic reviews on rhBMP-2, which are based on patient-level data were shared through YODA. The agreement between the YODA team and Medtronic (rhBMP-2 company) included two parts. Firstly, two independent research groups were selected through a competitive process to evaluate the quality of the studies and synthesize evidence regarding the effectiveness and safety of rhBMP-2. Secondly, the YODA team made the data available to others for potential scientific questions. In this way all the clinical trial data for this product should have been made available in order to be used by other investigators for further analysis^[39].

These two studies concluded in the same results after analyzing their data. Despite the higher fusion rate that was observed with the use of rhBMP-2, clinical results showed no significant differences between the use of iliac crest bone graft and rhBMP-2. The authors of both studies agreed that a clear safety risk is posed when rhBMP-2 is used in the anterior aspect of the cervical spine^[8]. As far as it concerns the carcinogenicity, one study showed significantly higher rate of cancer in patients who were treated with rhBMP-2, while the other presented statistically insignificant higher incidence of cancer in the rhBMP-2

group. Both teams of investigators reached to the same conclusion: Despite the higher rate of cancer appearance, the overall absolute risk of carcinogenesis due to the use of rhBMP-2 for spinal fusion is generally low^[40].

However, Carragee *et al*^[41] supported that despite access to Medtronic trial data, the YODA project will not be able to resolve many, if not most, fundamental safety and efficacy issues on various current uses because there are inadequate trials available.

CONCLUSION

RhBMP-2, due to its ability to stimulate bone formation may offer an effective alternative method of fusion in spine surgery. The clinical outcomes and fusion rates are comparable with those of iliac crest bone graft. In some challenging situations though, rhBMP-2 may have even better results. Its cost is higher compared with the cost of other bone graft substitutes, but concerning the total cost for a patient who needs multiple surgeries to achieve a solid spinal fusion, it seems that rhBMP-2 may be proved cost effective. RhBMP-2 is very often used in spinal applications that have not been studied and/or approved by the FDA, where their results may be unpredictable. Long-term outcomes from randomized control trials are warranted to further clarify the appropriate dose, carrier, and indications of rhBMP-2.

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Basic Study

Possibilities for arthroscopic treatment of the ageing sternoclavicular joint

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Abstract

AIM

To investigate if there are typical degenerative changes in the ageing sternoclavicular joint (SCJ), potentially accessible for arthroscopic intervention.

METHODS

Both SCJs were obtained from 39 human cadavers (mean age: 79 years, range: 59-96, 13 F/26 M). Each frozen specimen was divided frontally with a band saw, so that both SCJs were opened in the same section through the center of the discs. After thawing of the specimens, the condition of the discs was evaluated by probing and visual inspection. The articular cartilages were graded according to Outerbridge, and disc attachments were probed. Cranio-caudal heights of the joint cartilages were measured. Superior motion of the clavicle with inferior movement of the lateral clavicle was measured.

RESULTS

Degenerative changes of the discs were common. Only 22 discs (28%) were fully attached and the discs were thickest superiorly. We found a typical pattern: Detachment of the disc inferiorly in connection with thinning, fraying and fragmentation of the inferior part of the disc, and detachment from the anterior and/or posterior capsule. Severe joint cartilage degeneration \geq grade 3 was more common on the clavicular side (73%) than on the sternal side (54%) of the joint. In cadavers

< 70 years 75% had \leq grade 2 changes while this was the case for only 19% aged 90 years or more. There was no difference in cartilage changes when right and left sides were compared, and no difference between sexes. Only one cadaver - a woman aged 60 years - had normal cartilages.

CONCLUSION

Changes in the disc and cartilages can be treated by resection of disc, cartilage, intraarticular osteophytes or medial clavicle end. Reattachment of a degenerated disc is not possible.

Key words: Sternoclavicular; Degenerative; Cartilage; Disc; Arthroscopy

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Core tip: Arthroscopic treatment is an option in patients with symptoms from the ageing sternoclavicular joint (SCJ). However, knowledge of age-related changes is essential for planning of such arthroscopic procedures. In 78 human cadaveric SCJs with a mean age of 79 years (range: 59-96 years) we found that degenerative changes of the discs were common, in particular inferior detachment, and only 28% were fully attached. Severe cartilage degeneration was more common on the clavicular than the sternal side. When there was inferior detachment of the disc, we observed increased superomedial gliding of the clavicle. We conclude that a torn disc or degenerated articular cartilage might be treated by arthroscopic resection, debridement and clavicle end resection. Reattachment of a degenerated disc is not possible.

Rathcke M, Trantum-Jensen J, Krogsgaard MR. Possibilities for arthroscopic treatment of the ageing sternoclavicular joint. *World J Orthop* 2017; 8(7): 536-544 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i7/536.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i7.536>

INTRODUCTION

Arthroscopy has opened for specific procedures on the sternoclavicular joint (SCJ), *e.g.*, resection of a torn intraarticular disc. Changes of the joint with age might be expected just like it is seen in the acromioclavicular joint, due to the substantial gliding and rotation in both joints during movement of the arm^[1-3]. Resection of the lateral clavicle end is a common procedure for painful osteoarthritis of the acromioclavicular joint. The prevalence of symptoms from SCJ is unknown, but surgery on the joint is infrequent^[4-6], partly by tradition and perhaps of fear to injure vessels and lungs adjacent to its posterior capsule^[7].

Open resection of the articular disc and capsulorrhaphy in patients with degenerative disease of the

SCJ has been reported successful in 6 patients^[8]. Open resection of the medial clavicular end show good results in treatment for SCJ osteoarthritis^[9,10] when the costoclavicular ligament is kept intact^[10-12]. However, the scar after open surgery can be cosmetically prominent because of the location.

Arthroscopic surgery of the SCJ can be performed through two portals (Figure 1), leaving minor scars, using a 2.7 mm arthroscope and standard instruments (Figure 2). The two portals give access to both compartments of the joint on either side of the articular disc. The depth of the joint is about 1.5 cm, and care should be taken not to exceed this during introduction of the arthroscope, in order not to penetrate the posterior capsule. Once the arthroscope is introduced all structures are usually easy to identify, and resection of the disc, medial clavicle or intraarticular osteophytes, as well as synovectomy and removal of loose bodies can be performed under visual control without risk of penetrating into the mediastinum.

The articular disc of SCJ is superiorly attached to the medial end of the clavicle, inferiorly to the first rib at its junction with the manubrium and to the joint capsule. In older cadavers the disc is incomplete in 29%-56%^[13-16], with a central hole^[13,15,16] or a meniscoid appearance^[14]. During arthroscopy in younger patients (age mean 40 years, range: 16-70, 28 F/11 M) we have often found detachment of the disc from the anterior capsule and marked disintegration of the disc at the inferior part with detachment from manubrium (Figure 3) (unpublished).

These differences in reported changes are confusing in relation to whether there is an anatomic basis for arthroscopic treatment of the disc in the painful ageing SCJ.

Degenerative changes of the articular cartilage are reported to be more severe on the medial clavicle compared to manubrium^[16], which is surprising as the superior part of the clavicular cartilage only articulates when the arm is abducted.

Our aims were to study the anatomy of the SCJ, focusing on the occurrence of conditions that are potentially accessible for surgical intervention. Also, to evaluate if the hyaline cartilages on the clavicle and manubrium are equally affected by age, and if degenerative conditions and detachment of the disc has any influence on medial end clavicular stability.

MATERIALS AND METHODS

From 39 formalin embalmed human cadavers (age mean: 79 years, range: 59-96, 13 F/26 M) we obtained both SCJs. The sternum was cut at level of the second rib, and clavicles and first rib were cut lateral to the costoclavicular ligament. To be able to examine the capsular attachments of the intraarticular disc, each specimen was frozen and divided frontally with a thin band saw, so that both SCJs were opened in the



Figure 1 The two standard portals for sternoclavicular arthroscopy.

same section through the center of the disc (Figure 4). Examination of the joints was performed after the specimens had been thawed and stored in 30% ethanol. The cut surfaces were cleaned with a dry cloth. The height of the articular cartilage (cranio-caudal) on the clavicle and manubrium was measured (Figure 5). The attachments of the intraarticular disc to the clavicle and first rib-manubrium junction as well as to the anterior and posterior capsule were probed with a hooked arthroscopic probe (Figure 6). Any detachment was recorded. The disc was probed, and holes, fraying and flap lesions were visually inspected and recorded. The thickest and thinnest parts of the disc were measured with a caliper gauge designed especially for this purpose (Figure 7). The cartilage at the medial clavicular end and at manubrium was classified according to Outerbridge^[17] based on visual inspection and probing, and by agreement of two observers. Information about the age and sex of the cadavers was obtained after the measurements had been recorded. There were no signs of previous surgery to any of the SCJs.

Ethical considerations

The study was conducted on deceased who had bequeathed their bodies to science and education at the Department of Cellular and Molecular Medicine (ICMM) at the University of Copenhagen according to Danish legislation (Health Law #546, § 188). The study was approved by the head of the body donation program at ICMM. The study was performed at Department of Cellular and Molecular Medicine (ICMM), University of Copenhagen, Denmark.

Statistical analysis

The data are presented as mean ± SD. For the statistics, Student's *t* test was used. *P* < 0.05 was considered as statistically significant.

RESULTS

In the 26 males 4 discs were missing on the right side,



Figure 2 Sternoclavicular arthroscopy performed with the patient supine, using a 2.7 mm arthroscope and a 4.0 mm shaver.



Figure 3 Arthroscopic view of the left sternoclavicular joint showing degenerative changes in the partially resected disc (in the middle) and chondral degeneration of the clavicular cartilage (right side of photo). The shaver is introduced through the superior portal.

1 joint was ankylotic and 21 discs were present, but 4 of these had a central hole. On the left side 4 discs were missing, 22 were present and 3 of these had a central hole.

In the 13 females 3 discs were missing on the right side, 10 were present and 4 of these had a central hole. On the left side 2 discs were missing, 11 were present and 4 of these had a central hole.

Figure 8 visualizes the attachments of the discs, illustrating that the discs were most often detached inferiorly. Only 22 discs (28%) were fully attached.

In nearly all cases the disc was thickest superiorly.

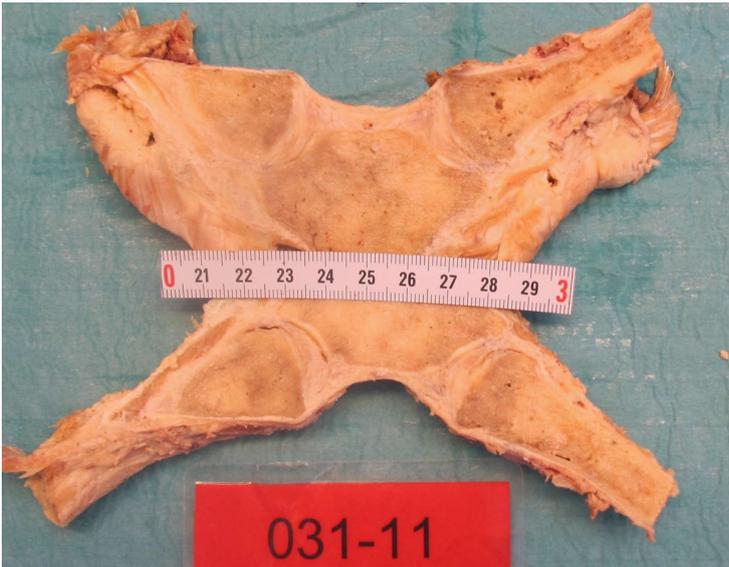


Figure 4 The sternoclavicular joints were divided frontally with a thin band saw so that both sternoclavicular joints were unfolded in the same section through the center of the discs.

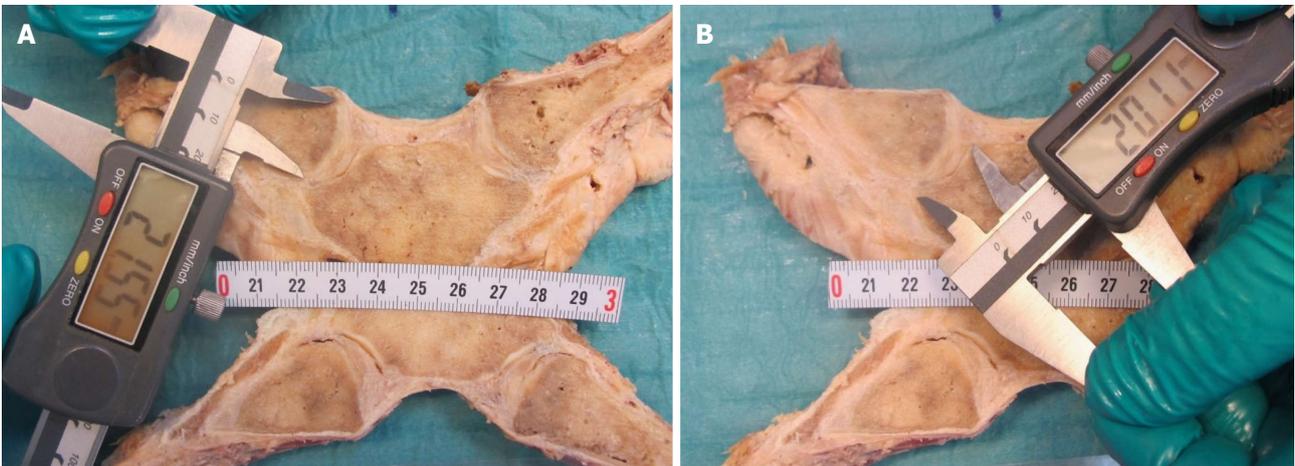


Figure 5 Measurement of the height of the articular cartilages (cranial-caudal) on the clavicle (A) and manubrium (B).



Figure 6 Probing the attachments of the intraarticular disc to the clavicle and first rib-manubrium junction as well as to the anterior and posterior capsule with a hooked arthroscopic probe.

All but one cadaver - a woman aged 60 years - showed degenerative changes of the cartilages. Grade 5 changes (no cartilage) were not seen in any of

the specimens, but one joint was ankylotic (no joint cavity). Severe degeneration \geq grade 3 was seen in 73% on the clavicular side and 54% on the sternal



Figure 7 Measurement of the thickest and thinnest parts of the intraarticular discs with a calliper gauge.

side, confirming that degenerative changes are more common on the clavicular side of the joint. In cadavers < 70 years 75% had \leq grade 2 changes, while this was the case for only 19% aged 90 years or more. In the age groups 70-79 and 80-89 years 33%-35% had \leq grade 2 changes. There was no difference in cartilage changes when right and left sides were compared, and no difference between sexes ($P > 0.05$).

We found a typical pattern: Detachment of the disc inferiorly with thinning, fraying and fragmentation of the inferior part of the disc, and detachment from the anterior and/or posterior capsule. Typical examples of changes in the discs are shown in Figure 9.

In the cases with inferior detachment we found a marked increase in supero-medial displacement of the medial clavicular end compared to cases with intact inferior attachment, when a light medially directed push was applied to the lateral clavicle shaft ($P < 0.05$) (Figure 9).

The mean cranio-caudal length \pm 1 SD of the joint cartilages was in male cadavers on the right side 26.0 \pm 3.1 mm on the clavicle and 18.1 \pm 2.0 mm on the sternum, and on the left side 25.4 \pm 2.9 mm and 17.9 \pm 2.3 mm, respectively, while in female cadavers on the right side it was 23.5 \pm 2.9 mm on the clavicle and 17.2 \pm 1.7 mm on the sternum, and on the left side 24.1 \pm 3.0 mm and 17.5 \pm 2.1 mm, respectively. All data are shown in Table 1.

DISCUSSION

Our main purpose was to evaluate if changes to the intraarticular disc in the ageing SCJ could explain painful mechanical symptoms that are seen in some patients. In light of previous reports we were surprised by the marked changes of the discs observed in the majority of the SCJs. In a large cadaver study^[16] 56% of discs were found to be incomplete, but the defects were described as a central hole and fraying.

In our study the changes were much more general; in particular inferior detachment was a common finding (20/39 right, 16/39 left). This pattern resembles what we have seen in arthroscopic examination of the SCJ in symptomatic patients with degenerative joint disease. An inferiorly detached disc is more likely to produce mechanical symptoms than a central hole as it is unstable and may cause locking during motion of the joint.

We have no information about symptoms, work or sports activity for the donors. Based on the increasing pathology with increasing age, it is likely, that the changes in the disc and cartilages are of degenerative nature. In the specimens with complete inferior detachment of the disc there was supero-medial instability of the medial clavicular end. Motion of the clavicle relative to manubrium is during most activities sliding with no compression^[2]. When the shoulder is depressed the clavicle acts as a lever arm (ratio about 7:1) with the center of rotation (the fulcrum) at its crossing of the first rib (*i.e.*, the site of the costoclavicular ligament), then the sternal end of the clavicle is lifted forcibly upwards. With increased motion of the clavicle, symptoms from an unstable, degenerated disc and degenerated cartilages are likely to increase. A forceful depression of the shoulder, *e.g.*, during lifting a heavy load, applies a substantial load on the interclavicular ligament^[1,15]. It is not known to which extent force is absorbed in the disc during lifting, but the attachment of the disc inferiorly on the manubrium and superiorly on the upper facet of the clavicular joint surface indicates that the disc in this respect may function as a ligament, working in synergy with the interclavicular ligament. Histological examination of the disc has shown the most common collagen fibers to be type I, III and V^[18] which are all strong fibrillar collagens, designed to resist force.

Slackness of the interclavicular ligament with age might result in increased tension on the disc during



Figure 8 Graphic visualization of the attachments we found of the discs in left (left) and right (right) sternoclavicular joints of males and females. Black lines: Full attachment of all four sectors; red lines: Attachment of three sectors; green lines: Attachment of two sectors; blue lines: Attachment of one sector only. inf: Inferior, sup: Superior; post: Posterior; ant: Anterior.

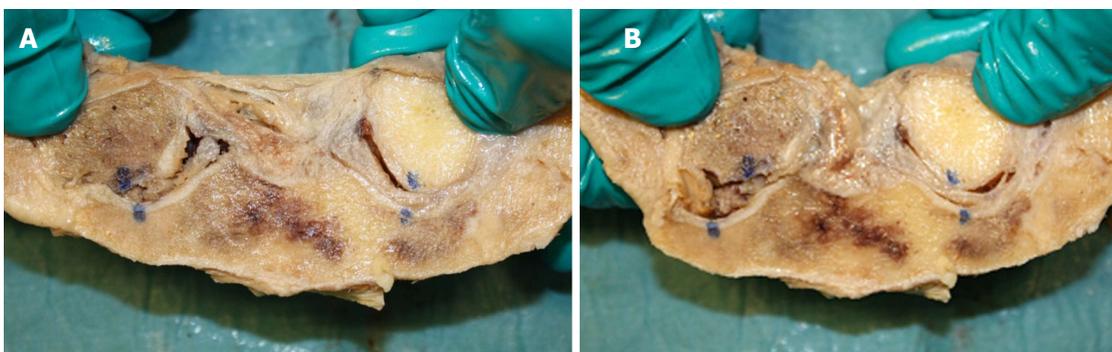


Figure 9 With inferior detachment (the sternoclavicular joint to the left) there was a substantial increase in supero-medial displacement of the medial clavicular end when a light medially directed push was applied to the lateral clavicle shaft (A: Light pull, B: Push). With full attachment of the disc (as seen in the joint to the right) this displacement was much smaller. Blue dots were marked when no external forces were applied to the joints.

lifting, and, in addition to the compressive forces on the inferior part of the disc during motion, this may

be an explanation for the high rate of thinning and detachment of the inferior part of the disc.

Table 1 Characteristics of the cadavers, the articular cartilage and the disc of the sternoclavicular joint

Age (yr)	Sex	Right thinnest/thickest part of disc mm ¹	Left thinnest/thickest part of disc mm ¹	Right attachment disc ²	Left attachment disc ²	Right cartilage C/S mm	Left cartilage C/S mm	Right cartilage quality C/S ³	Left cartilage quality C/S ³
59	F	2.1 i/3.1 s	2.2 i/4.4 s	1	5	21/15	22/14	2/2	3/3
60	F	0 i/3.9 s	0.5 i/3.9 s	5	1	23/18	25/20	0/0	0/0
65	M	2.3 i/4.3 s	4.4 i/6.4 s	1	1	24/17	26/17	2/1	2/1
65	F	1.7 i/4.8 s	0/2.4	1	5	27/18	24/21	1/1	4/4
66	M	2.2 i/4.3 s	0.9 i/4.2 s	5	1	30/19	26/21	1/1	3/1
71	M	1.2 i/4.5 s	2.2 i/6.3 s	4 + 5	1	32/20	29/21	3/2	2/3
71	M	0.6 i/1.6 s	0.9 i/2.2 s	3	5	21/17	22/13	3/3	3/3
72	F	0 i/1.4 s	0 c/2.6 s	2 + 5	1	25/18	26/19	3/2	3/2
73	M	Absent	Absent	Absent	Absent	31/20	29/21	3/3	3/3
73	M	0/3.2 anterior rim	0/4.0 anterior rim	3 + 4 + 5	3 + 4 + 5	28/18	24/17	3/4	3/4
74	M	2.9 i/3.8 s	2.0 s/3.3 i	2 + 4 + 5	1	29/19	28/17	3/2	3/2
75	F	Absent	2.1 i/2.8 s	Absent	5	19/15	18/14	3/2	1/1
75	M	2.5 i/3.5 s	1.1 i/4.1 s	5	1	25/14	25/18	3/3	2/3
76	M	0/2.2 i (flap)	2.3 i + s/3.8 c	3 + 4	1	27/17	25/17	4/4	2/3
78	M	3.5 i/4.5 s	3.5 i/5.7 s	3	1	27/19	25/22	3/3	3/3
78	M	2.3 i/3.0 s	1.0 i/2.9 s	5	5	26/17	27/18	2/1	2/1
78	M	Absent	0.9 i/3.4 s	Absent	1	25/17	29/19	4/4	3/3
79	M	0 i/0.8 s	0/2.7 s	5	5	21/17	21/17	2/3	3/2
79	M	2.0 i/3.7 s	Absent	5	Absent	29/21	28/20	3/3	2/2
79	M	0.5 i/3.9 s	0.1 i/4.4 s	1	1	24/16	21/16	3/2	4/2
79	M	Ankylosis	2.0 i/5.2 s	Ankylosis	4 + 5	25/20	23/16	Ankylosis	3/3
81	F	1.8 i/3.3 s	0/2.9 s	5	4 + 5	24/17	25/17	2/1	1/1
81	F	Absent	1.2 s/2.7 i	Absent	3	26/20	28/19	4/4	3/2
83	M	1.0 s/2.9 i	3.0 i/3.6 s	5	5	28/21	24/13	4/3	4/2
84	M	2.3 i/5.4 s	3.0 i/4.9 s	5	1	26/20	26/19	3/1	2/1
84	M	1.0 i/1.7 s	1.6 s/1.4 i	1	1	24/16	24/19	3/1	3/1
84	M	Absent	Absent	Absent	Absent	23/20	24/19	3/4	3/3
85	M	2.4 i/2.7 s	1.2 i/3.5 s	3 + 4 + 5	1	22/17	21/16	4/2	4/2
85	F	2.3 i/4.0 s	0/2.2 anterior rim	5	3 + 4 + 5	25/18	24/17	4/2	3/3
86	F	Absent	Absent	Absent	Absent	20/16	20/16	3/4	3/4
89	F	1.0 i/2.7 s	Absent	2 + 5	Absent	22/15	23/16	1/1	3/3
90	F	0.8 i/2.5 s	1.1 s/1.2 i	1	1	29/19	29/21	3/3	2/2
90	M	3.3 i/3.6 s	2.5 i/2.9 s	4 + 5	5	26/18	28/18	4/3	4/3
90	F	0/1.9 anterior rim	1.5 i/2.5 s	3 + 4 + 5	5	23/19	23/17	4/4	4/4
91	F	0 c/3.1 s	1.5 i/0 s	1	4	21/16	26/18	4/3	4/3
92	M	Absent	1.9 s/3.4 i	2 + 4 + 5	5	21/14	20/16	3/4	2/2
93	M	0/0 (absent)	0/3.2 s	Absent	4 + 5	31/18	31/17	3/3	4/4
94	M	1.7 i/3.3 s	Absent	2 + 5	Absent	26/21	27/21	3/2	4/4
96	M	0/2.2 anterior rim	0/3.8 anterior rim	3 + 4 + 5	3 + 4 + 5	26/18	28/17	4/4	4/4

¹i: Inferior; s: Superior. ²1: Full attachment; 2: Detachment anterior; 3: Detachment superior; 4: Detachment posterior; 5: Detachment inferior. ³Outerbridge classification: 0: Normal cartilage; 5: No cartilage. M: Male; F: Female.

In addition, the fact that the cranio-caudal length of the articular surface of the clavicle was about 40% longer than the articular surface on the manubrium, meaning that the upper third of the disc is not subject to compressive or frictional forces in most working situations, may explain why the superior part of the disc is often intact.

It is described that symptomatic SCJs with degenerative changes have an increased size of the clavicular head and a relative anterior subluxation of the clavicle compared to asymptomatic joints^[1], but not a superior subluxation. Even though the intraarticular disc in most of these joints must be expected to be severely changed and unable to prevent the clavicular head from superior motion during lifting, the enlargement of the head, related to the degenerative condition, might pull the interclavicular ligament superiorly, resulting in

a tightening of the ligament. This could explain why the clavicular head in this situation is not subluxating superiorly during depression of the shoulder^[19].

There was an overweight of thinning and detachment of the inferior part of the disc on the right side compared to left and fewer normal discs on the right side. Of danes 91% are right dominant and some activities are performed with more power by the dominant arm. This increases load on the SCJ, its ligaments and the disc, and may cause additional wear on the right SCJ on top of the degenerative wear that is affecting both sides.

We could confirm earlier findings of more severe changes of the cartilage on the clavicle compared to manubrium^[16]. Therefore, it makes sense to resect the clavicular and not the sternal part of the joint in case of surgery for osteoarthritis of the SCJ.

Arthroscopic surgery of the SCJ is described in a few series^[4-6,20]. Resection of the medial clavicular end is the procedure that has been reported in most of the cases^[4,5,20], and in open^[10] as well as arthroscopic^[4,5,20] series it resulted in marked pain reduction. The indication for this operation is degenerative changes that can be demonstrated by X-rays, MRI or CT-scan. In some cases of pain in the SCJ no such changes can be demonstrated. Our study shows that at least in the elderly population detachment of the articular disc is common. It is not known to which extent these changes in the disc are symptomatic, but detachment can probably lead to pain, locking and swelling, and technically it can be treated by arthroscopic debridement or resection of the disc as well as resection of the medial clavicular end. Pathology of the disc is not visible on X-rays or CT-scan, but can often be demonstrated on T2 weighted MRI-scans (personal experience). Persistent pain, locking and/or swelling of a SCJ without degenerative changes on X-rays or CT-scan might be caused by detachment or fraying of the disc, and an MRI-scan should be considered in these cases. The detachment and thinning of the discs inferiorly as found in our study means that surgical reattachment of the disc is impossible. Contrary, in case of traumatic detachment of otherwise normal discs in younger individuals, reattachment is an option in case of symptoms.

Detachment or destruction of the articular disc in the SCJ is a common finding in the aging population and can result in pain, locking and swelling which might be treated by resection of the torn disc. Degenerative changes of the articular cartilages are more common on the clavicle than on manubrium, and normal cartilage is rarely seen in this age group. Debridement, chondrectomy and medial clavicle resection may be relevant, but reattachment of the disc is not possible because of the marked tissue changes.

ACKNOWLEDGMENTS

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COMMENTS

Background

Arthroscopy of the sternoclavicular joint (SCJ) is a recently introduced technique that has opened for more specific procedures on this joint, e.g., resection or reinsertion of a torn disc, synovectomy, chondrectomy and removal of loose bodies. Knowledge of age-related changes is essential for planning of arthroscopic procedures, and previous cadaver studies have shown conflicting results.

Research frontiers

Open surgical procedures on the SCJ leave a scar at a cosmetically problematic location, and visualization of the deep part of the joint is often limited. Arthroscopy makes full inspection of the SCJ possible. The arthroscopic procedure that has previously been reported in the SCJ is clavicle end resection

for osteoarthritis.

Innovations and breakthroughs

This is the first study to describe the SCJ in cadaver specimens prepared without interference with the joint capsule and disc attachment sites. The authors found degenerative changes to disc and joint cartilages to be much more common than previously thought and showing in a typical pattern.

Applications

Arthroscopic resection of disc, cartilages and clavicular end of the SCJ may be applied in cases of pain, locking or swelling that is resistant to non-surgical intervention.

Peer-review

This is very classic study on degenerative SCJ. The study demonstrated the stage of cartilage in SC comprehensively.

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Retrospective Study

Epidemiology of open fractures in sport: One centre's 15-year retrospective study

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Abstract

AIM

To describe the epidemiology of sport-related open fractures from one centre's adult patient population over a 15-year period.

METHODS

A retrospective review of a prospectively-collected database was performed: The database contained information all sport-related open fractures, sustained from 1995 to 2009 in the Edinburgh, Mid and East Lothian Populations.

RESULTS

Over the 15-year period, there were 85 fractures recorded in 84 patients. The annual incidence of open sport-related fractures was 0.01 per 1000 population. The mean age at injury was 29.2 years (range 15-67). There were 70 (83%) males and 14 females (17%).

The 6 most common sports were soccer ($n = 19$, 22%), rugby ($n = 9$, 11%), cycling ($n = 8$, 9%), hockey ($n = 8$, 9%); horse riding ($n = 6$, 7%) and skiing ($n = 6$, 7%). The five most common anatomical locations were finger phalanges ($n = 30$, 35%); tibial diaphysis ($n = 19$, 23%); forearm ($n = 12$, 14%); ankle ($n = 7$, 8%) and metacarpals ($n = 5$, 6%). The mean injury severity score was 7.02. According to the Gustilo-Anderson classification system, 45 (53%) fractures were grade 1; 28 (33%) fractures were grade 2; 8 (9%) fractures were grade 3a; and 4 (5%) fractures were grade 3b. Out of the total number of fractures, 7 (8%) required plastic surgical intervention as part of management. The types of flaps used were split skin graft ($n = 4$), fasciocutaneous flaps ($n = 2$); and adipofascial flap ($n = 1$).

CONCLUSION

We analysed the epidemiology of open fractures secondary to sport in one centre over a 15-year period. Soccer and rugby were the most common causative sports while fractures of the finger phalanx and of the tibial diaphysis were the most common sites. Open fractures are uncommon in sport; however, when they are sustained they usually occur on muddy sport fields or forest tracks and therefore must be treated appropriately. It is important that clinicians and sports therapists have knowledge of these injuries, in order to ensure they are managed optimally.

Key words: Open; Fracture; Sport; Epidemiology; Injury; Trauma

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Core tip: We reviewed all open sport-related fractures presenting to our trauma centre over a 15-year period to provide comprehensive epidemiological data on this injury type. Open sport-related fractures occurred at an annual incidence of 0.01/1000 population. The mean age at injury was 29.2 years; the gender ratio was 7.4:1 (male:female). The most common causative sports were soccer and rugby. The most common fracture locations were finger phalanx and tibial diaphysis. Fourteen percent of the fractures were Gustilo-Grade 3; 8% required plastic surgical intervention. Open fractures in sport are a rare, but significant, injury; awareness and education is necessary among clinicians to optimize outcome.

Wood AM, Robertson GAJ, MacLeod K, Porter A, Court-Brown CM. Epidemiology of open fractures in sport: One centre's 15-year retrospective study. *World J Orthop* 2017; 8(7): 545-552 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i7/545.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i7.545>

INTRODUCTION

Open fractures are uncommon in the United Kingdom

sporting population, however they have a high morbidity, which makes the patient group significant. This institution has previously published work looking at the epidemiology of open fractures and found an incidence of 30.7 per 100000 per year^[1].

Sports and exercise is ever increasing in popularity, particularly team sports and multi-sport endurance^[2]. This is due to the impact of social and cultural influences, such as easier access to sporting facilities and social media. The epidemiology of acute sporting fractures has been described by Court-Brown *et al*^[3] 2008. The authors describe sports-related fractures as having a Type C distribution with unimodal peaks in both young males and females^[3]. They also noted a clear preponderance towards upper limb fractures in sports, the majority of which involve the finger phalanges, metacarpus or distal radius^[3]. Lastly they recorded an open fracture rate of 1.7% among sport-related fractures, with an annual incidence for open sport-related fractures of 0.02 per 1000 population. Court-Brown *et al*^[1] 2012 also described the epidemiology of open fractures, they conclude that 3.6% of all open fractures are a result of sport.

In order to obtain accurate epidemiological data, when the incidence of open fractures is this low, it is necessary to perform a long-term study of these fractures within a large population group^[3]. Thus, while there has been an increasing cohort of literature of the epidemiology of sport-related fractures, the literature describing the epidemiology of open fractures in sport remains minimal^[1,3].

We aim to provide the first long-term study describing the epidemiology of sport-related open fractures from one centre's adult patient population. This information will be useful for medical professionals treating patients participating in sport and sport governing bodies.

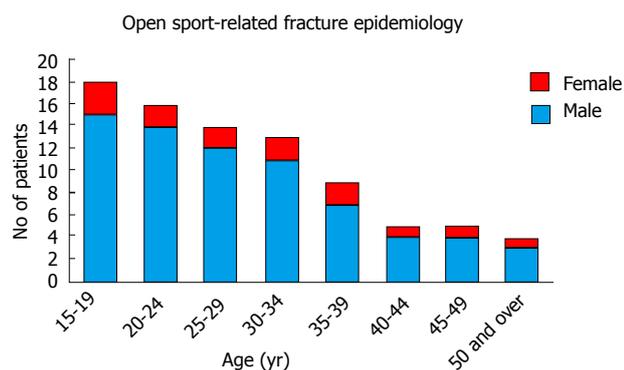
MATERIALS AND METHODS

All acute fractures presenting to the Royal Infirmary of Edinburgh, Orthopaedic Trauma Unit from the residents of Edinburgh, Mid and East Lothian, over the period of 1995 to 2009, were prospectively recorded on a database. This included all patients from the region, who were injured elsewhere, but were followed up under the Edinburgh Orthopaedic Trauma Unit: This was to provide accurate epidemiological data. Conversely, all non-resident patients who were injured within the region were excluded from the database. The mean population count for the region over the study period was 539858 (Population Count in 2000, $n = 534715$ ^[3]; Population Count in 2007, $n = 545000$ ^[4]).

The database was retrospectively reviewed in 2016, and all open fractures, sustained over the 15-year period (1995 to 2009), were identified. Subsequently, a subgroup, in which the injury was secondary to a sporting activity, was identified. Sporting activity was defined as participation in an athletic game or activity

Table 1 Total number of sport-related open fractures, divided by causative sport and the 5 most common fracture locations

Sport	Number	Percentage of the whole cohort (%)	Finger phalanx	Tibial diaphysis	Forearm	Ankle	Metacarpal
Soccer	19	22	3	9	1	1	0
Rugby	9	11	2	1	0	3	1
Cycling	8	9	3	1	2	0	0
Hockey	8	9	8	0	0	0	0
Horse riding	6	7	1	1	2	1	0
Skiing	6	7	3	1	2	0	0
Mountain bike	4	5	0	0	2	0	0
Quad bike	4	5	0	2	1	1	0
Basketball	3	4	2	0	1	0	0
Shinty	3	4	3	0	0	0	0
Sledging	3	4	0	2	0	1	0
Motorcross	2	2	0	0	0	0	2
Badminton	1	1	1	0	0	0	0
Bowling	1	1	1	0	0	0	0
Cricket	1	1	1	0	0	0	0
Golf	1	1	0	0	0	0	1
Snowboarding	1	1	0	1	0	0	0
Squash	1	1	1	0	0	0	0
Surfboard	1	1	1	0	0	0	0
Trampolining	1	1	0	0	1	0	0
White water rafting	1	1	0	1	0	0	0
Unknown	1	1	0	0	0	0	1
Totals	85	100	30	19	12	7	5

**Figure 1 Open sport-related fracture epidemiology.**

at time of injury. The Gustilo-Anderson classification^[5] was used to describe the extent of soft tissue injury associated with the fracture: For all the fractures, the grading of this classification was based on the intra-operative findings after surgical debridement.

The database contained information on patient age and gender, site of the fracture, mode of injury, sport participated at time of injury, Gustilo grading for each fracture, and required treatment, including both Orthopaedic and Plastic Surgical procedures. Review of each presenting radiograph, as well as confirmation of the designated Gustilo grading^[4], was performed by the senior author, a Professor of Orthopaedic Trauma Surgery.

For analysis purposes, niche sporting activities, of a very similar nature, were grouped to allow for more meaningful interpretation of the data: Grouping however was only performed if the sports were considered to be suitably similar. For instance road cycling and track cycling were combined as cycling;

however, mountain biking, was considered a separate sport.

RESULTS

Epidemiology

There were 85 fractures sustained by 84 people over the 15-year period. The annual incidence of open sport-related fractures was 0.01 per 1000 population. Of the 84 patients, 70 (83%) were male and 14 (17%) were female (Figure 1). The mean age of the total cohort was 29.2 (range 15-67; SD 11.75; 95%CI: 2.5). The mean age of the female population was 31.93 years and the mean age of the male population was 28.62 years. Forty fractures occurred during competitive sport, nine during training for competitive sport and thirty-six during recreational sport. Two fractures were sustained by professional athletes and eighty-three fractures were sustained by recreational athletes.

Causative sports

The 6 most common sports were soccer ($n = 19$, 22%), rugby ($n = 9$, 11%), cycling ($n = 8$, 9%), hockey ($n = 8$, 9%); horse riding ($n = 6$, 7%) and skiing ($n = 6$, 7%) (Figure 2). Other common sports were mountain biking ($n = 4$, 5%), quad biking ($n = 4$, 5%), basketball ($n = 3$, 4%), shinty ($n = 3$, 4%) and sledging ($n = 3$, 4%). Table 1 shows the total number of fractures, divided by sport, and by fracture location.

Fracture location

The top 5 fracture locations were finger phalanges, 35% ($n = 30$); tibial diaphysis 22% ($n = 19$); forearm 14% ($n = 12$); ankle 8% ($n = 7$) and metacarpals 6%

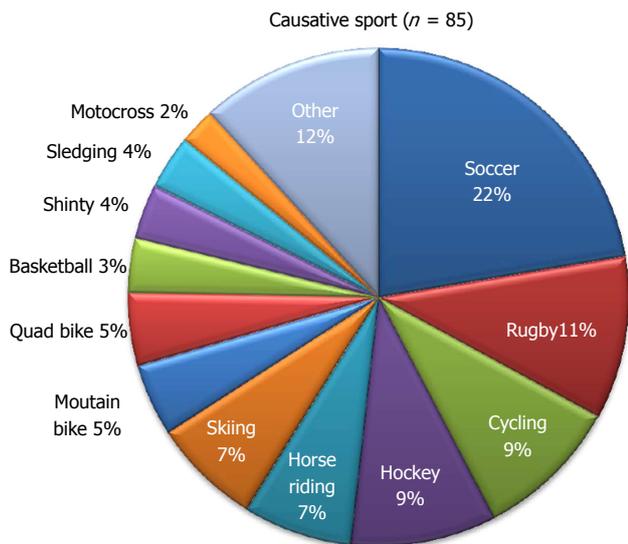


Figure 2 Causative sports for open sport-related fractures.

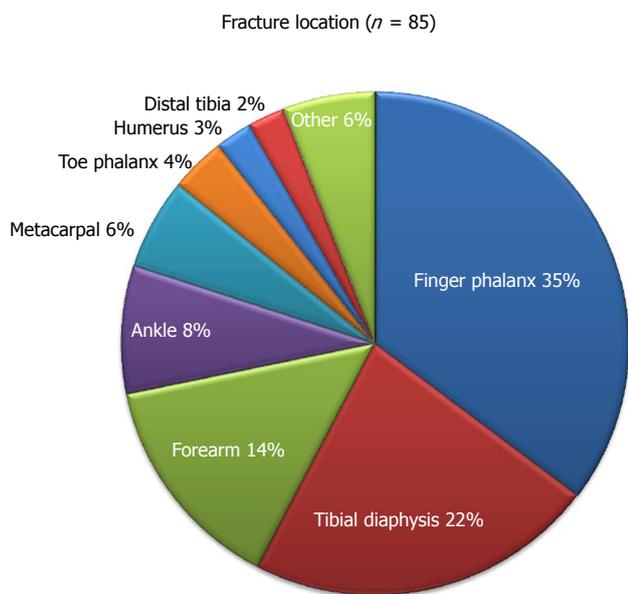


Figure 3 Fracture location for open sport-related fractures.

(*n* = 5) (Figure 3). Of the forearm fractures, four were of the distal radius, four were of the proximal ulna, three were of the combined radial and ulna diaphysis and one was of the ulnar diaphysis. Other fracture sites included toe phalanges (*n* = 3); humerus (*n* = 2); distal tibia (*n* = 2); pelvis (*n* = 1); clavicle (*n* = 1); femur (*n* = 1); patella (*n* = 1) and talus (*n* = 1). The fractures involving finger phalanges, included 5 of the little finger; 6 of the ring finger; 3 of the middle finger; 4 of the index finger; 10 of the thumb and in 2 cases the finger involved was unknown. Of all the fractures, 59% (50/85) were of the upper limb. Table 2 shows the fracture locations for the top 6 sports.

Injury severity

According to the Gustilo-Anderson classification

Table 2 The six most common causative sports and their anatomical distribution

Anatomical location	Soccer	Rugby	Cycling	Hockey	Horse riding	Skiing
Ankle	1	3	0	0	1	0
Clavicle	0	0	1	0	0	0
Distal radius	0	0	0	0	2	0
Distal humerus	1	0	0	0	0	0
Femur	0	0	1	0	0	0
Finger phalanx	3	2	3	8	1	3
Metacarpal	0	1	0	0	0	0
Patella	0	1	0	0	0	0
Distal tibia	1	1	0	0	0	0
Proximal ulna	0	0	2	0	0	1
Radius and ulna	1	0	0	0	0	1
Talus	0	0	0	0	1	0
Tibial diaphysis	9	1	1	0	1	1
Toe phalanx	3	0	0	0	0	0
Ulna	0	0	0	0	0	0
Total	19	9	8	8	6	6

system^[5], 45 (53%) fractures were Grade 1; 28 (33%) fractures were Grade 2; 8 (9%) fractures were Grade 3a; and 4 (5%) fractures were Grade 3b (Figure 4).

The mean Injury Severity Score was 7.02 (SD 4.33; 95%CI: 0.92). There were 2 deaths during the 15-year period; 1 road-cyclist who had an open proximal ulna fracture; and 1 soccer player, who sustained a grade 3a open tibia fracture.

Primary orthopaedic management

Regarding the primary index procedures: Twenty-two fractures were treated with wound management and cast/splint application; twenty-six fractures with wound management and open reduction internal fixation; eighteen fractures with wound management and intra-medullary nailing; eleven fractures with wound management and kirschner-wire fixation; five fractures with wound management and external fixator application; and three fractures with wound management and tension band wire fixation (Table 3).

Plastic surgical intervention

There were 7 fractures (8%) that required plastic surgical intervention as part of their management. The types of flaps used were split skin graft (*n* = 4), fasciocutaneous flaps (*n* = 2); and adipofascial flap (*n* = 1) (Table 4).

DISCUSSION

The aim of this study was to describe the epidemiology of sport-related open fractures. The main findings were that sport-related open fractures demonstrated a uni-modal incidence of injury, with an annual incidence of 0.01 per 1000 population, a mean age at injury of 29.2 years and a male to female ratio of 7.4:1. Ninety-eight percent of these injuries were sustained by non-professional athletes. Over half of all fractures were

Table 3 Orthopaedic management of the open fractures

Fracture location	Wound management + splint/cast	Wound management + ORIF	Wound management + intra-medullary nail	Wound management + K-wire fixation	Wound management + external fixator	Wound management + tension band wire
Finger phalanx	20	3	-	6	1	-
Tibial diaphysis	-	2	17	-	-	-
Ankle	-	7	-	-	-	-
Metacarpal	-	2	-	3	-	-
Distal radius	-	2	-	-	2	-
Proximal ulna	-	1	-	-	-	3
Radius and ulna	-	3	-	-	-	-
Toe phalanx	1	-	-	2	-	-
Distal humerus	-	2	-	-	-	-
Distal tibia	-	1	-	-	1	-
Ulna diaphysis	-	1	-	-	-	-
Clavicle	1	-	-	-	-	-
Pelvis	-	1	-	-	-	-
Patella	-	1	-	-	-	-
Femur	-	-	1	-	-	-
Talus	-	-	-	-	1	-
Total	22	26	18	11	5	3

ORIF: Open reduction internal fixation; K-wire: Kirschner wire.

Table 4 Sport-related open fractures requiring plastic surgical intervention

Sport	Gustilo grade	Procedure	Injury
Soccer	2	SSG	Tibial diaphysis
Soccer	3a	Adipofascial flap	Tibial diaphysis
Soccer	3a	SSG	Tibial diaphysis
Soccer	3b	Fasciocutaneous flap	Distal tibia
Quad bike	3b	SSG	Ankle
Quad bike	2	Fasciocutaneous flap	Tibial diaphysis
Sledging	3b	SSG	Ankle

SSG: Split skin graft.

located in the upper limb, with finger phalanx fractures the most common fracture location. Soccer was the most common causative sport, accounting for over one fifth of all injuries. Regarding injury severity, 14% were Gustilo-Anderson Grade 3 classification, with only 8% of all fractures requiring plastic surgical intervention.

This is in keeping with existing literature on sport-related fractures^[3,6]. Court-Brown *et al.*^[3,6] previously reported that 12.8% of all fractures are sustained during sporting activities. These injuries were noted to present in a uni-modal distribution, with a mean age at injury of 25.6 years and a gender ratio of 7.5:1^[3]. Upper limb sport-related fractures were also noted to be more common than lower limb sport-related fractures, with 77% of all sport-related fractures occurring within the upper limb fractures^[3,6]. One point seven percent (1.7%) of these sport-related fractures were open, providing an annual incidence of open sport-related fractures of 0.02 per 1000 population^[3,6]. Robertson *et al.*^[7,8] also noted that between 96% to 98% of all sport-related fractures occur in non-professional athletes.

In comparison of both studies, regarding the in-

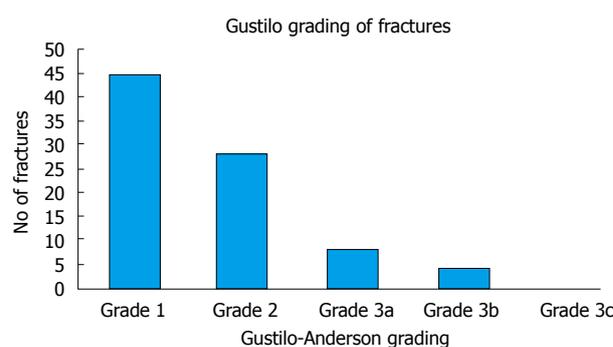


Figure 4 Gustilo-Anderson grading for open sport-related fractures.

creased mean age observed with our cohort, which specifically relates to open fractures, we feel this reflects a greater proportion of elderly athletes who sustain an open fracture during sport^[1]. Age has previously been identified as a risk factor for sustaining an open fracture: This is felt to be secondary both to the weakening effects of aging on the skin, as well as to the decreased levels of proprioception seen in the elderly, which predispose to more severe injury^[1,9]. Regarding the increased proportion of lower limb fractures in our cohort, we feel this is secondary to an increased proportion of tibial diaphyseal and ankle fractures, among the open fracture cohort. Both fractures have been noted to be at high risk of open injury with tibial diaphysis the second most common recorded open fracture and ankle fracture the fifth most common recorded open fracture^[1]. This provides a higher proportion of lower limb fractures among sport-related open fractures^[1].

Regarding the severity of injury within our study, the proportion of Gustilo-Anderson grade 3 fractures was slightly lower than that within previous studies^[9].

Court-Brown *et al.*^[1] reported a series of 2386 open fractures, within the general population, and 27% were Grade 3 grading. The difference between proportions is likely explained by the younger mean age of our "athletic" cohort at 29.2 years, with the mean age from Court-Brown *et al.*^[1] being 45.5 years. Age has been noted to be a risk factor to sustain a more serious grade of open fracture, due to the deleterious effects it has on the surrounding soft tissues and skin^[1,9]. This will also account for our marginally decreased requirement for plastic surgical intervention at 8%, compared to 13% from their data^[1,10].

In our study, soccer was the most common sport (22%) and within this category, the most common fracture was tibia diaphysis (47%). Soccer accounted for 4 of the 7 cases requiring plastic surgery intervention: 3 out of the 9 soccer-related tibial fractures were Gustilo-Anderson Grade 3. This represents the severity of these injuries. Robertson *et al.*^[7] have previously reported on soccer-related fractures. Similar to Court-Brown *et al.*^[1], they found that the majority of soccer-related fractures were of the upper limb (68%). In contrast, we found 74% of our soccer-related fractures were of the lower limb. Within our cohort, this reflects a high proportion of tibial diaphyseal, ankle and toe phalanx fractures, which have previously been documented as being high risk for open fractures^[1]. This contrast is likely explained by the higher energy "mechanism of injury" required to sustain an open fracture compared to a closed fracture^[1]: Within soccer, such higher energy "mechanisms of injury" most often involve high-speed collisions between players; with soccer being predominantly a lower limb sport, this then increases the likelihood of soccer-related open fractures being sustained in the lower limb^[1,3,7].

Rugby accounted for 11% of the open fractures secondary to sport. This is similar to the figures reported by Robertson *et al.*^[8] in their paper describing the epidemiology of rugby-related fractures, with rugby accounting for 17% of all sport-related fractures. To note in the present study, six of the nine rugby-related fractures were of the lower limb, with fractures of the ankle comprising half of the lower limb injuries. In contrast, both Robertson *et al.*^[8] and Garraway *et al.*^[11] reported that the upper limb was most at risk of fracture (83% and 42% of injuries respectively); however, as detailed above, there is an increased proportion of lower limb fractures in open fracture cohorts, due to higher proportions of tibial diaphyseal and ankle fractures^[1]. Indeed, Garraway and MacLeod^[11] did record that the lower limb was at greatest risk of dislocations and soft tissue injuries.

Cycling (including road cycling and track cycling) accounted for 9% of all fractures seen in the 15-year period. Mountain Biking accounted for only 5% and this may be a reflection of the protective equipment used in this sport, as road cyclists appear at a higher risk of open fracture compared to their mountain biking counterparts. Both sports showed a preponderance for upper limb injuries, with cycling recording 3 finger

phalanx fractures and 3 forearm fractures (out of a total of 6 fractures) and mountain biking recording 2 forearm fractures. This pattern of injury reflects the findings of Aitken *et al.*^[12], who reported that upper limb fractures occurred 10 times more commonly than lower limb fractures during mountain biking. To note, mountain biking is increasing in popularity, and with our trauma centre being located close to Scotland's largest mountain biking centre (Glentress), one may expect to detect a significant incidence of injuries from this sport. However, Aitken *et al.*^[12], in their comprehensive study on recreational mountain biking injuries 2011, noted a trend away from serious injury in this sport, as a result of the use of personal protective equipment. This likely accounts for the low incidence observed in our study period.

Similarly, hockey accounted for 9% of all open sport-related fractures. This sport also demonstrated a preponderance for upper limb injuries, with all such fractures occurring within the finger phalanx. Court-Brown *et al.*^[13] have already shown that fractures of the finger phalanx is common in hockey, comprising half of all such fractures in the sport^[3]. Furthermore, Aitken *et al.*^[13] found that while field hockey only accounted for 7% of all sport-related finger phalanx fractures, it was the cause of 50% of all of the open sport-related finger phalanx fractures. Comparatively, this study found that hockey accounted for 40% of all open fractures of the finger. Aitken *et al.*^[13] went on to reason that such injuries are likely due to accidental contact between the hand and either a hockey stick or a hockey ball travelling at speed, and this may be further explained by the pattern of grip around the stick. Players often hold the stick low to the ground during tackles thus increasing the chance of contact with the ball or entrapment with another player's stick^[13-15]. This continues to be an area where increased protection may benefit participants and decrease the incidence of these injuries^[13-15].

Horse riding accounted for 7% of the open fractures sustained. The mechanism by which injuries are sustained during horse riding are usually high energy - a fall from height at high speed - therefore, there is a clear potential for an open fracture to be sustained as a result of this mechanism^[16,17]. It is important to note that these fractures are often farmyard injuries and have a high risk of contamination^[16,17]. Therefore these fractures should be managed appropriately in line with BOAST guidelines^[18]. Previous studies on horse riding injuries, have shown that sprains are the most prevalent injury type (42%), followed by lacerations and bruises (40%), and then fractures and dislocations (33%)^[16]. There was a near equal proportion of upper and lower limb fractures in the current series (3 upper limb and 2 lower limb open fractures), and while our paper was specifically looking at open fractures, this finding is reflected in other studies. A retrospective study from the United States looking at horse riding injuries, showed that the lower extremity was injured

22.2% of the time and the upper extremity 21.5%, with the remaining injuries being to the head, chest and abdomen^[17].

Skiing accounted for 7% of all sporting-related open fractures. The majority of these were upper limb fractures (5 of 6), with 1 recorded ankle fracture. The low prevalence of open fractures secondary to skiing may reflect our institution's urban geographical location. However, it should be noted that there is an artificial ski slope on the outskirts of the city.

Within skiing, 50% of fractures were in the hand: This may be linked to the composition of the dry-ski slope material, with a high propensity to entrap fingers.

Anatomically, the most common location of fracture was the finger phalanx comprising 35% of all fractures. This again is in keeping with the findings from Court-Brown *et al.*^[3], who found the most common location for sport-related fractures was the finger phalanx, followed by distal radius, metacarpals, clavicle and ankle^[3]. Similar findings have been reported by Aitken *et al.*^[4] in another comprehensive series of sport-related fractures. In contrast, the current study found the next most common fracture locations for sport-related open fractures to be tibial diaphysis, forearm, ankle and metacarpal. This is in keeping with the incidence of open fractures within the general population, with the five most common fracture locations being finger phalanx, tibial diaphyseal, distal radius, toe phalanx and ankle^[1]. It would appear there is a difference between the common presenting locations for sport-related open fractures and sport-related closed fractures^[1,3,4,6]. The exact reasons behind this are difficult to fully define, though it appears that certain fracture locations (tibial diaphysis and ankle) are at an increased risk of open fractures: This is likely due to a combination of the common fracture patterns observed at these sites as well as the volume of surrounding soft tissue cover in these regions^[1]. As such, these fracture locations are more likely to be present within observational open fracture cohorts^[1]. Nevertheless, the number of fractures described in this series are low, and, while this reflects a low incidence of this injury type, we would recommend further large-scale studies on this topic, to better define the epidemiology of open fractures in sport^[1,3,4,6]. Similarly, as with previous papers from our institution, our study reflects the experience of our region: It is likely that the incidence of such fractures will vary in other centres, according to the types of sports that predominate in the studied area^[1,3,4,6].

Regarding further limitations of our study, patient outcomes were not obtained, and this certainly could be an area for future work. Obtained information on the time taken to return to sport or work after injury would be of significant relevance for sporting regulators: A high incidence of injuries requiring long periods of rehabilitation may lead to a review of rules and personal protective equipment: This can serve

to reduce the economic impact of such injuries in professional and recreational sport^[1,3,4,6,15].

In conclusion, the epidemiology of sport-related open fractures from one orthopaedic trauma centre over a 15-year period was reviewed. Soccer and rugby were the most common causative sports, while the finger phalanx and tibial diaphysis were the most common fracture locations. Only 14% of fractures were Gustilo Grade 3 and only 8% required plastic surgical intervention. While open fractures in sport are uncommon, they frequently occur on muddy sport fields or forest tracks and must be treated appropriately. A robust set of guidelines is in place from the British Orthopaedic Association and British Association of Plastic Reconstructive and Aesthetic Surgeons to enable this to be achieved, and these should be followed accordingly. Furthermore, a good understanding of the range and variety of sport-related open fractures is beneficial for clinicians and sports therapists, as this allows planning for treatment protocols, rehabilitation and injury prevention.

COMMENTS

Background

Open fractures are uncommon in the United Kingdom sporting population, accounting for less than 2% of all sport-related fractures. However they have a high morbidity, which makes the patient group significant. Currently there is limited evidence in the literature describing the epidemiology of open fractures in sport.

Research frontiers

Despite comprising less than 2% of all sport-related fractures, open fractures in sport represent a very significant injury for the athlete, often resulting from a high energy mechanism and being sustained in an environment with high risk of wound contamination. However, due to the limited incidence of this fracture type, minimal research has been previously performed regarding its epidemiology. Given the potential significant morbidity associated with such injuries, an accurate understanding of the range and variety of sport-related open fractures will allow clinicians and sports therapists to better plan treatment protocols, rehabilitation and injury prevention methods for these fractures.

Innovations and breakthroughs

In the study, the authors analysed the epidemiology of open fractures in sport within our population over a 15-year period. Open sport-related fractures occurred at an annual incidence of 0.01/1000 population. The mean age at injury was 29.2 years; the gender ratio was 7.4:1 (male:female). Soccer and rugby were the most common causative sports while fractures of the finger phalanx and of the tibial diaphysis were the most common sites. 14% of the fractures were Gustilo-grade 3; 8% required plastic surgical intervention. This is the first study to provide a comprehensive description of the epidemiology of this injury type.

Applications

A comprehensive understanding of the predicted patterns of injury and most common causative sports, with this fracture type, can allow sports teams and medical personnel to appropriately plan for such injuries, producing treatment protocols and instigating injury prevention measures. This allows both optimization of the management and outcome of these injuries, as well as potential reduction in their future incidence.

Terminology

An open fracture is a fracture with an associated skin wound which allows the

external environment to communicate with the fracture. The Gustilo-Anderson Classification is a classification system which grades the severity of open fractures into three grades, based on the wound size, the underlying damage to the peri-osteal and neuro-vascular structures, and the ability to achieve direct wound closure. Please refer to the provided reference for the formal classification. A Split Skin Graft is a skin graft which comprises the epidermis and a portion of the dermis: the full thickness of the dermis is not excised in this graft type. An Adipofascial Flap is a portion of adipose and fascial tissue that is based on a perforating artery. This is dissected and elevated from its native location, maintaining the perforator blood supply, and transferred locally to the damage area requiring soft tissue coverage. A Fasciocutaneous Flap is a portion of skin, subcutaneous tissue and fascial tissue that is based on a perforating artery. This is dissected and elevated from its native location, maintaining the perforator blood supply, and transferred locally to the damage area requiring soft tissue coverage.

Peer-review

It is very interesting finding.

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Retrospective Study

Acetabular revisions using porous tantalum components: A retrospective study with 5-10 years follow-up

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Author contributions: All authors contributed to drafting the work and approved it for publication; in particular, Evola FR and Sessa G designed and performed the research; Costarella L and Evola G dealt with the literature research; Barchitta M and Agodi A analyzed the data; Evola FR wrote the paper; Sessa G revised the manuscript.

Institutional review board statement: The Research Ethics Board has not considered it necessary to formulate authorization for this retrospective study because the data was analyzed anonymously and the results were reported in an aggregate manner.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest or financial relationships in the realization of this work.

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Abstract

AIM

To evaluate the clinical and X-ray results of acetabular components and tantalum augments in prosthetic hip revisions.

METHODS

Fifty-eight hip prostheses with primary failure of the acetabular component were reviewed with tantalum implants. The clinical records and X-rays of these cases were retrospectively reviewed. Bone defect evaluations were based on preoperative CT scans and classified according to Paprosky criteria of Radiolucent lines and periprosthetic gaps; implant mobilization and osteolysis were evaluated by X-ray. An *ad hoc* database was created and statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, version 23.0). Statistical analyses were carried out using the Student's *t* test for independent and paired samples. A *P* value of < 0.05 was considered statistically significant and cumulative survival was calculated by the Kaplan-Meier method.

RESULTS

The mean follow-up was 87.6 ± 25.6 mo (range 3-120 mo). 25 cases (43.1%) were classified as minor defects, and 33 cases (56.9%) as major defects. The preoperative HHS rating improved significantly from a mean of 40.7 ± 6.1 (range: 29-53) before revision, to a mean of 85.8 ± 6.1 (range: 70-94) at the end of the follow-up (Student's *t* test for paired samples: $P < 0.001$). Considering HHS only at the end of follow-up, no statistically significant difference was observed between patients with a major or minor defect (Student's *t* test for independent samples: $P > 0.05$). Radiolucent lines were found in 4 implants (6.9%). Postoperative acetabular gaps were observed in 5 hips (8.6%). No signs of implant mobilization or areas of periprosthetic osteolysis were found in the x-rays at the final follow-up. Only 3 implants failed: 1 case of infection and 2 cases of instability. Defined as the end-point, cumulative survival at 10 years was 95% (for all reasons) and 100% for aseptic loosening of the acetabular component.

CONCLUSION

The medium-term use of prosthetic tantalum components in prosthetic hip revisions is safe and effective in a wide variety of acetabular bone defects.

Key words: Porous tantalum; Bone defect; Acetabular revision; Osseointegration; Biological fixation; Augment; Retrospective study

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Core tip: Revisions of acetabular implant components are frequently associated with bone defects. Porous tantalum acetabular cups and augments were introduced to improve biological fixing and restore the normal centre of rotation. The greatest advantage is for major bone defects, where the tantalum cup and augments provide stable primary fixing with the biological potential for bone ingrowth. Nowadays, porous tantalum represents the ideal bone substitute in prosthetic revisions.

Evola FR, Costarella L, Evola G, Barchitta M, Agodi A, Sessa G. Acetabular revisions using porous tantalum components: A retrospective study with 5-10 years follow-up. *World J Orthop* 2017; 8(7): 553-560 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i7/553.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i7.553>

INTRODUCTION

The revision of the acetabular component of a prosthetic implant is frequently associated with a bone defect. Different types of treatment and its complications are described in the literature: The use of structural allograft from cadaver or synthetic bone substitutes with anti-protrusion rings or reconstruction

cages do not fix biologically and are at high risk of medium-term failure (15%-45% within 10 years)^[1-7]. The use of morcellised bone grafts (impaction grafting) with cemented acetabular inserts can cause fractures, resorption with implant migration, and transmission of infectious diseases^[8,9]. Implanting bilobed oblong cups or extra-large uncemented hemispherical so-called "jumbo cups" can destroy the rear column because the upper and lower bone defects are larger than the front and back ones^[10,11]. High hip centres alter joint bio-mechanics and are associated with greater risks of dislocation and mobilization^[12,13]. Cementless fixing in primary and revision implants has demonstrated greater survival in the medium and long-term compared to cemented fixing^[13-15].

Biological bone integration of the implant requires intimate contact between the components and bone and immediate mechanical stability during the operation; often the surgeon is forced to implant the acetabular component high up in the revisions leading to altered abductor muscle function and heterometry of the limbs^[16]. In the last decade porous tantalum-made acetabular cups and augments have been introduced to improve biological fixing in bone defects and allow the normal centre of rotation to be restored^[13,17].

Tantalum is a ductile metal, inert and bio-compatible *in vivo*. Porous tantalum, produced through a process of chemical deposition of the metal in a reticulated skeleton in glassy carbon, is 80% porous, has an average pore size of 550 microns, an elastic modulus of 3.1 Gigapascals (Gpa) and a friction coefficient of 0.88 to form a structure very similar to cancellous bone^[17]. Due to its three-dimensional structure and bioactivity, porous tantalum has shown complete bone integration in animal models in 4-6 wk from implantation^[18]. Furthermore, compared to titanium implants, it can fill up periprosthetic gaps of up to 5 mm^[17,18]. Therefore the use of tantalum components represents a viable alternative to traditional surgical techniques, especially in the presence of large bone defects, because the implant can achieve immediate stability. There are only a few studies in the literature with small samples of tantalum components in hip revisions, the majority of these studies being short term.

The aim of this study is to evaluate the clinical and radiographic results of acetabular components and tantalum augments in prosthetic hip revisions, and assess whether bone defect types can compromise outcomes or the medium term survival of the implants.

MATERIALS AND METHODS

From December 2006 to December 2011, 58 hip prostheses with primary failure of the acetabular component were reviewed with implants in tantalum. A retrospective review of the clinical records and X-rays of these cases was performed. Patients underwent clinical and radiographic evaluation before and after the review procedure at regular intervals. Clinical

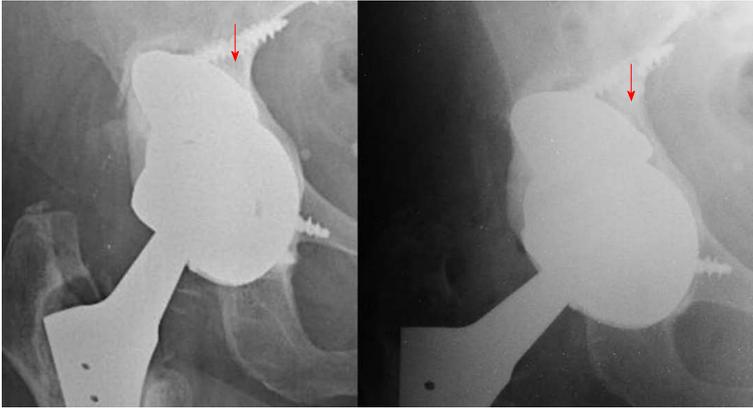


Figure 1 Radio-lucent line in the prosthesis.

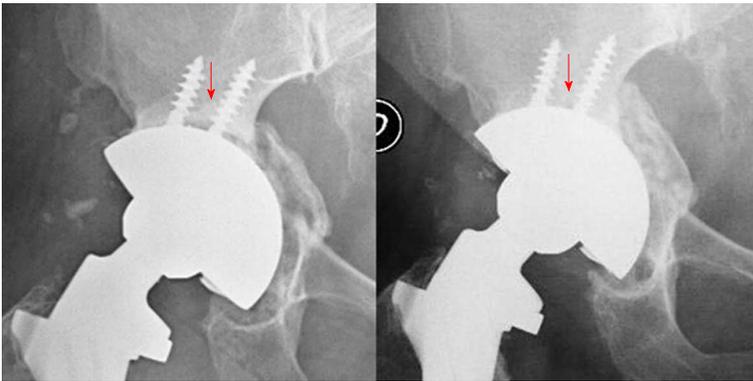


Figure 2 Gaps in the prosthesis.

evaluation was performed pre-operatively and at the end of the follow-up, using the Harris Hip Score (HHS): A score of 91 to 100 was considered as "excellent", 81 to 90 as "good", 71 to 80 as "fair", and below 70 as "poor".

Radiographic evaluation was performed with axial and front-rear views of the pelvis; X-rays were evaluated by two independent orthopedists (GL and SB) who did not take part in this project. Radio-lucent lines, periprosthetic gaps, implant mobilization and osteolysis were evaluated radiographically. Radio-lucent lines of the acetabular components and augments were described according to the DeLee *et al.*^[19] criteria and measured through a transparent ruler; radio-lucent lines are considered significant if > 2 mm or progressive (Figure 1). Acetabular gaps were defined as areas in which the prosthesis surface did not achieve direct initial contact with the bone in early postoperative X-rays. The gaps differentiate from radio-lucent lines appearing on subsequent X-rays and are measured through a transparent ruler; acetabular gaps were considered positive when > 1 mm on the initial postoperative X-ray (Figure 2). Implant mobilization is defined by angle inclinations over 8° compared to postoperative X-ray checks or the presence of radiolucent lines in all three DeLee and Charnley zones^[20,21]. X-ray evidence of stable implant fixing was shown by prosthesis contact with the bone and no radiolucent lines in 2 of the 3 zones. Osteolysis is the presence of a > 4 mm lucent area (by X-ray) near the prosthesis^[22].

The evaluation of bone defects was based on

preoperative CT scans and classified by Paprosky criteria^[23]. Type 1: Limited bone defect, with unaltered rhyme, wall and columns; type 2 (A, B, C): Unaltered columns, but with deformed rhyme and walls; type 3 (A and B): Destroyed posterior column.

According to Watson-Jones, an anterolateral approach has been used in all procedures, regardless of the type of surgery previously performed. Twenty-eight (48.3%) uncemented press-fit Trabecular Metal Monoblock Acetabular Cups (Zimmer®) and thirty (51.7%) Trabecular Metal Revision Shells (Zimmer®) were implanted. The decision to use adjunctive screw fixes in uncemented Monoblock cups was taken intra-operatively. For complex acetabular revisions, Revision Shells offer the most versatile option, because the polyethylene liner is cemented inside the cup with adjustable inclination and anteversion; furthermore, the non-modular component offers advantages over the modular component having a lower modulus of elasticity and better screw fixing and positioning directly through the tantalum shell.

The tantalum augments, of different shapes and sizes, with rim screw holes, are used to restore the center of rotation and the normal bio-mechanics of the hip, fill large bone defects ($> 50\%$) and restore the acetabular support margins, to allow greater prosthesis-bone contact and better mechanical stability^[16,18,22].

The decision to use augments was based on bone defect and intraoperative prosthetic stability. Augments are screw-fixed into the acetabulum and separated from the prosthesis with a thin layer of polymethyl-



Figure 3 Acetabular revisions with minor bone defects.

methacrylate; they also reduce the use of morcellised bone or structural cadaver bone and are resistant to fractures, mobilization, and resorption, which, however, can affect massive grafts as a result of vascular integration and periprosthetic bone remodelling^[24]. Augments were used in 16 cases: 3 type 2C, 8 type 3A, 5 in type 3B. Autologous morcellised bone from acetabular reamers, or homologous from the frozen head of the femur, was inserted between the implant and the remaining bone defect and has been used in 38 revision procedures of (29 major and 3 minor). Structural bone grafts, synthetic bones nor demineralized bone matrices were not used.

Experienced prosthetic hip surgeons performed the revisions. After surgery, an abduction brace was applied for two days after surgery and partial load with crutches for at least thirty days was recommended. A specific rehabilitation program was used to prevent mobilization or early dislocation of the implant. Data were analyzed anonymously and results were reported in an aggregate manner.

Statistical analysis

All the data was made into an *ad hoc* database and statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, version 23.0). Descriptive statistics were used to characterize the population using frequencies and means ± SD. Statistical analyses of HHS were carried out using the Student’s *t* test for independent and paired samples. A *P* value of < 0.05 was considered statistically significant. A standard life table was constructed, and cumulative survival was calculated by means of the Kaplan-Meier method, using all causes and infections of the acetabular component as end-points.

Statistical analyses were performed by two Authors (Antonella Agodi and Martina Barchitta) using the SPSS software (IBM SPSS Statistics for Windows, version 23.0).

RESULTS

During the study period, a total of 58 acetabular

Table 1 Main characteristics of patients and procedures *n* (%)

Characteristic	
Age, mean ± SD, yr	71.9 ± 5.5
Gender	
Male	27 (46.6)
Female	31 (53.4)
Revision motive	
Aseptic loosening	49 (84.5)
Polyethylene wear	7 (12.1)
Infection	2 (3.4)
Paprosky’s classification	
Type 2A	11 (19.0)
Type 2B	14 (24.1)
Type 2C	13 (22.4)
Type 3A	15 (25.9)
Type 3B	5 (8.6)
Augment usage among 2C, 3A and 3B	16 (48.5)
Average follow-up, mo, (± SD; range)	87.6 (± 25.6; range 3-120)

revisions were performed and reviewed. The main patient and procedure characteristics are reported in Table 1. There were 31 women (53.4%) and 27 men (46.6%) with a mean age of 71.9 years (range: 42-82 years) at the time of revision. The most frequent indicator for revision was aseptic loosening of the implant (84.5%).

According to Paprosky’s classification, 11 hips (19.0%) were type 2A, 14 (24.1%) were type 2B, 13 (22.4%) were type 2C, 15 (25.9%) were type 3A and 5 (8.6%) were type 3B. Thus, a total of 25 cases (43.1%) were classified as minor defects (types 2A and 2B) (Figure 3) and 33 cases (56.9%) as major defects (types 2C, 3A and 3B) (Figure 4).

The mean follow-up was 87.6 ± 25.6 mo (range 3-120 mo).The preoperative HHS rating improved significantly from a mean of 40.7 ± 6.1 (range: 29-53) before revision, to a mean of 85.8 ± 6.1 (range: 70-94) at the end of the follow-up (Student’s *t*-test for paired samples: *P* < 0.001), with 75.6% of patients in the “excellent” or “good” categories.

Considering only the HHS at the end of the follow-up, no statistically significant difference was observed between patients with a major defect (types 2C, 3A and 3B, mean HHS 86.3 ± 4.9) and patients with a minor defect (types 2A and 2B, mean HHS 85.3 ± 7.5) (Student’s *t* test for independent samples: *P* > 0.05). HHS ratings of patients with implant failure were not included in these analyses.

Radiolucent lines were found in 4 implants (6.9%): In 3 implants the lines were not more than 2 mm or progressive and involved only one of the three DeLee and Charnley areas, while in 1 implant, which was revised because of infection, they were progressive. Therefore all implants, except the one revised for an infection, were X-ray defined as stable. The excellent osteoconductive properties of tantalum enabled rapid strong biological fixing, even where there was limited vital bone, especially in major defects.

Postoperative acetabular gaps were observed in 5 hips (8.6%) all of which disappeared during the initial

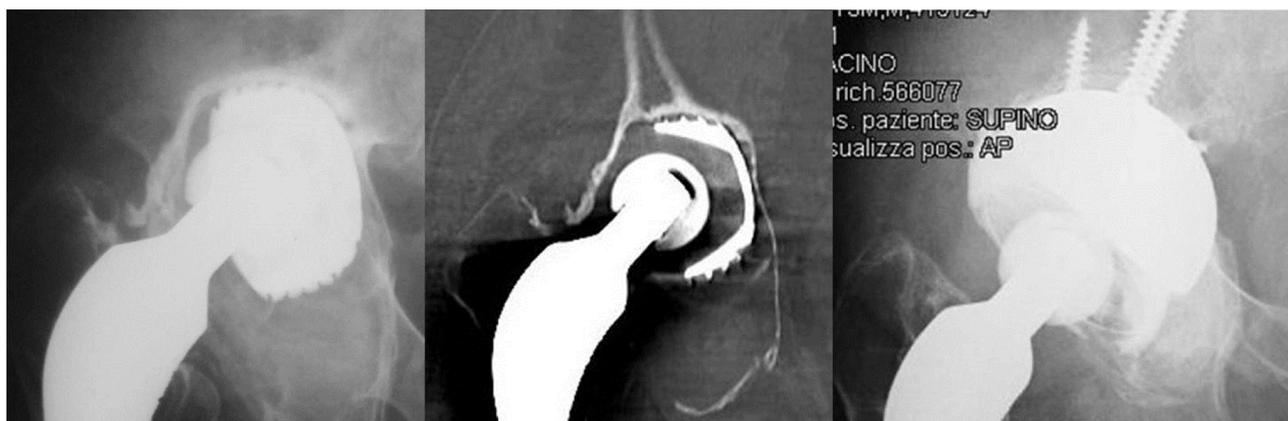


Figure 4 Acetabular revisions with major bone defects.

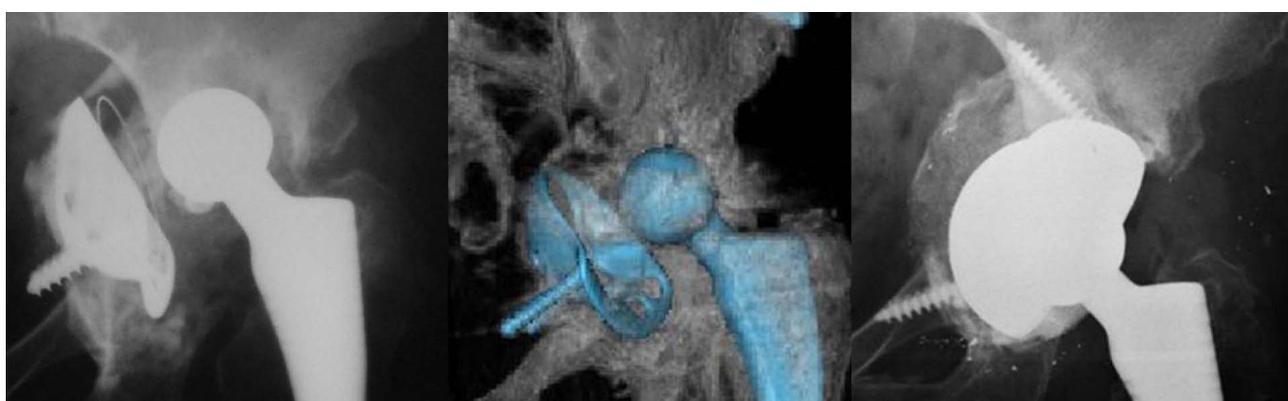


Figure 5 Failure of acetabular revision.

12 mo after surgery and thus were not found at the final follow-up.

No signs of implant mobilization or areas of periprosthetic osteolysis were found in the X-rays at the final follow-up. Morcellised bone grafts with augments to fill bone defects showed no signs of resorption in regular X-ray controls. Only 3 implants failed: 1 case of infection (6 mo after surgery) (Figure 5) and 2 cases of instability (3 and to 4 mo after surgery). The first patient with instability was treated with dislocation reduction and a tutor for 30 d; the second patient with instability required revision surgery implant a constrained liner for chronic instability. In the patient with infection, because of poor general condition and limited functional requirements, the implant was removed and treated with Girdlestone resection arthroplasty. Minor complications were: 2 cases of deep vein thrombosis treated with heparin, 1 case of superficial infection treated with surgical revision of the wound, 1 case of neuro apraxia of the sciatic nerve resolved spontaneously after 2 mo from surgery. None of the patients underwent revision for aseptic loosening until the final follow-up.

Defined as the end-point, cumulative survival at 10 years was 95% (for all reasons) and 100% for aseptic

loosening of the acetabular component (Figure 6).

DISCUSSION

Treatment of a failed acetabular component in total hip prosthesis is technically demanding because immediate and long term stability of the implant is required, as well as maintaining or increasing bone stock, restoring the centre of rotation, and preventing limb discrepancy.

Traditional hemispherical cups (titanium alloy and cobalt chromium alloy) are an effective solution in revisions where adequate bone stock (> 50%) is available to support the acetabular component and allow for bone ingrowth^[16,17,22,25,26]. In cases where the biological potential and mechanical stability of the prosthetic implant are compromised by bone deficit (< 50% acetabular bone available to support the acetabular component), alternative treatments should be used^[7,27].

Porous tantalum implants have been used since 1997 and provide excellent initial stability and bone ingrowth. The higher porosity (80%) promotes better growth of vascularized bone inside the prosthesis (microfixing) in comparison to common porous sur-

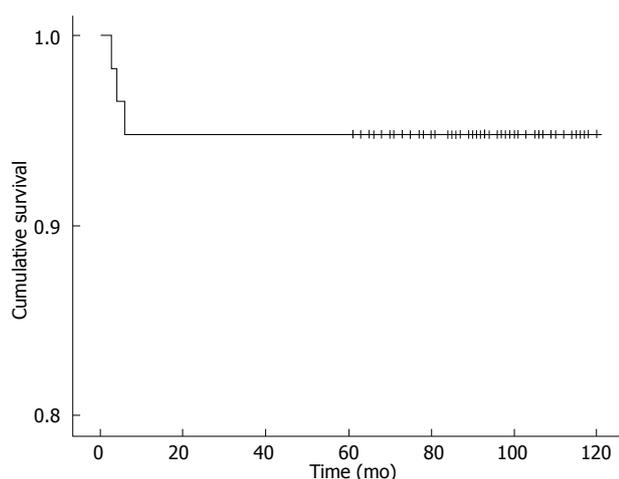


Figure 6 Survival analysis of the study's 58 patients.

faces; the high coefficient of friction to the cancellous (0.88) and cortical (0.74) bone ensures greater primary stability (macrofixing); the low modulus of elasticity (3.1 GPa) brings the material closer to the trabecular bone (1.5 GPa) compared to titanium (110 GPa) and cobalt-chromium (220 GPa), allowing greater load-induced bone remodelling and minimized stress shielding near the cup^[17]. The three-dimensional structure and excellent osteoconductive properties of porous tantalum provide faster and stronger biological fixing when there is limited vital bone availability, and facilitate the restoration of the bone stock^[28].

The ingrowth properties of porous tantalum are superior to bone graft in revision surgery; allograft reabsorption can lead to component instability, while porous tantalum maintains its structure and stability^[26]. A stable bone-implant interface and favourable osteoconductive properties of the material are important for bone ingrowth of prostheses. Furthermore, the availability of augments in tantalum has reduced the need for structural bone grafts in revisions and safer recovery of the hip rotation centre.

Clinical evaluation at the final follow-up showed a statistically significant increase in preoperative HHS from 40.7 to 85.8. In this study we did not find a statistically significant association between bone defect size and increased clinical results at final follow-up, demonstrating that the clinical results of acetabular revisions with tantalum components do not seem to be influenced by the degree of preoperative bone defect. However, other authors have shown that clinical outcomes are influenced by bone defects when using traditional techniques, such as structural bone grafting and reconstruction cages^[18,29].

X-rays revealed no prosthetic implant migration. Some non-progressive radiolucent lines in three implants were probably due to some fibrous fixing in part of the implant, and requires X-ray monitoring in the future.

Several authors report instability as the main

cause of failure of tantalum implants^[1,16]. In this study the survival of the implants for 10 years was 95%, considering the revision for any reason as end-point. Of the three reported failures, two were for implant dislocation. Only one failure showed incorrect positioning of the socket.

High numbers of dislocations in the literature suggest that special attention should be addressed to correcting the centre of rotation and implant positioning, and to using constrained implants in cases of deficient abductor mechanisms.

Limitations

This study has several limitations: (1) it is a retrospective study with a limited sample size, heterogeneous patient ages and a variety of bone defects; (2) restoring the normal rotation centre of the implant was not monitored by X-ray (calculating the vertical and horizontal distance from the inter-teardrop line); (3) the study did not consider the size of the acetabular component and femoral head diameter according to preoperative bone defect; and (4) this study has not control group for comparison. A future multi-centre study including homogeneous samples by age and bone defect would be useful in assessing the medium and long-term clinical and X-ray results of tantalum implants in prosthetic hip revisions.

In conclusion, the medium-term use of prosthetic tantalum components in prosthetic hip revisions is safe and effective in a wide variety of acetabular bone defects. The greatest advantage is found in major bone defects, where the tantalum cup and augments provide stable primary fixation with the biological potential for bone ingrowth. Despite these advantages, the metallic debris effects of this material are still unknown. Long-term studies are needed to evaluate the longevity of these implants and demonstrate their advantages over conventional methods such as massive grafting and reconstruction cages. Nowadays, porous tantalum represents the ideal bone substitute in prosthetic revisions.

COMMENTS

Background

This study evaluates the results of acetabular components and tantalum augments in prosthetic hip revisions, assessing whether the type of bone defect can compromise the outcome or the medium-term survival of the implants. In this study the authors did not find a statistically significant association between the size of the bone defect and increased clinical results. Defined as the end-point, cumulative survival at 10 years was 95% (for all reasons) and 100% for aseptic loosening of the acetabular component.

Research frontiers

Treating the failure of the acetabular component in total hip prosthesis is technically demanding because of significant bone defect. Nowadays, studies are being directed towards searching for a material which possesses bone-like biomechanical characteristics. Porous tantalum implants provide excellent initial stability, bone ingrowth and allow for greater load-induced bone remodelling near the cup.

Innovations and breakthroughs

There are few studies on hip revisions with tantalum components in the literature where the samples are small, have non-homogeneous bone defect severity and short term follow-ups. This study evaluates the medium-term clinical and X-ray results of tantalum components in acetabular revisions with major bone defects.

Applications

The use of prosthetic tantalum components in prosthetic hip revisions is safe and effective for large acetabular bone defects. Nowadays, porous tantalum represents the ideal bone substitute in prosthetic revisions and provides excellent mechanical stability of the implants.

Terminology

Tantalum is a ductile metal, inert and bio-compatible *in vivo*. Due to its three-dimensional structure and bioactivity, porous tantalum has a structure very similar to cancellous bone.

Peer-review

This is an interesting manuscript dealing with a popular field of revision hip arthroplasty.

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Retrospective Study

Non-ossifying fibromas: Case series, including in uncommon upper extremity sites

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Author contributions: Sakamoto A drafted the manuscript; Arai R and Okamoto T participated in the design of the study; Matsuda S conceived of the study, participated in its design and coordination, and helped draft the manuscript; all authors read and approved the final manuscript.

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Abstract**AIM**

To investigate non-ossifying fibromas (NOFs) common fibrous bone lesions in children that occur in bones of the lower extremities.

METHODS

We analyzed 44 cases of NOF including 47 lesions, which were referred with a working diagnosis of neoplastic lesions. Lesions were located in the upper extremities (1 proximal humerus, 1 distal radius) and the lower extremities (25 distal femurs, 12 proximal and 4 distal tibias, and 4 proximal fibulas).

RESULTS

Three cases had NOFs in multiple anatomical locations (femur and fibula in 1 case, femur and tibia in 2 cases). Overall, larger lesions > 4 cm and lesion expansion at the cortex were seen in 21% and 32% of cases, respectively. Multiple lesions with bilateral symmetry in the lower extremities suggest that these NOFs were developmental bone defects. Two patients suffered from fracture and were treated without surgery, one in the radius and one in the femur. Lesions in the upper extremities (*i.e.*, humerus of a 4-year-old female and radius of a 9-year-old male) expanded at the cortex and lesion size increased with slow ossification.

CONCLUSION

NOFs in the lower extremity had fewer clinical problems, regardless of their size and expansiveness. In these two upper extremity cases, the NOFs had aggressive biological features. It seems that there is a site specific difference, especially between the upper extremity and the lower extremity. Furthermore, NOFs in the radius are predisposed to fracture because of the slender structure of the radius and the susceptibility to stress.

Key words: Non-ossifying fibroma; Humerus; Radius; Fibula; Upper extremity

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Core tip: Non-ossifying fibromas (NOFs) are common lesions in the lower extremities of children. We analyzed 44 cases of NOF including 47 lesions comprising 2 upper extremity cases and 45 lower extremity cases. Larger lesions > 4 cm and lesion expansion at the cortex were seen in 21% and 32% of cases, respectively. Lesions in the upper extremities in the humerus and the radius expanded at the cortical bone, and lesion size increased with slow ossification, suggestive of aggressive biological features. Furthermore, NOFs in the radius are predisposed to fracture because of the slender structure of the radius and the susceptibility to stress.

Sakamoto A, Arai R, Okamoto T, Matsuda S. Non-ossifying fibromas: Case series, including in uncommon upper extremity sites. *World J Orthop* 2017; 8(7): 561-566 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i7/561.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i7.561>

INTRODUCTION

Non-ossifying fibromas (NOFs) are a common type of benign fibrous lesion that tend to occur in the metaphysis of the long bones in the lower extremities^[1,2]. NOF can be diagnosed based on its presentation on plain radiographs^[3,4] where it typically appears as a small, cortical osteolytic lesion. Approximately 30% of young patients in their first or second decade of life can have a NOF^[2]. Typically, NOFs are asymptomatic and lesions are found incidentally. A lesion is usually self-limiting and disappears by the age of 20 to 25 years in most cases^[3]. Therefore, lesions are considered to be a developmental bone defect rather than a true neoplasm^[1,2]. Histologically, NOFs are composed of spindle-shaped fibroblasts, multinucleated giant cells, and foamy histiocytes, which are identical to a benign fibrous histiocytoma (BFH), which is a neoplastic lesion^[2]. BFHs occur predominantly in adults, and a BFH is considered to have more aggressive biological features compared with a NOF. Interestingly, the current case series includes some patients with NOFs in less common sites such as the humerus, radius, and

fibula. Herein we discuss upper and lower extremity NOFs and emphasize the anatomical differences between them.

MATERIALS AND METHODS

A clinical summary of the 44 cases of NOF is shown in Table 1. A total of 47 lesions were referred to our institution with a working diagnosis of neoplastic lesions. A diagnosis of NOF was made based on plain radiographic findings. NOF appears as a cortically based osteolytic lesion with an osteosclerotic rim. In cases with atypically large lesions, a magnetic resonance image (MRI) examination was added in order to exclude aggressive bone tumors, such as osteosarcomas. The NOF cases we analyzed were in 26 males and 18 females. The average age at the first visit was 10.5 (range, 4 to 16) years. The NOFs were located in a humerus ($n = 1$), radius ($n = 1$), femurs ($n = 25$), tibias ($n = 16$), and fibulas ($n = 4$). Among these cases, lesions occurred in multiple locations in 3 cases with femur involvement, in 2 cases with tibia involvement and in 1 case with femur and fibula involvement. Bilateral lesions, in which the size and the location were almost symmetrical such that we counted them as a single lesion, were seen in 3 cases with femur involvement. The location of each lesion was also classified as anterior, medial, lateral, posterior, or inter-medullary. Findings of expansion at the cortices adjacent to lesions were assessed. A lesion > 4 cm in size was defined as large.

RESULTS

Among the NOF cases, a lesion size > 4 cm was seen in 10 out of 47 (21%) cases. Cortical expansions were seen in 15 out of 47 (32%) cases. The cases of upper extremity NOFs involved 1 humerus and 1 radius. A 4-year-old female had a NOF on the proximal side of her humerus. Plain radiographs revealed a multinodular osteolytic lesion in the cortex on the anterior aspect of the humerus. Thinning and expansion of the adjacent cortex was observed. During a 7-mo follow-up, it was noted that the size of the lesion had increased. Ossification was seen, but the earlier osteolytic finding was still prominent on a follow-up radiograph taken 31 mo later (Figure 1). A 9-year-old male had a NOF on the distal diaphysis of his radius. The lesion was discovered when he sustained a pathological fracture at the site of the lesion. Upon initial assessment, the plain radiographs revealed an irregularity of the adjacent cortex, suggesting a fracture. An osteolytic lesion with marginal sclerosis was seen. The size of the lesion was observed to increase at a 2 years and 5 mo follow-up because the patient had refractured his radius at the lesion site. Although ossification was evident on the proximal aspect of the lesion, an osteolytic lesion was also prominent at the 3-year follow-up (Figure 2).

The cases of lower extremity NOFs involved femurs,

Table 1 Clinical summary of 44 cases with non-ossifying fibromas

Bone site	NOFs, <i>n</i>	M:F	Mean age, yr	R/L/B extremities, <i>n</i>	Lesion > 4 cm, <i>n</i> (%)	Ant/med/lat/post/intramed location, <i>n</i>	Expansion, <i>n</i> (%)	Fracture, <i>n</i> (%)
Humerus	1							
Proximal	1	0:1	4.0	1/0/0	1 (100)	1/0/0/0/0	1 (100)	0
Radius	1							
Distal	1	1:0	7.0	0/1/0	0	0/0/0/0/1	1 (100)	1 (100)
Femur	25							
Distal	25	15:10	9.2	9/9/7	5 (20)	0/5/0/20/0	5 (20)	1 (4)
Tibia	16							
Proximal	12	8:4	14.5	6/6/0	2 (17)	0/4/1/7/0	3 (25)	0
Distal	4	2:2	13.5	3/1/0	2 (50)	0/0/4/0/0	2 (50)	0
Fibula	4							
Proximal	4	2:2	12.5	2/2/0	0	0/0/1/3/0	3 (75)	0
Total lesions ¹	47	26:18	10.5	21/19/7	10 (21)	1/9/6/30/1	15 (32)	2 (4)

¹Total cases *n* = 44. Ant: Anterior; B: Bilateral; F: Female; intramed: Intramedullary; L: Left; lat: Lateral; M: Male; med: Medial; NOFs: Non-ossifying fibromas; post: Posterior; R: Right.

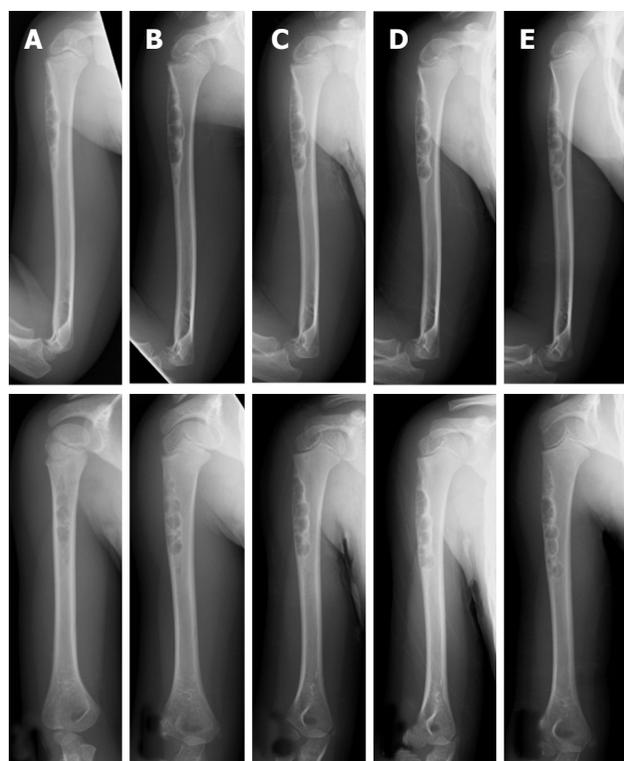


Figure 1 Plain radiographs of a non-ossifying fibroma in the humerus of a 4-year-old female. An osteolytic lesion is shown at the cortex in the proximal humerus (A). Radiographs taken after 7 mo (B), 1 year (C), 1 year and 7 mo (D), and 2 years and 7 mo (E) together reveal the location of the lesion became more distal with growth of the child. The size of the lesion increased as it slowly ossified (plain radiographs: Anteroposterior view, top; lateral view, bottom).

tibias, and fibulas. All femoral lesions were at distal locations. Both large-sized lesions with expansion at the cortex were seen in 20% of cases with femoral involvement. One case of NOF in the femur was diagnosed with a concurrent fracture based on an MRI finding of a high signal intensity at the cortex adjacent to the lesion (Figure 3). Of the 16 cases with tibia involvement, 12 lesions were in a proximal location and 4 were distal. Large-sized lesions occurred in 2

out of 12 (17%) cases in the proximal tibia and in 2 out of 4 (50%) cases in the distal tibia. Extension at the cortex was seen in 3 out of 12 (25%) cases in the proximal tibia and in 2 out of 4 (50%) cases in the distal tibia. These femoral and tibial lesions were in either the medial, lateral, or posterior locations, in contrast to the anterior location in the case of humerus involvement. All 4 cases of NOFs in fibulas presented with lesions in proximal locations. NOF cases with cortical expansion were seen in 3 out of 4 (75%) cases with fibula involvement. One fibular case had multiple lesions that included the femur (Figure 4).

DISCUSSION

NOF predominantly occurs in the lower extremities, especially around the knee^[1,2]. In the current series, the frequency of a distal location in the femur was rather low, because all the referred cases were considered as potential neoplastic lesions, and when small more typical NOFs in the distal femur were identified, the patients were not referred. NOFs are not considered to be true neoplasms, but rather a developmental bone defect^[1-3]. Cases with multiple affected locations, such as the femur and fibula or the femur and tibia, support the notion of a natural developmental defect.

Findings of lesion size increases with expansion at the cortex suggest NOFs can be more aggressive in nature. Cytological abnormalities of translocation (1;4)(p31;q34) and del(4)(p14) supplied evidence for some NOFs with neoplastic characteristics^[5,6]. It is possible that NOFs could have a neoplastic nature because histologically they are indistinguishable from the neoplastic lesions of BFH, which are more aggressive in nature than those of NOFs^[7]. Using image analysis techniques to differentiate between BFHs and NOFs, BFHs appear more likely to have less distinct borders that are central rather than eccentric^[7,8]. BFHs tend to occur in adults, while the vast majority of cases of NOF occur in children. However, it has been

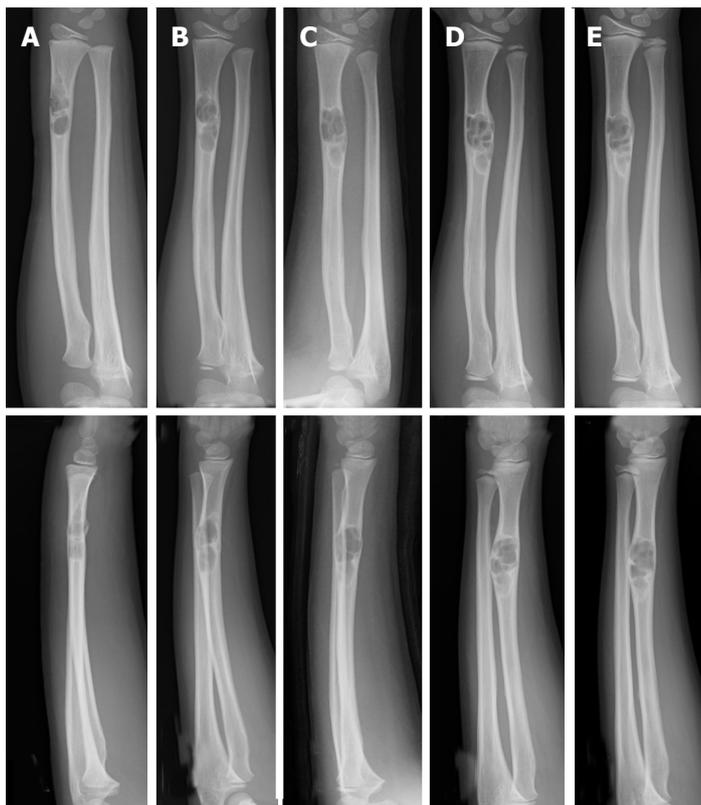


Figure 2 Plain radiographs of a non-ossifying fibroma in the radius of a 9-year-old male. At the initial assessment an osteolytic lesion in the distal radius is shown with an osteosclerotic rim. Fracture of the irregular adjacent cortex is revealed (A). Radiographs taken after 11 mo (B), 2 years and 1 mo (C), 2 years and 5 mo (D), and 3 years (E). The size of the lesion increased and ossification at the distal end was observed (plain radiographs: Anteroposterior view, top; lateral view, bottom).



Figure 3 Plain radiograph and MRI of a NOF in the femur of a 13-year-old male who sustained a fracture. The plain radiographs reveal a multinodular lesion located at the medial posterior part of the distal femur. The lesion is osteolytic at the distal end and ossified at the proximal end. The lesion has expanded at the medial cortex (A). T2-weighted fat-suppression MRIs show high signal intensity and suggest the presence of a fracture (B) (coronal, top; axial, bottom). Radiographs taken after 1 year (C), 1 year and 8 mo (D), and 2 years and 8 mo (E); these radiographs reveal the lesion had enlarged as well as ossified (plain radiographs: anteroposterior view, top; lateral view, bottom).

proposed that BFHs may be underestimated among patients less than 20 years of age, and the diagnosis

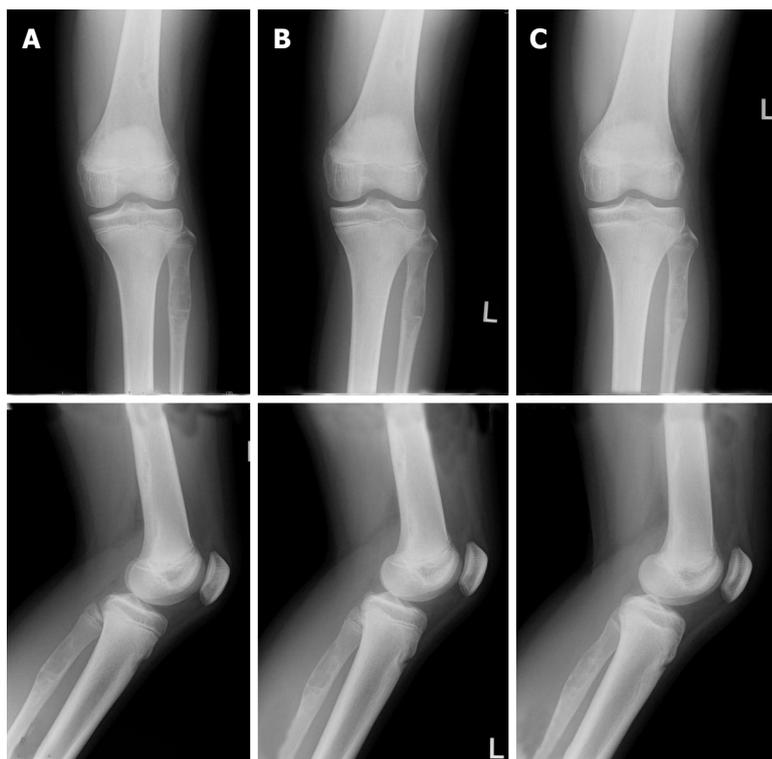


Figure 4 Plain radiographs of non-ossifying fibromas in the femur and the fibula of a 13-year-old female. The radiographs reveal an osteolytic lesion in the proximal fibula, as well as a NOF in the distal femur (A). Radiographs taken after 9 mo (B) and 1 year and 9 mo (C); the femoral and fibular lesions ossified (plain radiographs: Anteroposterior view, top; lateral view, bottom).

of BFH should be considered when NOF-like pathology is accompanied by pain or rapid lesion growth^[7]. In the current series, NOFs in the lower extremities ossified, even in cases with large lesions that increased in size, but none was diagnosed as BFH.

NOFs located in the humerus and radius were included in this study although the upper extremities are an uncommon site for these lesions. Both lesions had extended at the cortex and lesion size increased over time; however, ossification was observed despite osteolytic findings still being prominent at 3 years of follow up. Although the number of upper extremity NOF cases was small, they can have an aggressive nature with BFH-like features when compared with the NOFs in the lower extremities. The NOF located in the radius resulted in a complication when the patient sustained repeated fractures. NOF lesions that occupy more than 50% of the transverse diameter of the involved bone are more likely to lead to a fracture^[2,9]. The slender anatomical structure of the radius would also have contributed to the risk of a pathological fracture at the location of the NOF in this case.

In conclusion, NOFs in lower extremities have the non-neoplastic characteristics of a developmental bone defect. In contrast, NOFs in the humerus and the radius tended to have more aggressive biological characteristics similar in nature to those of BFHs with expansion at the cortex, an increase in size, and slow ossification. It seems that there is a site specific difference between the upper and lower extremities.

In addition, NOFs in the radius are potentially prone to fracture because of the slender structure of the affected bone.

COMMENTS

Background

Non-ossifying fibromas (NOFs) are a common type of benign fibrous lesion that tend to occur in the metaphysis of the long bones in the lower extremities. The upper extremity is less common for NOFs. NOFs are considered to be a developmental bone defect rather than a true neoplasm. However, the histology of NOFs is identical to that of benign fibrous histiocytoma, which is a neoplastic lesion.

Research frontiers

Small NOFs have no clinical significance. The neoplastic characterization of NOFs was difficult. Therefore, the authors collected NOF cases that were referred with a working diagnosis of neoplastic lesions. Consequently, large NOFs with possible aggressive characteristics, as well as NOFs in rare locations, were collected.

Innovations and breakthroughs

The authors analyzed 44 cases of NOFs including 47 lesions comprising two upper extremity cases and 45 lower extremity cases. Clinical information and plain radiographs were collected. The findings associated with possible aggressiveness were further analyzed, such as incidence of fracture and radiographic observations of size and expansiveness. It seems that there is a site specific difference between the upper and lower extremities. NOFs in the lower extremity are considered to be a developmental bone defect rather than a true neoplasm, even though NOFs can be large and have expansion at the cortex. Lesions in the humerus and the radius were expanded at the cortex and lesion size increased with slow ossification. Furthermore, NOFs in the radius are predisposed to fracture because of the slender structure of the radius and

its susceptibility to stress.

Applications

The results are useful for clinicians in the making a diagnosis of NOF and following up the patients.

Terminology

NOF: Non-ossifying fibroma; BFH: Benign fibrous histiocytoma; MRI: Magnetic resonance image.

Peer-review

This is a well-designed paper about a rarely seen clinical condition.

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Observational Study

Distal radius volar rim plate: Technical and radiographic considerations

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Author contributions: All authors mentioned in this paper have been involved in the construction of this paper; Ng W and Matthews J were involved in data collection; Spiteri M and Roberts D were involved in data collection, analysis and interpretation, and drafting of the manuscript; Power D was involved in the conception and design of the study and draft of the manuscript.

Institutional review board statement: Data was collected during routine clinic review appointments according to the institution's policy.

Informed consent statement: Data was collected during participants' routine follow up appointments, with verbal consent.

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Abstract

AIM

To determine technical considerations and radiographic outcomes of the Synthes volar rim distal radius plate to treat complex intra-articular fractures.

METHODS

This review highlights technical considerations learnt using this implant since it was introduced in a major trauma unit in November 2011, including anatomical reduction and whether this was maintained radiographically.

RESULTS

Twenty-six of the 382 internally fixed distal radial fractures at our unit (6.8%) were deemed to require this plate in order to achieve optimal fracture fixation between November 2011 and May 2014. A further dorsal and/or radial plate was necessary in 35% and variable angle screws were used in 54% of cases. Post-operatively, mean radial height, inclination, volar tilt and ulnar variance restored were 11.7 mm, 21°, 4.3° and -1.2 mm respectively. There were no cases of non-union or flexor/extensor tendon rupture; one case of loss of fracture reduction. Overall incidence of plate removal was 15% with one plate removed for flexor and one for extensor tendon irritation

CONCLUSION

The use of a rim plate enables control of challenging far

distal fracture patterns. However, additional plates were required to improve and maintain reduction. Variable angle screws were necessary in half the cases to avoid intra-articular screw penetration. If used judiciously, this implant can achieve stable fixation despite the complexity of the fracture pattern.

Key words: Distal radius fractures; Volar rim plate; Volar plating distal radius

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Core tip: Far distal intra-articular fractures of the distal radius are not easily treated with standard volar plates. The rim plate is designed to sit distal to the watershed line, allowing purchase of bone fragments and subchondral support of the articular surface, enabling early mobilization. In view of the implant's design, variable angle screws are necessary to avoid intra-articular screw penetration. Intra-operatively, reduction and stable fixation should be assessed fluoroscopically during wrist movement, and if necessary, an additional dorsal plate applied to allow mobilization. Judicious use of this implant can restore anatomical reduction and stable fixation in this complex subset of fractures.

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INTRODUCTION

The application of locking plate technology to distal radius fracture fixation enables dorsally unstable fracture configurations to be reliably reduced and internally fixed using a volar approach and volar implant placement. The volar approach has gained widespread popularity due to the perceived benefits of greater soft tissue cover over the implant and less tendon irritation than with the dorsal approach. This technique may be used for the majority of distal radius fractures, however an understanding of fracture anatomy and biomechanics as well as correct implant choice and placement are critical to a successful outcome. Indeed one implant cannot provide a stable fixation for all configurations through the volar approach^[1]. The non-specialist trauma surgeon will be familiar with the volar approach but should recognize those fracture configurations that may need dorsal or combined volar and dorsal approaches. In these complex intra-articular cases the use of pre-operative computerised tomography (CT) aids planning the surgical approach and choice of implant.

The AO-23B3 fracture with a small distal and volar fragment and the AO-23C3 fracture with articular

comminution are two fracture subtypes where a standard volar plate positioned proximal to the watershed line^[2] will not provide a sufficient buttress for the distal fragments and there is a risk of secondary volar displacement of the fragment along with the carpus distal to the plate. An early plate design for these fracture subtypes was the Synthes juxta-articular plate but due to the distal plate positioning and angular design tendon irritation was problematic, often necessitating implant removal after fracture union. The distal screws were originally inserted in a fixed angle configuration that is proximally directed to avoid screw penetration of the radio-carpal joint, which was a significant risk if the distal fragment was small or the volar tilt incompletely corrected. In addition, there was no second row angled buttress for dorsal joint surface support.

The Synthes variable angle two column plate design was developed from the extra-articular and juxta-articular designs and offers an anatomically contoured plate, which is positioned close to the watershed line and can be used for fixation of the majority of distal radius fractures. However, reliable fixation of the far distal fracture subtype remains problematic. The variable angle distal radius rim plate was introduced in our unit in autumn 2011 and is designed for these complex fractures. It is inserted *via* a volar approach and is placed over the watershed line as it is pre-contoured to fit the volar rim of the distal radius. The edges of the plate are designed to provide a smooth surface against which the flexor digitorum profundus and flexor pollicis longus tendons may glide with minimal irritation. Due to the distal placement of the plate, there is a theoretical risk of intra-articular screw placement. To reduce this risk, the screw options include fixed or variable angle subtypes to allow proximal direction of screws away from the joint. These also allow purchase of small fracture fragments where a fixed angle screw would enter a fracture line. There are a number of important technical considerations for plate positioning, anatomical fracture reduction, avoiding screw penetration to the joint and minimising the risk of secondary displacement. This is especially pertinent with the AO-23C3 fracture configuration when successful volar buttress of small distal fragments may unmask distal and dorsal instability necessitating supplementary dorsal plating.

MATERIALS AND METHODS

This paper reports on a series of twenty-six consecutive cases of Synthes variable angle 2.4 distal radius rim plates used for distal radius fracture fixation at a major trauma and tertiary referral hand centre between November 2011 and May 2014. All patients treated with this implant were identified from a database of distal radius fracture fixations compiled from theatre logbooks and cross-referenced with implant logbooks. The pre-operative radiographs and CT scans were used to assess



Figure 1 Posteroanterior and lateral radiographs of fracture fixation using a Synthes variable angle 2.4 distal radius rim plate to highlight the distal placement of the implant.

fracture configuration. All post-operative radiographs were reviewed to measure volar tilt, inclination and radial height in order to assess restoration of anatomy. All radiographs were reviewed taken in the same radiology unit using the same machine calibration. Operative records and imaging, medical and therapy records were used to monitor progression of the fracture to union and retention of post-operative fracture reduction.

The primary outcome measures were initial and final radiographic alignment parameters to assess maintenance of fracture reduction, and implant removal. Secondary outcome measures were the use of variable angle screws, the need for accessory plate support and tendon irritation/rupture.

RESULTS

During the study period, 382 distal radius fractures were treated operatively with internal fixation, the majority using a volar approach (83.5%). Twenty-six distal radius fixations utilised rim plates accounting for 6.8% of all operations. The rim plate was used in isolation in seventeen cases (Figure 1), however an additional dorsal or dorso-radial approach to reduce and maintain reduction of fracture fragments was required in 35% of cases. This equates to half the total number of distal radial fractures requiring combination plating, highlighting the complexity of the fractures for which rim plates were used.

The use of variable angle screws was higher in this subset of patients, with 54% of cases requiring a median of four such screws. Variable angle screws were required to reduce the risk of joint penetration and to optimise screw configurations in comminuted fractures when a fixed angle screw would sit within a fracture line and not provide sufficient subchondral support.

All fractures were classified as either AO-23B3 or AO-23C3 with a significant degree of articular and metaphyseal comminution. To evaluate the degree of fracture comminution, the size of the dorso-ulnar and radial styloid fracture fragments were assessed on pre-

operative CT scans.

Analysis of the CT coronal and axial sections demonstrated no significant difference in the size of the dorsal fragments between the groups treated with a single volar rim plate and those treated with a combined approach using a second dorso-ulnar buttress plate.

In all twenty-six cases there was a significant level of comminution, which also involved the distal radio-ulnar joint in twenty-two cases (five of these cases having a simple coronal split through this joint and the others having multi-fragmentary fracture configurations) (Figure 2). The main sites of articular comminution were in the dorso-ulnar and volar-ulnar regions of the distal radius rather than the radial styloid, where most of the fragmentation was metaphyseal.

In six cases (23%) there was a volar instability pattern at presentation with volar translation of the carpus together with the distal volar ulnar fragments. Involvement of the lunate fossa had a die punch fracture configuration in all cases (Figure 3). The dorso-ulnar fragments sustained a higher degree of comminution when compared to their volar counterpart in sixteen of the twenty six cases (Figure 4).

Standard volar variable angle plates are sited too proximal to secure and buttress these volar lip marginal fragments (Figure 4), therefore allowing carpal translation to occur despite apparent adequate fixation intra-operatively. By stabilizing these volar marginal lip fragments, the rim plate avoids this potential for secondary displacement^[1,2].

Fracture reduction was assessed by measuring volar tilt, radial inclination, radial height and ulnar variance on the post-operative radiographs. Alignment was restored to 4.3 ± 5.5 degrees volar tilt, mean radial inclination of 21.2 degrees (range: 15-30 degrees), 11.7 mm (range: 7-16 mm) radial height and -1.2 mm (range: -4.5-2.5) ulnar variance.

Six patients did not complete follow-up in our unit. Two patients were not from our region and attended follow-up at their local units, and four patients declined the offer of follow-up beyond six weeks. The patients who discontinued follow up have not been referred back to our unit with complications of tendon irritation or rupture.

The 20 patients completing follow-up all demonstrated radiographic fracture union by 12 wk from surgery. There are no cases of either flexor or extensor tendon rupture and two cases of tendon irritation. Post-operative loss of reduction occurred in one polytrauma case, with loss of volar tilt and height. No intervention was required and the patient was asymptomatic at eighteen months after surgery.

Four patients required removal of metalwork. One patient clinically had first extensor compartment tendon irritation due to a prominent screw following an isolated volar operative approach; one patient had pain on grip strength testing, which may have represented flexor tendon irritation. This resolved after removal of the volar plate and a dorsal lunate fossa fragment buttress

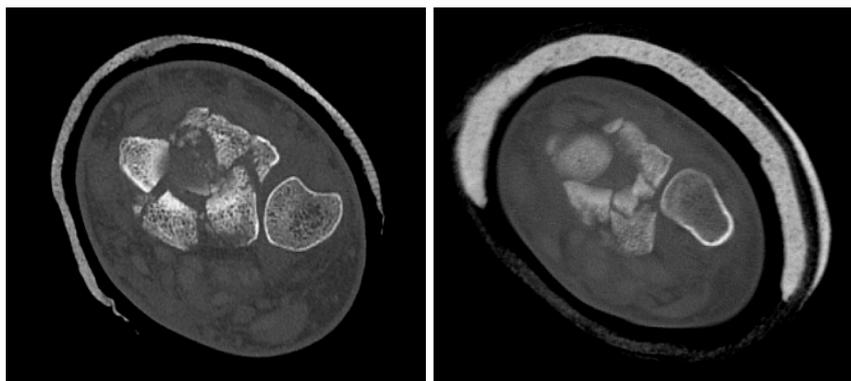


Figure 2 Axial computerised tomograms showing far distal involvement and comminution of the distal radio-ulnar joint.

plate. One case had radiographic signs of avascular necrosis of the lunate fossa fragment. This was asymptomatic until a second fall after which the patient developed new onset dorso-radial pain symptoms. A diagnostic arthroscopy identified screw penetrance into the joint; one case had the volar plate removed at the same time as a triangular fibrocartilagenous complex repair for symptoms of distal radio-ulnar joint instability.

DISCUSSION

The indications for a variable angle volar rim plate are for the infrequent AO-23B3 and AO-23C3 distal radius fractures where the distal and volar fragments cannot be adequately buttressed with standard extra-articular and variable angle two column volar plates.

Prior to the launch of the volar rim plate these distal fractures were managed in our unit with a volar juxta-articular plate or with an extra-articular plate and supplementary distal lag screws. However, this plate has a higher profile and angular design and therefore is more likely to cause flexor tendon irritation necessitating implant removal.

Alternatively they were treated by a dorsal only approach if the primary instability was thought to be dorsal, however an unmasked volar instability could result in volar displacement of the carpus with the volar distal fracture fragment at the lunate facet buttress.

Rarely they were treated with an external fixator or a temporary 3.3 mm 16 hole distraction bridge plate spanning the fracture site and carpus^[3]. Both of these techniques offer reliable fracture union, but unlike the volar rim plate, it is not possible to restore most aspects of distal radius anatomy as well as radio-carpal and distal radio-ulnar congruity. They also have other specific complications, including stiffness, pin tract infection and metacarpal fracture at the site of distal pin or screw insertion^[4].

Due to the complexity of these fractures, a pre-operative CT scan is required for in depth assessment of the fracture configuration. Unfortunately, there were no predictors on the scans which can be used to identify

fractures that are more likely to need additional plating *via* a dorsal or dorso-radial approach. We attempted to correlate the size of the fracture fragments with the need for additional plates, but no correlation was evident. This decision was made intra-operatively on assessment of fracture stability after volar plating.

In this series of rim plate fixations of distal radius fractures a combined dorsal and volar plating approach was required in 35% of procedures (Figure 5). If the distal fracture configuration with potential for volar and dorsal instability is identified from the pre-operative CT scan it is important that the treating surgeon is familiar with the dorsal approach in case an adjuvant dorsal plate is required. The alternative is to refer the case on to a specialist wrist surgeon who is familiar with both approaches. Whilst the rim plate increases the numbers of fractures and configurations that may be managed with internal fixation through the volar approach it does not obviate the need for the dorsal approach.

The rim plate has a low profile to allow its placement distal to the watershed line without increasing the risk of flexor tendon irritation. Despite its distal placement, in this series, there were no cases of flexor tendon rupture and only two of the four cases of implant removal were for flexor or extensor tendon irritation. This is consistent with the literature which suggests that attrition flexor tendon rupture is infrequent yet may occur with prominent higher profile plates placed at the watershed line, but is unlikely in cases where plates are designed to be placed more distal to this line, probably due to their contoured design and low profile^[5].

Signs of tendon irritation were noted at clinic review between three and six months post-operatively when range of motion had been restored and the patients had regained grip strength and pre-injury activity levels. None of the other cases were symptomatic or had signs of tendon irritation up to one year after surgery. Hence we suggest a minimum follow up until six months post-operatively and removal of implants if there are clinical signs of tendon irritation, rather than awaiting patients to be symptomatic thus decreasing



Figure 3 Axial computerized tomograms showing far distal involvement and comminution of the distal radio-ulnar joint.



Figure 4 Sagittal computerized tomogram showing the pattern of significant intra-articular comminution of the far distal dorso-ulnar and volar-ulnar regions of the distal radius and the volar lip marginal fragment.

the risk of attrition tendon ruptures. The published recommendations for removal of previous volar plate designs include only symptomatic patients who had plate prominence more than 2 mm volarly at the watershed line or plate position within 3 mm of the volar rim^[6].

The volar rim of the lunate fossa is anatomically designed to resist volar carpal translation and the short radiolunate ligament, which attaches to the volar lip fragment, stabilizes the carpus on the distal radius. The carpus can therefore translate volarly with the distal volar and ulnar fracture fragment of the distal radius. This fragment must be anatomically reduced and buttressed to prevent this volar instability. Standard volar variable angle plates are sited too proximal to secure and buttress these volar lip marginal fragments, therefore allowing carpal translation to occur despite apparent adequate fixation intra-operatively. The rim plate contour is designed to overhang and engage the distal volar lip fragments avoiding this potential for secondary displacement. Due to the variable angle screw option, this plate also allows purchase on these small fragments without joint penetration.

Even though the radial styloid had more metaphyseal than distal comminution in this series, variable angle screws were required, as fixed angle screws



Figure 5 PA and lateral radiograph showing combined dorsal and volar plating using a volar rim plate.

did not adequately engage the bone fragments due to their fixed trajectory, and in most cases the angle of these screws was changed as necessary to ensure stable fixation.

Unfortunately, this was not always enough to achieve adequate fracture stabilization. After volar plate fixation, all fractures were assessed for stability to ensure that the fracture and carpus are stable through a full range of motion. In 35% of cases this was not the case. Therefore an additional plate was placed either along the radial styloid to bridge and secure this styloid fracture; or over the lunate fossa fragment *via* a dorsal approach. In the latter cases, which all had a higher degree of dorso-ulnar than volar-ulnar comminution, rim plates were used to engage the distal volar lip fragments and act as a subchondral raft supporting the radio-carpal joint, aiding adequate restoration of radial height, tilt and angulation. The additional dorsal plates were then applied to buttress the dorso-ulnar fragments, preventing their displacement and translation whilst enhancing radio-carpal and distal radio-ulnar joint stability.

The distal radio-ulnar joint was involved in 85% of cases, with varying degrees of central comminution; a simple split in the coronal plane occurred in only 5 cases. Congruity was restored through the volar approach by using the variable angle screw option and changing the angle of screw insertion to capture the dorso-ulnar fragments. However this was not possible in all cases and an additional buttress plate was applied to the dorso-ulnar fragments in cases of significant comminution.

Besides allowing bone purchase of the distal radial fragments, which is important for fracture stability^[7], variable angle screws decrease the risk of intra-articular screw penetration into the radio-carpal and distal radio-ulnar joints by allowing multidirectional angulation of screws, if necessary. This risk is heightened due to the degree of intra-articular comminution in these fractures and small size of the fragments that are often only large enough to allow fixation with a single screw, sometimes only by using this variable angle option. Some studies have highlighted increased incidence of

removal of metalwork^[8] due to intra-articular placement of fixed angle screws probably as a result of incomplete restoration of volar tilt, distal plate positioning or angulation of the plate.

In this series there was only one case of radio-carpal screw penetration which was noted arthroscopically in a patient who was asymptomatic until sustaining a fall six months following fracture fixation and subsequently developed dorso-radial wrist pain. The implant was removed at the same sitting. In this case, it is hard to determine whether the screw was placed in an intra-articular position at surgery, whether this occurred after the second fall, or whether it was due to avascular necrosis of the lunate fossa fragments secondary to the original injury and plate fixation.

This low incidence of intra-articular screw penetration was perhaps due to careful pre- and intra-operative planning of screw positioning, the liberal use of variable angle screws and the use of additional dorsal plates to aid stability if volar screw placement to capture the dorsal fragments was deemed to be at risk of breaching the articular surface.

Post-operative radiographs showed correction of radial height, inclination and ulnar variance similar to that quoted in the literature for standard volar locking plates used for AO-23A2, A3, C1-3^[9], with only one case of loss of volar tilt correction after fracture fixation using a solitary volar approach. This required no further surgical intervention as the patient remained asymptomatic.

The main difference with this implant is the inability to restore volar tilt to the same extent as with standard volar plates, where a mean correction of 6 degrees (0-18 degrees) is described in the literature^[10-13] and 4.3 degrees in our series. Our results using the rim plate are therefore within the lower limits of this range for standard volar locking plates. This is partly due to the complexity of the fracture pattern and metaphyseal comminution, but also due to the far distal plate position requiring wrist hyperextension for adequate plate and distal screw placement, hence placing limitations on the degree of correction of volar tilt that can be achieved. The joint comminution precludes distal first fixation and then reduction to the shaft of radius.

Limitations

Ideally, the study should include a larger cohort of patients, and a longer duration of follow up in clinic can be considered. Unfortunately, as these fractures are not common this is not possible unless a multicentre approach is used.

In conclusion, this case series of variable angle distal radius rim plates highlights the fact that these implants are indicated for the far distal and complex intra-articular fractures of the distal radius, but cannot achieve enough stability in isolation for all fractures. Some fractures require additional plating techniques, therefore we recommend that all AO-23C3 fractures

should be assessed with a pre-operative CT scan. If trauma surgeons are not confident with dorsal plating techniques, it would be appropriate to consider referral to a specialised wrist surgeon who can base decisions on a combination of factors including pre-operative imaging, intra-operative findings and their experience with the various techniques and implants available. When used appropriately, good results can be achieved using this plate with correction and maintenance of distal radial anatomy. There were few cases of tendon irritation and no cases of flexor or extensor tendon rupture but we recommend prompt removal of implants if there are signs of tendon irritation.

Key considerations

Pre-operative CT scan provides information of fracture configuration and consideration of referral to specialist wrist surgeon if necessary; Radial styloid fixation often requires variable angle screws as the fixed angle trajectory does not always provide adequate hold; Variable angle screws in the lunate facet buttress may prevent penetration of the radio-carpal or DRUJ but may not adequately capture dorsal fragments; Volar tilt restoration is less reliable than the other alignment parameters due to the technique of plate insertion; Intra-operative assessment of stability of fracture fixation necessary after volar plating for assessment of dorsal fracture stability; additional dorsal and/or radial plates are necessary to stabilize these fractures in 35% of cases; plate positioning distal to the watershed line can lead to tendon irritation and risk of attrition rupture requiring removal of implant.

COMMENTS

Background

Far distal intra-articular fractures of the distal radius involving the volar rim are a specific subset of fractures which are difficult to treat in view of the small size of the fracture fragments, location and instability. If stable fixation is not achieved, volar carpal subluxation can occur due to the attachment of the marginal bone fragments to the short radiolunate ligament. Standard volar plate placement proximal to the watershed line poses problems when treating these fractures.

Research frontiers

In recent years, various plates have been designed with various contours and lower profiles to facilitate fracture fixation and decrease the risk of tendon irritation yet still achieve anatomical reduction, stable fixation and allow early mobilization.

Innovations and breakthroughs

The rim plate is a pre-contoured low profile implant, having standard locking and variable angle locking screw options, to allow plate placement distal to the watershed line whilst decreasing the risk of screw penetration into the joint. The aim of this design is to allow fixation of the intra-articular fractures of the distal radius which involve the marginal volar rim. Besides the risk of screw penetration into the radio-carpal and distal radio-ulnar joints when using such a distally sited plate, the other main risk is tendon irritation and rupture. Recent literature has shown that low profile plates can be safely applied at and beyond the watershed line if used appropriately.

Applications

This study shows that this implant allows subchondral support of the articular

surface achieving anatomical reduction. Judicious use of a combination of distal standard locking and variable angle locking screws allows purchase of bone fragments, especially of the dorso-ulnar fragment and avoids intra-articular screw penetration. The manuscript also provides information about the need for additional fixation in certain cases and the risk of tendon irritation.

Peer-review

The manuscript aimed to retrospectively report the clinical outcomes of fixation of far distal intra-articular distal radial fractures using variable angle distal radius rim plate. This topic is interesting and the language is excellent.

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Return to sport following tibial plateau fractures: A systematic review

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Author contributions: Robertson GAJ, Wong SJ and Wood AM conceived the methodology for the manuscript, performed the literature search and analyses for the study, and wrote the manuscript.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at greg_robertson@live.co.uk. The dataset consisted of anonymised synthesis evidence from published studies. Thus no informed consent for data sharing was required.

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Abstract

AIM

To systematically review all studies reporting return to sport following tibial plateau fracture, in order to provide information on return rates and times to sport, and to assess variations in sporting outcome for different treatment methods.

METHODS

A systematic search of CINAHAL, Cochrane, EMBASE, Google Scholar, MEDLINE, PEDro, Scopus, SPORTDiscus and Web of Science was performed in January 2017 using the keywords "tibial", "plateau", "fractures", "knee", "athletes", "sports", "non-operative", "conservative", "operative", "return to sport". All studies which recorded return rates and times to sport following tibial plateau fractures were included.

RESULTS

Twenty-seven studies were included: 1 was a randomised controlled trial, 7 were prospective cohort studies, 16 were retrospective cohort studies, 3 were case series. One study reported on the outcome of conservative management ($n = 3$); 27 reported on the outcome of surgical management ($n = 917$). Nine studies reported on Open Reduction Internal Fixation (ORIF) ($n = 193$), 11 on Arthroscopic-Assisted Reduction Internal Fixation (ARIF) ($n = 253$) and 7 on Frame-Assisted Fixation (FRAME) ($n = 262$). All studies recorded "return to sport"

rates. Only one study recorded a "return to sport" time. The return rate to sport for the total cohort was 70%. For the conservatively-managed fractures, the return rate was 100%. For the surgically-managed fractures, the return rate was 70%. For fractures managed with ORIF, the return rate was 60%. For fractures managed with ARIF, the return rate was 83%. For fractures managed with FRAME was 52%. The return rate for ARIF was found to be significantly greater than that for ORIF (OR 3.22, 95%CI: 2.09-4.97, $P < 0.001$) and for FRAME (OR 4.33, 95%CI: 2.89-6.50, $P < 0.001$). No difference was found between the return rates for ORIF and FRAME (OR 1.35, 95%CI: 0.92-1.96, $P = 0.122$). The recorded return time was 6.9 mo (median), from a study reporting on ORIF.

CONCLUSION

Return rates to sport for tibial plateau fractures remain limited compared to other fractures. ARIF provides the best return rates. There is limited data regarding return times to sport. Further research is required to determine return times to sport, and to improve return rates to sport, through treatment and rehabilitation optimisation.

Key words: Tibial; Plateau; Fracture; Knee; Return; Sport; Rate; Time

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Core tip: We performed a systematic review assessing all studies which reported return rates and times to sport following tibial plateau fractures. Twenty-seven studies were included: All recorded return rates; only one study recorded return times. One study reported on conservative treatment; all 27 studies reported on surgical treatment. The surgical techniques comprised Open Reduction Internal Fixation (ORIF), Arthroscopic-Assisted Reduction Internal Fixation (ARIF) and Frame-Assisted Fixation (FRAME). The return rates were: Total Cohort-70%; conservatively-managed cohort-100%; surgically-managed cohort-70%; ORIF-60%, ARIF-83%, FRAME-52%. ARIF provided the best return rates to sport. Data however is limited, particularly for return times to sport. Further research in this area is required.

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INTRODUCTION

Tibial plateau fractures comprise 1% of all fractures^[1,2]; despite their limited frequency, due to their intra-articular nature, they commonly result in significant functional morbidity^[2-5]. These fractures involve either

the lateral tibial plateau, the medial tibial plateau, or both; injury patterns are commonly classified by the Schatzker or the AO/OTA classification^[2-5]. Such injuries normally arise from high energy trauma: The common reported mechanisms include road traffic accidents, falls from a height, pedestrian struck by motor vehicle or high-impact sporting collision^[1-5]. Despite sport being a well-documented cause for this injury, there is limited evidence on the predicted return rates and return times to sport following tibial plateau fractures^[2,4,5]. This arises for the fact that most outcome studies on this injury type provide validated functional outcomes scores, failing to differentiate specific details on recovery of sporting function^[2,4,5].

The treatment of tibial plateau fracture is based on the location and displacement of the fracture^[2-5]. All undisplaced fractures are routinely managed non-operatively, with a period of knee immobilisation for 4 to 8 wk in a cast or a brace: This is combined with sequential range of motion exercises and a graduated weightbearing protocol^[3]. For displaced fractures, the standard treatment is surgical reduction and fixation of the fracture^[2-5]. A number of surgical techniques have been reported in the literature, and the choice of technique is directed by the fracture pattern^[2-5]. Techniques can be classified into three categories: Those which involve open reduction and internal fixation of the fracture (ORIF), those which involve arthroscopic-assisted reduction and fixation of the fracture (ARIF), and those which involve frame (external fixation) assisted fixation of the fracture (FRAME)^[2-5]. The choice of internal fixation can vary from cannulated screws to multiple locking plates, depending on the nature of the fracture^[2-5]. Associated intra-articular injuries, when present, are also commonly treated in conjunction with fracture fixation^[2-5]. While there is growing evidence on the clinical and radiological outcomes of such techniques, there remains limited evidence on return to sport following such injuries^[2-5].

The aim of this systematic review was to assess all studies reporting return rates and times to sport following treatment for tibial plateau fractures, in order to provide clarification on the optimal treatment methods for this injury, as well as to provide prognostic information on return to sport following these fractures.

MATERIALS AND METHODS

Literature search

A systematic literature search was carried out in January 2017 from the following databases: MEDLINE (PubMed), Cochrane Collaboration Database, EMBASE, SPORTDiscus, CINAHAL, Google Scholar, Physiotherapy Evidence Database (PEDro), Scopus and Web of Science. This was to locate all articles, published in English language, in peer-reviewed journals, reporting on return rates and return times to sports following treatment for tibial plateau fractures. No distinction

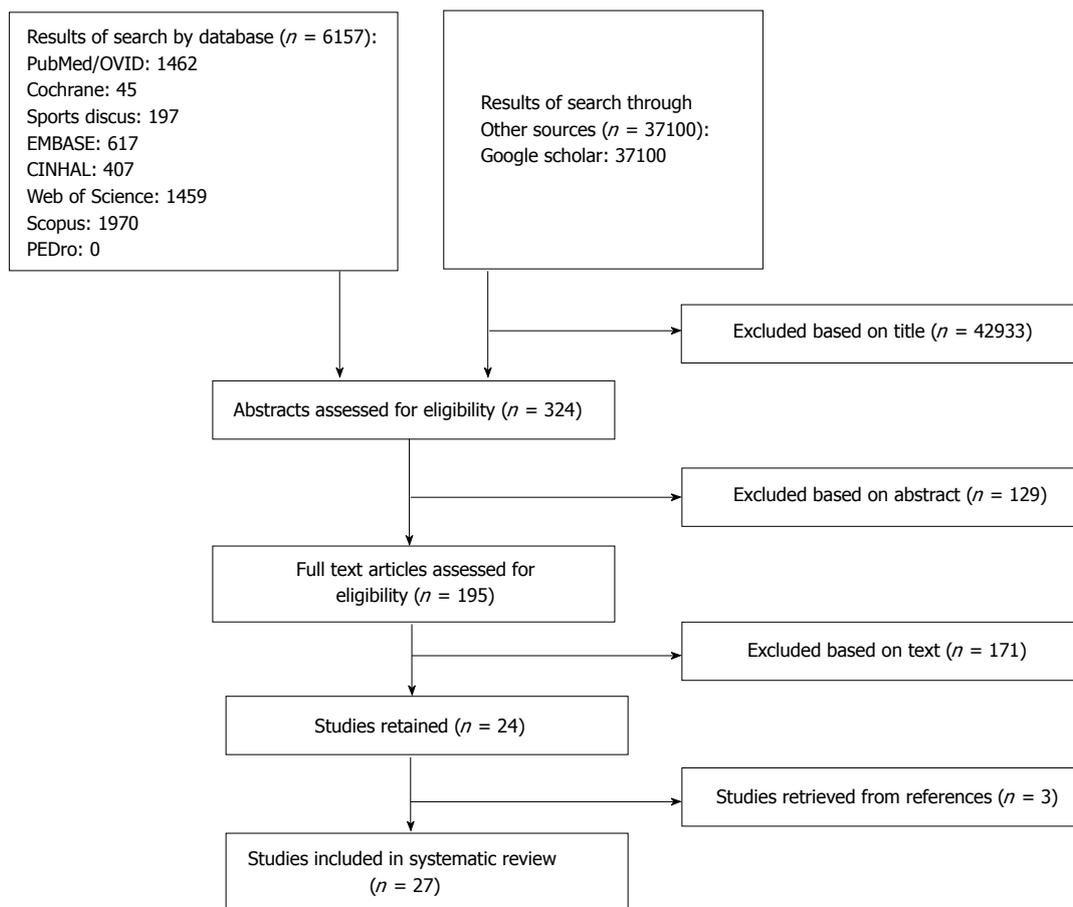


Figure 1 Selection of articles for inclusion in the review in accordance with the PRISMA protocol^[6].

was made regarding the location or nature of fracture, nor level and type of sports activity performed. The keywords used for the search were “tibial”, “plateau”, “fractures”, “knee”, “athletes”, “sports”, “non-operative”, “conservative”, “operative”, “return to sport”. There was no limit regarding the year of publication.

The authors followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines to design the review^[6]. The abstract of each publication was independently reviewed by all three authors (Greg AJ Robertson, Seng J Wong and Alexander M Wood) to establish its suitability for inclusion within the review. As per the PRISMA guidelines, the inclusion and exclusion criteria for review are listed in Table 1^[6]. The quality of reporting of meta-analyses flow diagram in Figure 1 presents the search results and selection process for the review^[6]. Article categories excluded from the review included case reports, expert opinions, literature reviews, instructional courses, biomechanical reports, and technical notes. If exclusion could not be confirmed from the abstract alone, the full-text version of the study was accessed to confirm eligibility. Review of the reference lists of relevant articles were also performed to identify additional studies that could be suitable for inclusion. Discrepancies between the reviewers’ choice of articles for inclusion were resolved

by consensus discussion.

The review database contained data on patient demographics, mode of injury, pre-operative radiological investigations, fracture location, fracture classification, operative and non-operative management techniques, rehabilitation protocols, return rates to sport, return times to sports, rate of fracture union, time to fracture union, complications, required re-interventions and predictive factors for return to sports.

The primary outcome measures were return rates to sport and return times to sport. The secondary outcome measures were return rates to pre-injury level of sport, rate of fracture union, time to fracture union and associated complications. Return to sport was defined as resumption of sporting activities following completion of treatment; return to pre-injury level of sport was defined as the return to specified pre-injury level of sporting activities following completion of treatment. Return time to sport was defined as: The time period from commencement of non-operative modalities to sporting return for conservatively-managed patients; and the time period from primary surgical treatment to sporting return for surgically-managed patients. Where return to sport or fracture union was not possible from the primary treatment method alone, with requirement for conversion to a secondary treatment, this was

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Acute tibial plateau fractures	Extra-articular proximal tibial fractures
Elite or recreational athletes	Stress fractures of the proximal tibial
Return rate to sporting activity reported	No sporting outcome data reported
Return time to sporting activity reported	Paediatric fractures (age under 15)
Two or more fractures reported	Reviews, case reports, abstracts or anecdotal articles
Peer-reviewed journals	Animal, cadaver or <i>in vitro</i> studies
English language	

recorded as a failure for the primary treatment method.

Quality assessment

The modified Coleman Methodology Score (CMS) was used to assess the quality of the included papers^[7]. This is a 10-point-criteria validated scoring system, which has been previously used in multiple similar systematic reviews^[7-10]. The scoring methodology utilised is that presented by Del Buono *et al.*^[7]. This provides a final score ranging from 0 to 100, indicating the quality of study included^[7]. Two of the authors (Greg AJ Robertson and Alexander M Wood) performed scoring of each of the included studies. Using the intra-class correlation co-efficient statistic, the inter-observer reliability of the scores was noted as 0.91 (95%CI: 0.89-0.93).

Statistical analysis

Meta-analysis comparisons were performed for return rates to sport between cohorts of the synthesis data of sufficient size. There was insufficient data to perform meta-analysis comparisons on return times to sport. The meta-analysis was performed on RevMan Version 5.3 (The Cochrane Group). Odds ratios (ORs), with a random effects model, were used to assess comparisons between the dichotomous data. The heterogeneity of included studies was analysed with the I^2 statistic and was judged to be significant if I^2 was > 50%. The significance level was $P < 0.05$.

RESULTS

Search

The details of the selection process for the included articles are listed in Figure 1. In total, 324 unique abstracts and 195 unique articles were assessed.

Patient demographics

We identified 27 relevant publications^[11-37], published from 1988^[18] to 2016^[14], focusing on clinical and functional outcomes of patients who returned to sports activity after tibial plateau fractures (Tables 2-6). One was a randomised controlled trial (RCT)^[11], 7 were prospective cohort studies^[14,16,25,26,28,30,32], 16 were retrospective cohort studies^[12,13,15,17,18,20-24,27,29,34-37] and

3 were case series^[19,31,33].

Of the 1134 fractures, 613 (54%) occurred in male patients, 428 (38%) in female patients, and 93 (8%) failed to specify gender. Ninety-nine of the fractures were open injuries^[11,12,17,20-23]. Two patients had bilateral tibial plateau fractures^[22]. Of the 1134 fractures recorded, sport-related follow-up data was available for 920 (81.1%). The mean age at the time of injury ranged from 34.8 years^[31] to 52.2 years^[37]. The commonly reported modes of injury were road traffic accidents, falls from height, pedestrian struck by motor vehicle and collisions during sports: The most commonly reported sport was skiing (Tables 2-6).

Fracture classification and location

Twenty-six of the twenty-seven studies used formal fracture classifications to describe the fracture types^[11-17,19-37]. Six studies used the Schatzker Classification alone to define fracture pattern^[17,20,27-29,32]. Five studies used the AO/OTA classification alone^[13,22,30,35,37]. Three studies used the Hohl and Moore Classification alone^[14,19,24]. Twelve used both the AO/OTA and the Schatzker Classification^[11,12,15,16,21,23,25,26,31,33,34,36]. One study reported on postero-lateral tibial plateau fractures with no classification used^[18].

The reported fracture configurations from each study are recorded in Tables 2-6. Four studies in the ARIF cohort, restricted patient inclusion to low-energy fracture patterns (Schatzker I-III, AO/OTA A-B)^[27,30,31,33]. There were no restriction of fracture types in the ORIF^[11-19] and FRAME^[11,12,20-24] cohorts. One study reported on undisplaced fractures^[18]; all 27 studies reported on displaced fractures^[11-37]. Seven studies included open fractures: All used the Gustillo-Anderson Classification to classify the soft tissue damage^[11,12,17,20-23].

Twenty-one studies recorded associated injuries^[11-14,16-22,24-30,32,34-36]. For twelve studies, the reported injuries comprised solely of intra-articular knee injuries^[12,14,16,18,19,28-30,32,34-36]. For six studies, the reported injuries comprised both intra-articular knee injuries and non-knee-related trauma injuries^[11,17,21,22,24,25]. For three studies, the reported injuries comprised solely of non-knee-related trauma injuries^[13,20,27]. The commonest intra-articular knee injuries were meniscal tears, tibial spine avulsions fractures, anterior cruciate ligament (ACL) ruptures, posterior cruciate ligament ruptures and medial collateral ligament ruptures^[11,12,14,16-19,21,22,24,25,28-30,32,34-36]. The non-knee-related trauma injuries comprised head, chest and abdominal traumatic injuries, as well as associated spinal, upper limb and lower limb fractures^[11,13,17,20-22,24,25,27].

Of the 920 tibial plateau fractures with follow-up data, 917 were surgically managed^[11-37] and 3 were conservatively managed^[18]. Of the surgically managed fractures, 193 were treated with ORIF^[11-19], 253 were treated ARIF^[24-34] and 262 were treated with FRAME^[11,12,20-24]. For 209 fractures, the outcome data

Table 2 Conservatively managed fractures - only patients with follow-up data included

Ref.	N	Study design	Mean follow-up	Treatment	Mode of injury	Fracture types	Report of IA injuries	IA injury repair	Coleman score	Return rate	Return rate by treatment modality	Return rate to same level of sport	Return time (range)	Rate of union	Time to union (range)
Waldrop <i>et al</i> ^[18] (1988)	3	RCS	59 mo	Knee immobilisation	Falls RTA skiing	Postero-lateral (undisplaced)	Yes	Yes	69	3/3 (100%)	Cons: 3/3 (100%)	3/3 (100%)	N/A	N/A	N/A

Mean values unless otherwise stated. RCS: Retrospective cohort study; RTA: Road traffic accident; Cons: Conservative; N/A: No data available; IA: Intra-articular.

Table 3 Fractures treated by Open Reduction Internal Fixation - only patients with follow-up data included

Ref.	n	Study design	Mean follow-up	Treatment	Mode of injury	Fracture types	Report of IA injuries	IA injury repair	Coleman score	Return rate	Return rate by treatment modality	Return rate to same level of sport	Return time (range)	Rate of union	Time to union (range)
Ahearn <i>et al</i> ^[12] (2014)	21	RCS	40.5 mo	PF (21)	Falls RTA pedestrian	Schatzker VI Bicondylar	No	Not reported	62	14/21 (67%)	PF: 14/21 (67%)	4/21 (19%)	N/A	21/21 (100%)	N/A
Brunner <i>et al</i> ^[19] (2009)	5	CS	39 mo	PF (5)	Skiing (4) Falls (1)	Moore type II	Yes	Yes	61	5/5 (100%)	PF: 5/5 (100%)	N/A	N/A	N/A	N/A
Canadian Orthopaedic Trauma Society ^[11] (2006)	33	RCT	24 mo	PF (33)	Falls RTA Pedestrian Sports Work Cycling	Schatzker V and VI	Yes	Yes	74	4/33 (12%)	PF: 4/33 (12%)	4/33 (12%)	N/A	N/A	N/A
Chang <i>et al</i> ^[6] (2014)	16	PCS	28.7 mo	PF (16)	N/A	Schatzker VI AO/OTA C2-3	Yes	Yes	66	14/16 (88%)	PF: 14/16 (88%)	14/16 (88%)	N/A	16/16 (100%)	20.2 wk
Keogh <i>et al</i> ^[3] (1992)	13	RCS	17 mo	PSF (13)	RTA (5) Falls (5) Work (2) Sport (1)	Schatzker I-VI	No	Not reported	45	11/13 (85%)	PSF: 11/13 (85%)	N/A	N/A	N/A	N/A
Morin <i>et al</i> ^[14] (2016)	15	PCS	18.2 mo	SF (15)	Skiing (15)	Postero-Medial Moore Type I	Yes	Yes	73	13/15 (87%)	SF: 13/15 (87%)	0/15 (0%)	N/A	N/A	N/A
Stevens <i>et al</i> ^[27] (2001)	46	RCS	100 mo	PF (46)	RTA (13) Pedestrian (13) Falls (9) Sports (6) Work (2)	Schatzker I-VI	Yes	Yes	70	21/46 (46%)	PF: 21/46 (46%)	6/46 (13%)	N/A	46/46 (100%)	N/A
van Dremel <i>et al</i> ^[15] (2015)	26	RCS	74 mo	SF PF	Falls (57%) RTA (25%) Other (14%)	Schatzker I-VI AO/OTA B1-C3	No	Not reported	79	15/26 (58%)	SF: N/A PF: N/A	15/26 (58%)	6.9 (2-18) mo (median)	N/A	N/A
Waldrop <i>et al</i> ^[18] (1988)	3	RCS	59 mo	PF (6) ORBG (12)	Falls RTA Skiing	Postero-Lateral (displaced)	Yes	Yes	69	18/18 (100%)	PF: 6/6 (100%) ORBG: 12/12 (100%)	17/18 (100%)	N/A	N/A	N/A

Mean values unless otherwise stated. RCS: Retrospective cohort study; PCS: Prospective cohort study; RCT: Randomised controlled trial; CS: Case series; ORIF: Open reduction internal fixation; PF: Plate fixation; SF: Screw fixation; PSF: Percutaneous screw fixation; ORBG: Open reduction and bone grafting; RTA: Road traffic accident; Pedestrian - Pedestrian struck by Motor Vehicle; AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association; N/A: No data available; IA: Intra-articular.

was reported within combined surgical cohorts, with no differentiation for treatment method used^[35-37].

Choice of radiological imaging

All of the studies used plain radiographs as initial

Table 4 Fractures treated by Arthroscopic-Assisted Reduction and Internal Fixation - Only patients with follow-up data included

Ref.	n	Study design	Mean follow-up	Treatment	Mode of injury	Fracture types	Report of IA injuries	IA injury repair	Coleman score	Return rate	Return rate by treatment modality	Return rate to same level of sport	Return time (range)	Rate of union	Time to union (range)
Chan <i>et al</i> ^[26] (2003)	18	PCS	48 mo	APF (18)	RTA (17) Falls (1)	Schatzker V and VI	Yes	Yes	68	13/18 (72%)	APF: 13/18 (72%)	13/18 (72%)	N/A	N/A	N/A
Chan <i>et al</i> ^[25] (2008)	54	PCS	87 mo	APF (54)	RTA (50) Falls (4)	Schatzker I-VI	Yes	Yes	80	48/54 (89%)	APF: 48/54 (89%)	48/54 (89%)	N/A	54/54 (100%)	N/A
Chiu <i>et al</i> ^[34] (2013)	25	RCS	86 mo	APF (25)	N/A	Schatzker IV-VI	Yes	Yes	73	22/25 (88%)	APF: 22/25 (88%)	22/25 (88%)	N/A	25/25 (100%)	N/A
Duan <i>et al</i> ^[29] (2008)	39	RCS	34 mo	APSF (37)	RTA (19) Falls (11) Sports (9)	Schatzker I-V	Yes	Yes	57	30/39 (77%)	APSF: 30/39 (77%)	30/39 (77%)	N/A	39/39 (100%)	12 (11-14) wk
Gill <i>et al</i> ^[28] (2001)	25	PCS	24 mo	APSF (25)	Skiing (25)	Schatzker I-IV	Yes	Yes	79	21/25 (84%)	APSF: 21/25 (84%)	21/25 (84%)	N/A	N/A	N/A
Guanche <i>et al</i> ^[31] (1993)	5	CS	N/A	APSF (5)	N/A	Schatzker I-III	No	Not reported	55	5/5 (100%)	APSF: 5/5 (100%)	5/5 (100%)	N/A	5/5 (100%)	N/A
Holzach <i>et al</i> ^[30] (1994)	15	PCS	35.3 mo	APSF (10)	Skiing (15)	AO/OTA B2.2 and B3.1	Yes	Yes	76	13/15 (87%)	APSF: 13/15 (87%)	13/15 (87%)	N/A	N/A	N/A
Hung <i>et al</i> ^[32] (2003)	31	PCS	36 mo	APF (31)	RTA (30) Falls (1)	Schatzker I-VI	Yes	Yes	76	26/31 (84%)	APF: 26/31 (84%)	26/31 (84%)	N/A	31/31 (100%)	12 (11-14) wk
Itokazu <i>et al</i> ^[24] (1996)	16	RCS	30 mo	APSF (5) ACF (7) APF (4)	N/A	Hohl II and III	Yes	Yes	49	16/16 (100%)	APSF: 5/5 (100%) ACF: 7/7 (100%) APF: 4/4 (100%)	16/16 (100%)	N/A	16/16 (100%)	N/A
Kampa <i>et al</i> ^[27] (2016)	20	RCS	30 mo	APSF (20)	Falls (52%) Sport (48%)	Schatzker I-III	Yes	Yes	71	10/20 (50%)	APSF: 10/20 (50%)	10/20 (50%)	N/A	20/20 (100%)	N/A
Pizanis <i>et al</i> ^[33] (2012)	5	CS	24 mo	APF (5)	N/A	AO/OTA B2 and B3	No	Not reported	61	5/5 (100%)	APF: 5/5 (100%)	5/5 (100%)	N/A	N/A	N/A

Mean values unless otherwise stated. RCS: Retrospective cohort study; PCS: Prospective Cohort Study; CS: Case series; APSF: Arthroscopic-assisted reduction and percutaneous screw fixation; ACF: Arthroscopic-assisted reduction and cement filling; APF: Arthroscopic-assisted plate fixation; RTA: Road traffic accident; AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association; NA: No data available; IA: Intra-articular.

Table 5 Fractures treated by frame application - only patients with follow-up data included

Ref.	n	Study design	Mean follow-up	Treatment	Mode of injury	Fracture types	Report of IA injuries	IA injury repair	Coleman score	Return rate	Return rate by treatment modality	Return rate to same level of sport	Return time (range)	Rate of union	Time to union (range)
Ahearn <i>et al</i> ^[12] (2014)	15	RCS	41 mo	Frame and IF (15)	Falls (15) RTA Pedestrian	Schatzker VI (Bicondylar)	No	Not reported	62	11/15 (73%)	Frame and IF: 11/15 (73%)	3/15 (20%)	N/A	15/15 (100%)	N/A
				Non-Bridging Frames (15)											

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Chin <i>et al</i> ^[20] (2005)	18	RCS	28 mo	Frame and IF (16) Arthro Frame (2) Bridging Frames (3) Non-Bridging Frames (15)	RTA Pedestrian Falls Skiing Cycling	Schatzker V and VI	No	Not reported	61	15/18 (83%)	Frame and IF: N/A Arthro Frame: N/A	7/18 (39%)	N/A	15/18 (83%)	14 (11-22) wk
Canadian Orthopaedic Trauma Society ^[11] (2006)	33	RCT	24 mo	Frame and IF (33) Bridging Frames (4) Non-Bridging Frames (29)	Falls RTA Pedestrian Sports Work Cycling	Schatzker V and VI	Yes	Yes	74	10/33 (30%)	Frame and IF: 10/33 (30%)	10/33 (30%)	N/A	N/A	N/A
Itokazu <i>et al</i> ^[24] (1996)	1	RCS	30 mo	Arthro Frame (1) Non-Bridging Frame (1)	N/A	Hohl II and III	Yes	Yes	49	1/1 (100%)	Arthro Frame: 1/1 (100%)	1/1 (100%)	N/A	1/1 (100%)	N/A
Katsenis <i>et al</i> ^[21] (2005)	46	RCS	38 mo	Frame and IF (46) Bridging Frames (30) Non-Bridging Frames (16)	RTA Falls	Schatzker V and VI AO/OTA C1-3	Yes	Not reported	72	25/46 (54%)	Frame and IF: 25/46 (54%)	N/A	N/A	45/46 (98%)	13.5 (11-18) wk
Katsenis <i>et al</i> ^[22] (2009)	127	RCS	60 mo (minimum)	Frame and IF (127) Bridging and Non-Bridging Frames (127)	RTA (96) Falls (29) Sports (2)	AO/OTA C1-3	Yes	Not reported	68	68/127 (54%)	Frame and IF: 68/127 (54%)	N/A	N/A	126/127 (99%)	13.7 (10-20) wk
Weigel <i>et al</i> ^[23] (2002)	22	RCS	98 mo	Frame and IF (22) Non-Bridging Frames (22)	RTA (16) Fall (3) Pedestrian (2) Assault (1) Sport (1) Crush (1)	Schatzker II, IV, V and VI AO/OTA C1-3	No	Not reported	54	7/22 (32%)	Frame and IF: 7/22 (32%)	N/A	N/A	N/A	N/A

Mean values unless otherwise stated. RCS: Retrospective cohort study; PF: Plate fixation, PSF: Percutaneous screw fixation; APSF: Arthroscopic Percutaneous screw fixation; Arthro Frame: Arthroscopic-assisted frame application; Arthro Frame and IF: Arthroscopic-assisted frame application with internal fixation; RTA: Road traffic accident; AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association; N/A: Data not available; IA: Intra-articular.

assessment of the fractures^[11-37]. Eleven studies reported using a combination of plain radiographs and CT Scans

for fracture imaging^[14,16,19,20,22,24,25,29,30,32,34]. Four studies, reported using a combination of plain radiographs, CT

Table 6 Surgical cohorts with combined outcome data - only patients with follow-up data included

Ref.	n	Study design	Mean follow-up	Treatment	Mode of injury	Fracture types	Report of IA injuries	IA injury repair	Coleman score	Return rate	Return rate by treatment modality	Return rate to same level of sport	Return time (range)	Rate of union	Time to union (range)
Kraus <i>et al</i> ^[36] (2012)	79	RCS	53 mo	PF PSF APSF	Sports (54%)	Schatzker I-VI AO/ OTA Falls A2-C3 (18%)	Yes	Yes	47	65/79 (82%)	ORIF: N/A PSF: N/A APSF: N/A	N/A	N/A	N/A	N/A
Loibl <i>et al</i> ^[37] (2013)	92	RCS	94 mo	PF PSF ARSF	Skiing (92%)	AO/ OTA B1-C3	No	Not reported	55	81/92 (88%)	ORIF: N/A PSF: N/A APSF: N/A	57/92 (62%)	N/A	N/A	N/A
Scheerlinck <i>et al</i> ^[35] (1998)	38	RCS	62 mo	APSF (30) Arthro Frame (2) Arthro Frame and IF (6)	N/A	AO/ OTA B1-C3	Yes	Yes	68	32/38 (84%)	APSF: N/A Arthro Frame: N/A Arthro Frame and IF: N/A	24/38 (63%)	N/A	N/A	N/A

Mean values unless otherwise stated. RCS: Retrospective cohort study; PF: Plate fixation; PSF: Percutaneous screw fixation; APSF: Arthroscopic percutaneous screw fixation; Arthro frame: Arthroscopic-assisted frame application; Arthro frame and IF: Arthroscopic-assisted frame application with internal fixation; RTA: Road traffic accident; AO/OTA: Arbeitsgemeinschaft für osteosynthesefragen/orthopaedic trauma association; N/A: Data not available; IA: Intra-articular.

and MRI Scans for fracture imaging^[21,26-28].

Study design

The mean CMS for all the studies was 65.5 (range 45-80) (Tables 2-6)^[11-37]. For the study reporting on conservative management, the CMS was 69 (Table 2)^[18]. For the studies reporting on surgical management, the mean CMS was 65.5 (range 45-80) (Tables 3-6)^[11-37]. For the ORIF cohort, the mean CMS was 66.6 (range 45-79) (Table 3)^[11-19]. For the ARIF cohort, the mean CMS was 67.7 (range 49-80) (Table 4)^[24-34]. For the FRAME cohort, the mean CMS was 62.9 (range 49-74) (Table 5)^[11,12,20-24].

Management

Conservative management: This comprised of knee immobilisation for 4 to 8 wk, during which the patient performed quadriceps strengthening exercises^[18]. Following this, the patients commenced range of motion exercises, with progressive weightbearing and physiotherapy^[18].

Surgical management: The surgical technique could be categorised into three main categories: ORIF, ARIF, FRAME.

For the ORIF cohort, surgical techniques comprised open reduction of the fracture followed by internal fixation^[11-19]. Depending on the severity of the fracture, the internal fixation ranged from cannulated screws to locked plate fixation (Table 3). Concomitant management of intra-articular injuries was performed in six studies^[11,14,16-19]. Bone graft was used in three studies to augment fixation^[11,12,19]; synthetic bone

graft substitute was used in one study to augment fixation^[16].

For the ARIF cohort, surgical techniques comprised reduction of the fracture under arthroscopic guidance followed by internal fixation^[24-34]. Depending on the severity of the fracture, the internal fixation ranged from cannulated screws to locked plate fixation (Table 4). Concomitant management of intra-articular injuries was performed in nine studies^[24-30,32,34]. Bone graft was used in six studies to augment fixation^[25-27,29,30,32]; synthetic bone graft substitute was used in four studies to augment fixation^[27,28,33,34].

For the FRAME cohort, surgical techniques comprised fracture reduction by traction and open intervention, followed by Frame Application^[11,12,20-24]. In six studies, limited internal fixation was performed as part of the procedure^[11,12,20-23]. In two studies, reduction of the fracture was assisted by arthroscopic visualisation of the fracture^[20,24]. Four studies used either bridging or non-bridging frames, with bridging frames reserved for cases with significant knee joint instability^[11, 20-22]; three studies used non-bridging frame exclusively^[12,23,24] (Table 5). Concomitant management of intra-articular injuries was performed in two studies^[11,24]. Bone graft was used in three studies to augment fixation^[11,12,20]; synthetic bone graft substitute was used in two studies to augment fixation^[21,22].

Post-operative rehabilitation regimes were reported by all but one study^[11-22,24-37]. These comprised limited weightbearing for 6 to 12 wk^[11-22, 24-37]. There was a variety of range of motion (ROM) protocols based on the severity of fracture, the surgical technique used and associated injuries: Some studies advocated full

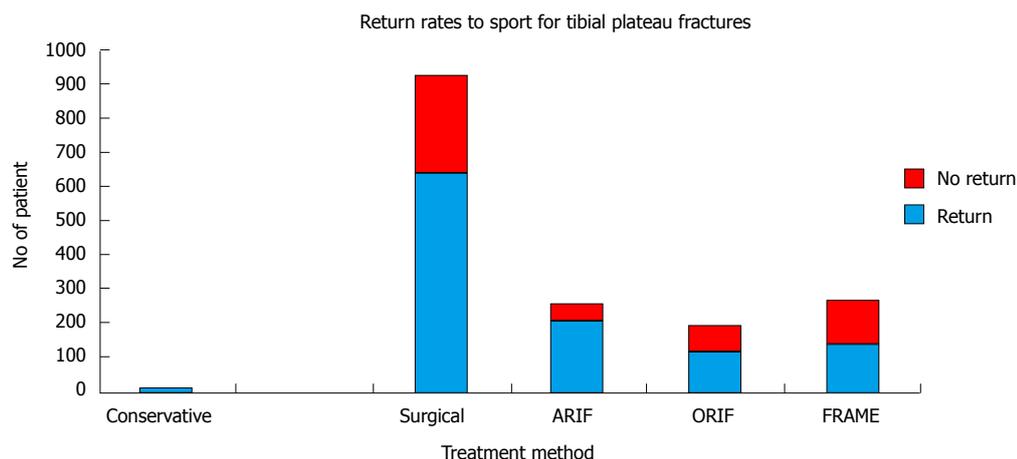


Figure 2 Return rates to sport for tibial plateau fractures. ARIF: Arthroscopic-Assisted Reduction Internal Fixation; ORIF: Open Reduction Internal Fixation; FRAME: Frame-Assisted Fixation.

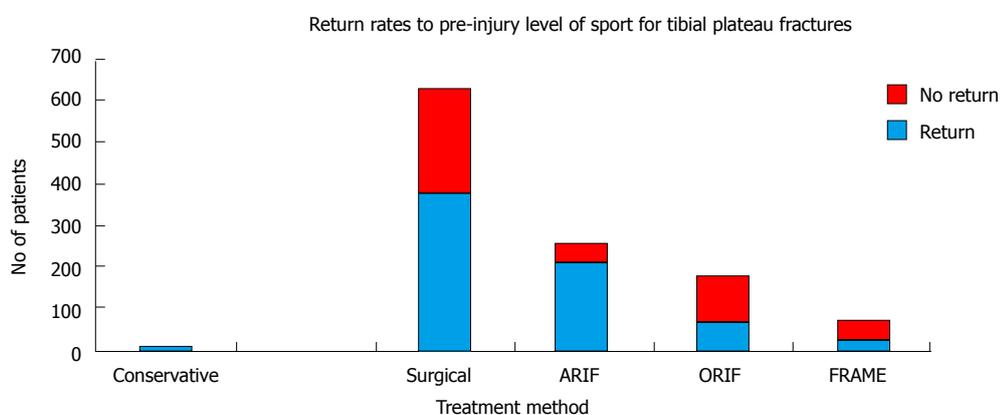


Figure 3 Return rates to pre-injury level of sport for tibial plateau fractures. ARIF: Arthroscopic-Assisted Reduction Internal Fixation; ORIF: Open Reduction Internal Fixation; FRAME: Frame-Assisted Fixation.

ROM exercises immediately post-operative, while other advised knee immobilisation for 4 to 6 wk post-operative^[11-22,24-37].

Associated surgical procedures

Seventeen of the studies reported concomitant management of intra-articular knee injuries at the time of surgical procedures^[11,14,16-19,24-30,32,34-36]. These included meniscal repair, partial and total (medial or lateral) meniscectomy, tibial spine avulsions fixation and ACL re-attachment/repair^[11,14,16-19,24-30,32,34-36].

Functional assessment

Twenty-six of the studies used validated scoring systems to assess post-intervention functional status^[11-30,32-37]. These included both the conservatively managed^[18] and surgically-managed patients^[11-30,32-37]. The only study not to use a validated scoring systems was in the ARIF cohort^[31]. The most commonly used scores were the Rasmussen Score (7 studies)^[13,25,26,28,29,33,34], the Lysholm Knee Score (6 studies)^[14,19,27,33,36], the Short-Form 36 (SF-36) health status questionnaire (6 studies)^[11,12,17,19,20,23] and the Hospital for Special

Surgery Knee Score (4 studies)^[11,16,32,35].

Return rates to sports

Conservative management: The return rates for the conservatively-managed tibial plateau fractures are provided in Table 7 and Figure 2.

The return rates to pre-injury level sport for the conservatively-managed tibial plateau fractures are provided in Table 7 and Figure 3.

Surgical management: The return rates for the various methods of surgical management are provided in Table 7 and Figure 2.

On meta-analysis of the synthesis data, the return rates for the ARIF cohort were found to be significant higher than both: The return rates for the ORIF cohort (OR = 3.22, 95%CI: 2.09-4.97, $P < 0.001$; $I^2 = N/A$); and the return rates for the FRAME cohort (OR 4.33, 95%CI: 2.89-6.50, $P < 0.001$; $I^2 = N/A$). There was no significant difference between the return rates of the ORIF cohort and the FRAME cohort (OR 1.35, 95%CI: 0.92-1.96, $P = 0.122$; $I^2 = 0\%$, $P = 0.40$). The return rates to pre-injury level sport for the various methods

Table 7 Summary of the return times to sport, return rates to sport, times to union and rates of union by treatment modality

Mode of treatment	n (total)	Return rates to sport	Return times to sport	Return rate to pre-injury level	Rates of union	Mean times to union
All ^[11-37]	920	642/920 (70%) ^[11-37]	6.9 mo (median) ^[15]	374/628 (60%) ^[11,12,14-18,20,24-35,37]	475/480 (99%) ^[12,16,17,20-22,24-27,29,31,34]	13.6 wk ^[16,20-22,29,32]
Non-surgical ^[18]	3	3/3 (100%) ^[18]	N/A	3/3 (100%) ^[18]	N/A	N/A
Surgical ^[11-37]	917	639/917 (70%) ^[11-37]	6.9 mo (median) ^[15]	371/625 (59%) ^[11,12,14-18,20,24-35,37]	475/480 (99%) ^[12,16,17,20-22,24-27,29,31,34]	13.6 wk ^[16,20-22,29,32]
Surgical						
ORIF ^[11-19]	193	115/193 (60%) ^[11-19]	6.9 mo (median) ^[15]	60/175 (34%) ^[11,12,14-18]	83/83 (100%) ^[12,16,17]	20.2 wk ^[16]
ARIF ^[24-34]	253	209/253 (83%) ^[24-34]	N/A	209/253 (83%) ^[24-34]	190/190 (100%) ^[24-27,29,31,34]	12.0 wk ^[29,32]
FRAME ^[11,12,20-24]	262	137/262 (52%) ^[11,12,20-24]	N/A	21/67 (31%) ^[11,12,20,24]	202/207 (98%) ^[12,20-22,24]	13.7 wk ^[20-22]
Non-specific surgical cohort ^[35-37]	209	178/209 (85%) ^[35-37]	N/A	81/130 (62%) ^[35,37]	N/A	N/A

ORIF: Open Reduction Internal Fixation; ARIF: Arthroscopic-Assisted Reduction Internal Fixation; FRAME: Frame-Assisted Fixation; NA: No data available.

of surgical management are provided in Table 7 and Figure 3.

On meta-analysis of the synthesis data, the return rates to pre-injury level sport for the ARIF cohort were found to be significant higher than both: The return rates to pre-injury level sport for the ORIF cohort (OR 9.10, 95%CI: 5.80-14.29, $P < 0.001$; $I^2 = N/A$); and the return rates to pre-injury level sport for the FRAME cohort (OR = 10.40, 95%CI: 5.65-19.15, $P < 0.001$; $I^2 = N/A$). There was no significant difference between the return rates to pre-injury sport of the ORIF cohort and the FRAME cohort (OR 1.14, 95%CI: 0.63-2.09, $P = 0.664$; $I^2 = 3%$, $P = 0.31$).

Return times to sports

Conservative management: There were no reported return times for the conservatively-managed tibial plateau fractures (Table 7).

Surgical management: Only one study on the surgically managed fractures reported return times to sport. This was from the ORIF cohort. The reported return time was 6.9 mo (median) with a range of 2 to 18 mo^[15]. This represented a return time to full level sport^[15].

Fracture union

Conservative management: The study reporting on conservatively-managed fractures, did not record post-treatment fracture union^[18].

Surgical management: Fracture union was recorded in 13 studies^[12,16,17,20-22,24-27,29,31,34], with all 13 studies recording rates of union^[12,16,17,20-22,24-27,29,31,34] and only 6 studies recording times to union^[16,20-22,29,32] (Table 7). For those managed by ORIF, the union rate was 100%^[12,16,17] and the mean time to union was 20.2 wk^[16]. For those managed by ARIF, the union rate was 100%^[24-27,29,31,34] and the mean time to union was 12.0 wk^[29,32]. For those managed by FRAME, the union rate

was 98%^[12,20-22,24] and the mean time to union was 13.7 wk^[20-22].

Complications

Conservative management: For the conservatively-managed tibial plateau fractures, there were no complications reported^[18].

Surgical management: For the ORIF cohort, 8 of the studies reported complications^[11-13,15-19]: One study reported no complications^[14]. The reported complications included wound infection (0%-40%), prominent metalwork (0%-56%), post-operative knee stiffness requiring intervention (0%-8%), nerve-related symptoms (0%-6%), and loss of fixation requiring revision (0%-10%)^[11-19]. Removal of metalwork ranged from 0%-56% (mean 27%); re-intervention rate ranged 0%-93% (mean 39%)^[11-19].

For the ARIF cohort, nine of the studies reported complications^[24-30,32,34]; two studies reported no complications^[31,33]. The reported complications included wound infection (0%-7%), prominent metalwork (0%-20%), post-operative knee stiffness requiring intervention (0%-8%), DVT (0%-10%), nerve-related symptoms (0%-20%), loss of fixation requiring revision (0%-3%)^[24-34]. Removal of metalwork ranged from 0%-20% (mean 2%) and re-intervention rate ranged 0%-20% (mean 4%)^[24-34].

For the FRAME cohort, all studies reported complications^[11,12,20-24]. These included pin site infection (0%-57%), nerve-related symptoms (0%-10%), DVT (0%-13%) delayed union (0%-14%) post-treatment knee stiffness requiring intervention (0-5%), and post-treatment mal-alignment requiring intervention (0%-18%)^[11,12,20-24]. All cases required frame removal; beyond this, re-intervention rate ranged 0%-35% (mean 14%)^[11,12,20-24].

Predictive factors

A randomised controlled trial by the Canadian Orth-

opaedic Trauma Society^[11], comparing ORIF to FRAME for Schatzker VI fractures, found that there was a trend towards earlier return to pre-injury sporting activity levels at 6 mo ($P = 0.031$) and 12 mo ($P = 0.024$) post-injury for FRAME compared to ORIF. This difference, however, disappeared at 24 mo post-injury ($P = 0.128$)^[11].

These results are in keeping with those from Ahearn *et al.*^[12], who found there was no significant long-term difference between FRAME and ORIF, in terms of return to sporting activities, at a mean follow-up of 41 mo.

Loibl *et al.*^[37] noted poorer outcomes regarding return to sport for the more severe fracture types (AO/OTA B3 and C3). They also found that participation in downhill skiing post-injury decreased more for patients 61 years and older (56% decline) compared to patients younger than 60 years (45% decline): Post-injury frequency of sports ($r = 0.22$, $P < 0.05$) and duration of sports ($r = 0.25$, $P < 0.05$) was weakly correlated with the patient's age at injury^[37].

Kraus *et al.*^[36] found that, while patients with high-energy fracture patterns (AO/OTA Type C) could continue to participate in sports post-injury, at a frequency and duration similar to those of low-energy fracture patterns (AO/OTA Type A and B) ($P = 0.357$), the variety of sports they could return to was significantly reduced ($P < 0.004$). Conversely, however, they found that the presence of a concomitant ligamentous injuries was not associated with a poorer return to sporting activity ($P = 0.365$)^[36].

DISCUSSION

The main findings of this review are that seventy percent of patients with a tibial plateau fracture returned to sport following injury, with only sixty percent able to return to their pre-injury level of sport. Conservative management offered very acceptable results for undisplaced fractures, with a return to sport rate of 100%. Regarding surgical techniques for displaced fractures, ARIF offered the best return rates at 83%; however, such results were likely influenced by less severe fracture patterns being more amendable to this technique. There was no difference seen in return rates between ORIF and FRAME. There was a significant limitation in the reporting of data with only one study reporting return times to sport for this fracture type.

In comparison to previous similar systematic reviews, the methodological quality of the studies in this review was improved, with a mean modified CMS of 66^[7-10]. In keeping with this, there was one recorded RCT^[11]. However, all other included studies comprised Level 2 to 4 evidence^[11-37], demonstrating a need for further high quality research in this field to better define the optimal treatment modalities for these injuries.

From our data we found that conservative manage-

ment offered a good return rates to sport at 100%. Similarly, return rates to previous level of sport were very satisfactory at 100%. However, this was from a cohort of three fractures, on which there were no return times reported^[18]: This reflects a significant limitation of data in this area. Despite this, the rate of persisting symptoms and complications following this treatment was 0%^[18]. Thus, with the restricted evidence available, conservative management appears to be a very acceptable treatment for undisplaced fractures. Clinicians should, however, remain vigilant for fracture displacement during follow-up: If this is occurs, surgical management should be offered^[3].

From our data we found that surgical management offered limited return rates to sport at 70%. Again, the evidence in this area was restricted, with only one study in this cohort reporting return times to sport^[15]. Despite such limitations, with the reported median return time of 6.9 mo, it appears that sporting rehabilitation following such injuries is notably prolonged^[15]. Despite the restricted reporting on return times to sport, there was sufficient data on return rates to sport to allow comparison between the three main treatment methods: ORIF, ARIF and FRAME. ARIF offered the best return rates at 83%, with a similar value for return to pre-injury level of sport. In comparison, the return rates for ORIF and FRAME were 60% and 52% respectively, and the return rate to pre-injury level of sport were 34% and 31%. The positive findings for ARIF are in keeping with the current literature: A recent systematic review found ARIF to provide encouraging clinical and radiological outcomes from an assessment of 12 studies^[2]. It has been suggested that this technique provides the surgeon with a superior assessment of fracture reduction intra-operatively, as well as allowing direct intra-operative assessment and management of concomitant intra-articular knee injuries^[2]. Indeed, within our review, 9 of the 11 studies using ARIF, reported associated arthroscopic procedures at time of surgery^[24-30,32,34]. However, to note, six of the nine studies in the ORIF cohort also reported associated management of intra-articular injuries, with a number of these studies avoiding arthroscopic-assisted reduction due to the complexity of fractures encountered^[11,14,16-19]. It has been noted that the use of arthroscopic-assisted reduction techniques for Schatzker V and VI fractures can significantly prolong operating time, and increase the risk of post-operative infection and compartment syndrome^[38]. Certainly, on assessment of the fracture types recorded in the studies of the ARIF cohort, at least four studies restricted the technique to low-energy fracture patterns (Schatzker I-III, AO/OTA Type A and B)^[27,30,31,33]. In comparison, there were no such restrictions of fracture types in the ORIF^[11-19] and FRAME^[11,12,20-24] cohorts. Thus, it is likely that selection of fracture type had a confounding influence on the results from our review^[36,37]. Nevertheless, it appears that, particularly for the lower-energy fracture patterns,

ARIF offers athletes the best possibility to return to sport post-treatment.

Other notable findings were that FRAME offered a quicker return to pre-injury sporting levels than ORIF for Schatzker V and VI fractures^[11]. This may reflect a lesser insult to the surrounding soft tissue with FRAME compared to ORIF, so enabling a quicker return of function^[11]. However, return rates to sport for the two techniques, beyond 2 years follow-up, from two studies, showed no difference^[11,12]: Thus it remains debatable if FRAME is truly better than ORIF in allowing return to sport following high energy bicondylar tibial plateau fractures. Further notable findings were that two other studies found that return to sport following tibial plateau fractures was adversely affected by increasing severity of fracture pattern and by advancing age of the patient^[36,37]. It would appear that for increasing severity of fracture pattern, with the associated damage to cartilage and surrounding structures, recovery of sporting function in the knee becomes more challenging^[36,37]. Such effects are then confounded by increasing age of the patient, through the reduced physiological reserve and reduced healing potential that is often associated with this^[36,37].

In comparison to previous studies, there was an improvement in the reporting of both rehabilitation methods and functional outcome scores^[7-10]. All but one of the studies reported comprehensive rehabilitation protocols, with the majority providing detailed descriptions of weight-bearing status, immobilisation method and range of motion protocols^[11-22,24-37]. Similarly, twenty-six of the twenty-seven studies used formal validated scoring methods to allow assessment of post-treatment function^[11-30,32-37].

Assessment of the rehabilitation methods revealed there was notable variation between the techniques. These were largely centred on range of motion protocols and methods of post-operative immobilisation^[11-22,24-37]. With the numbers available, it was not possible to assess the effect of variation in rehabilitation methods on return to sport. Appreciably, such variations are guided by the severity of the injury and associated damage to the surrounding ligaments^[11-22,24-37]. However, with the considerable variations observed, it appears there is definite ability, within future studies, to assess, refine and optimise rehabilitation techniques.

The most notable finding, in comparison to previous similar reviews^[7-10], was the significant lack of reporting on return times to sport. This, in part, reflects the limited description of return to sport in the included studies, with this often being briefly reported a secondary outcome measure^[11-37]. However, this also reflects the prolonged rehabilitation associated with such fractures, with return to sport often outdating the standard follow-up duration for these injuries^[3,15]. Nevertheless, the restricted reporting on return to sport for these fractures was a significant shortcoming, limiting both inter-study comparisons and collection

of certain relevant details such as return to pre-injury level of sport^[7-10]. Future studies should aim to provide more comprehensive descriptions of return rates and times to sport, detailing the level of sport to which the athlete returned, as well as the time taken to return to both training and full-level sport.

There are several limitations to this review

Firstly, due to the limited reporting in most studies, it was not possible to develop synthesis data for return times to sport for this injury. Given the usefulness of such information for athletes and clinicians alike, future studies should be encouraged to record such information as able.

Similar to this, due to the paucity of reporting in the included studies, it was not possible to analyse the synthesis data for the effect of certain factors such as fracture severity, concomitant injuries, and required re-intervention on sporting return. Given the importance of such data on treatment decisions and final outcome, the generalised data provided can be of limited value for the individual athlete. However, the authors have tried to illustrate such information, where possible, including details on fracture severity, the presence of associated intra-articular injuries and rates of complications and further surgery accordingly.

Thirdly, the reporting of return rates to sport throughout the studies was limited. Few provided comprehensive descriptions, with the majority only providing a brief summary of sporting outcomes. This limits our ability to compare sporting outcome both between studies as well as between treatment modalities. In order to limit this effect, sporting outcome was divided in two distinct categories (return to sport, return to same level of sport), enabling a clear outcome from each study.

Lastly, due to the limited size of certain sub-cohorts within the synthesis data, it was only possible to perform six meta-analysis comparisons: further comparisons between sub-sets of the surgical techniques would have been preferable but unfortunately this was not possible due to sub-cohort size.

In conclusion, thirty percent of all athletes who suffer a tibial plateau fracture may not be able to return to sport post-injury. Conservative management forms the first-line treatment for all undisplaced fractures, and provides good results regarding return to sport. Surgical fixation is reserved for displaced fractures. The choice of surgical technique is guided by the severity and pattern of the fracture. With low-energy fracture patterns, ARIF appears to offer the best possibility of return to previous level of sport. With high-energy fracture patterns, there appears no clear difference between ORIF and FRAME for return rates to sport. There was a significant limitation on reporting of return times to sport following these injuries. Thus, despite the available data, further well-designed research is required to better define return rates and

times to sport following tibial plateau fractures.

COMMENTS

Background

Tibial plateau fractures account for 1% of all fractures. The main causes for these injuries include road traffic accidents, falls from a height, pedestrian struck by motor vehicle and high-impact sporting collisions. Despite sport being a common cause for this injury, the literature on return rates and return times to sport for this fracture type remains limited. Such data is valuable to sporting medical personnel and sports teams alike, as this can allow optimisation of management and rehabilitation technique for this injury, ensuring optimisation of sporting outcome for the affected athletes.

Research frontiers

Despite comprising only 1% of all fractures, tibial plateau fractures represent an injury with significant morbidity, due to the intra-articular nature of the fracture. This is particularly the case for athletes sustaining this injury, as return to sport can be significantly affected. Despite sport being a well-documented cause for this injury, data on return to sport following this fracture remains limited, as most studies present outcome data through combined scoring systems, failing to differentiate sporting outcomes. Given the significant difficulties experienced by athletes planning to return to sport following this injury, accurate information on the return rates and return times to sport for this fracture type, stratified by fracture classification and treatment modality, can allow sporting medical personnel and sports team to appropriately select the optimal treatment modality for each patient and adequately schedule rehabilitation programmes following these injuries. By optimising the treatment and rehabilitation of these injuries, this can ensure that affected athletes achieves the optimal sporting outcome possible.

Innovations and breakthroughs

In this systematic review, the authors identified 27 studies which reported either return rates or return times to sport following tibial plateau fractures: All studies recorded return rates; only one study recorded return times. One study reported on the outcome of conservative-managed fractures; all 27 studies reported on the outcome of surgically-managed fractures. The surgical techniques comprised Open Reduction Internal Fixation (ORIF), Arthroscopic-Assisted Reduction Internal Fixation (ARIF) and Frame-Assisted Fixation (FRAME). The return rates were: Total cohort 70%; Conservatively-Managed cohort 100%; Surgically-Managed cohort 70%. For the different surgical techniques, the return rates were: ORIF cohort 60%, ARIF cohort 83% and FRAME cohort 52%. The recorded return time was 6.9 mo (median), from a study reporting on ORIF. ARIF was more commonly used for lower energy fracture patterns (Schatzker I-III; AO/OTA Type A and B), while ORIF and FRAME were used for all fracture patterns. ARIF provided the best return rates to sport, particularly for the lower energy fracture patterns. Data however is limited, particularly for return times to sport. Further research in this area is required.

Applications

A comprehensive understanding of the expected return rates and return times to sport following tibial plateau fractures, stratified by fracture pattern and treatment modality, ensures the treating clinician can appropriately select the optimal method of management, to allow the best possibility of return to sport post-injury. Such information can also allow sports team to realistically plan rehabilitation schedules, with a better understanding of the required treatment duration before athletes will be able return to sport. This allows optimization of both the management and outcome of these injuries.

Terminology

ARIF: Fixation of a Tibial Plateau Fracture with Internal Fixation and an Arthroscope to ensure accurate articular surface reduction; FRAME: Fixation of a Tibial Plateau Fracture with an External Fixation Device; Non-Bridging Frame: An External Fixation Device which does not bridge across the knee joint; Bridging Frame: An External Fixation Device which bridges across the knee joint; Arthroscopic-Assisted Frame Application: Fixation of a Tibial Plateau Fracture with an External Fixation Device and an Arthroscope to ensure accurate articular surface reduction; Frame Application with Internal Fixation: Fixation of a Tibial

Plateau Fracture with an External Fixation Device along with Internal Fixation; AO/OTA Classification: The Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association Tibial Plateau Fracture Classification. This comprises three main categories: Type A: Extra-Articular; Type B: Partial Articular; Type C: Articular; Schatzker Classification: The Schatzker Tibial Plateau Fracture Classification. This comprises six groups: I - Lateral Plateau Split Fracture; II - Lateral Plateau Split-Depression Fracture; III - Lateral Plateau Depression Fracture; IV Medial Plateau Fracture; V - Bicondylar Fracture; VI - Bicondylar Fracture with Metaphyseal-Diaphyseal Disassociation.

Peer-review

The manuscript is nice and well written.

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Systematic review on the use of autologous matrix-induced chondrogenesis for the repair of articular cartilage defects in patients

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Abstract

AIM

To systematically review the results of studies looking at autologous matrix-induced chondrogenesis (AMIC) in humans.

METHODS

A literature search was performed, adhering to the PRISMA guidelines, to review any studies using such techniques in humans. Our initial search retrieved 297 articles listed on MEDLINE, Google Scholar, CINAHL and EMBASE. From these studies, 15 studies meeting the eligibility criteria were selected and formed the basis of our systematic review.

RESULTS

The study designs, surgical techniques and outcome measures varied between the studies. Although all studies reported improvements in patient outcome measures, this was not necessarily correlated with magnetic resonance imaging findings. Although there were many additional procedures performed, when AMIC was performed in isolation, the results tended to peak at 24 mo before declining.

CONCLUSION

Although short-term studies suggest improved patient reported outcomes with a variety of scaffolds, surgical techniques and rehabilitation regimes, the literature remains equivocal on whether the defect size and location, and patient factors affect the outcome. Patient

benefit appears to be maintained in the short-to-medium term but more high level studies with extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

Key words: Autologous matrix-induced chondrogenesis; Cartilage defects; Humans, PRISMA

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Core tip: Studies looking at autologous matrix-induced chondrogenesis (AMIC) in humans suggest improved patient reported outcomes in the short-to-medium term but there is significant variation in the scaffolds, surgical techniques and rehabilitation regimes used. The literature remains equivocal on whether the defect size and location, and patient factors affect the outcome. More high level studies with extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

Shaikh N, Seah MKT, Khan WS. Systematic review on the use of autologous matrix-induced chondrogenesis for the repair of articular cartilage defects in patients. *World J Orthop* 2017; 8(7): 588-601 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i7/588.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i7.588>

INTRODUCTION

Cartilage defects have a limited capacity for repair^[1,2]. Untreated focal defects have the potential to progress to more generalised lesions and can cause significant morbidity. The frequent outcome for arthritis in large joints such as the knee is surgical intervention for joint replacement. This procedure is generally successful in older sedentary patients, but the limited lifetimes of prostheses make it much less desirable for younger and develop new strategies for the treatment of focal cartilage defects to prevent secondary osteoarthritis.

Various surgical procedures have been implemented to reduce pain, and postpone or prevent the need for joint replacement, while simultaneously withstanding the daily activities of the patient^[3]. These include the use of bone marrow stimulation techniques pioneered by Pridie by introducing the concept of subchondral drilling^[4,5]. This was further developed by Steadman who introduced the notion of microfracture^[6]. A range of chondrocyte implantation techniques have also developed including autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), mosaicplasty and osteochondral autologous transplantation (OATS)^[7-10].

In 2003 after funding issues were raised for two-

step procedures such as ACI and MACI partly in view of associated costs, a new one-step procedure was introduced for the repair of cartilage defects called autologous matrix-induced chondrogenesis (AMIC) that brings together microfracture with a collagen matrix scaffold^[11]. There is increasing interest in AMIC as it provides a cost-effective alternative to cell-based therapies for articular cartilage repair, and it is highly autologous in nature. Benthien and Behrens^[1] first described the AMIC procedure using an awl to perform perforations in the subchondral bone, and "partial autologous fibrin glue" (PAF) using commercially available fibrin glue to adhere Chondro-Gide[®] (Geistlich Biomaterials, Wolhausen, Switzerland) collagen membrane to the lesion. The TGF β component of fibrin may contribute to the chondrogenic differentiation of mesenchymal stem cells (MSCs)^[10]. Since then the procedure has been described with variations in the drilling technique, scaffold and fixation.

The results with AMIC in the literature have been variable. As there are limited studies on AMIC, variability in the type of scaffold used^[12-15], the surgical procedure^[1,13,15-17], defect size and location, and patient variability may all contribute to variable results. In addition, we are not aware of the longevity of these results. We performed a systematic review of the literature identifying studies looking at AMIC to determine their clinical outcome, and address these three questions: (1) does the type of scaffold, surgical technique or rehabilitation regime affect outcome? (2) does the defect size and location, and patient factors affect outcome? and (3) does the outcome change with time?

MATERIALS AND METHODS

A systematic review of the published literature was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines^[18]. This search was completed on November 30, 2016 using search databases MEDLINE, Google Scholar, Cumulative Index to Nursing and Allied Health Literature, AMED and EMBASE. No restrictions regarding publication date were applied during the literature search, due to the relatively new nature of AMIC and the limited number of related articles that have been published. Keywords used in the search include "autologous matrix-induced chondrogenesis" and "AMIC". The Cochrane library was also searched using the terms "autologous matrix-induced chondrogenesis" and "AMIC". Abstracts of the selected articles were reviewed to ensure they met the selection criteria, after which the full article was obtained. The bibliographies and in-text references of the retrieved articles were searched for any articles that may have been missed during the initial search. Unpublished or grey literature was identified using databases including System for Information on Grey Literature in Europe, the National

Technical Information Service, the National Research Register (United Kingdom), UKCRN Portfolio Database, the National Technical Information Service, the British Library's Integrated Catalogue, and Current Controlled Trials database. Published and unpublished material including university theses and dissertations, and conference proceedings in the English literature were also reviewed.

The inclusion criteria were clinical studies in English language looking at outcomes after AMIC in partial- and full-thickness focal chondral or osteochondral defects (ICRS grade III or IV) of any joint. Studies with a level of evidence I-IV as described by the Oxford Centre for Evidence-based Medicine^[19] were included. Studies not meeting these criteria, single-patient case studies, techniques, comments, letters, editorials, protocols and guidelines were excluded. Animal and cadaveric studies were also excluded.

The titles and abstracts of all citations were reviewed by the three authors (Shaikh N, Seah MKT and Khan WS). Full manuscripts of citations adhering to the inclusion criteria and those that were uncertain were downloaded. Reference lists of all full manuscripts and applicable review articles were reviewed to identify any further articles omitted from the initial search. The same investigators then reviewed all full manuscripts against the inclusion criteria and any disagreement on eligibility was resolved by discussion. The corresponding author of the paper was contacted if any queries arose. They were also consulted as to any additional citations that may address the research question.

Data was extracted from papers that satisfied the eligibility criteria. The variables that were determined for each study were study type, treatment period, study size, gender, mean age, patients lost to follow-up, mean and range of follow-up, joint involved, size, grade and location of lesion, inclusion and exclusion criteria, source of funding, surgical technique, previous and associated surgeries, rehabilitation and outcome scores. The extracted data was entered onto Microsoft Excel (Microsoft Corporation, Washington, DC) by one investigator (Shaikh N), and re-evaluated and verified by the other authors (Seah MKT and Khan WS). The investigators were blinded to the source or authors of the identified papers. Although the systematic review protocol was approved by the host institution, the systematic review protocol was not formally registered in a registry. A systematic review was performed rather than a meta-analysis in view of the lack of randomised controlled trials and consistent outcome measures, where the results could be combined to allow statistical analyses.

Study quality assessment

The Coleman Methodology Score (CMS)^[20] was used to evaluate the quality of the studies and to determine if the outcomes and claims made in particular studies

should be given more weighting than others. The ratings were also used as a guide to assess the level of confidence from which conclusions could be drawn from a particular study. CMS consists of two parts; Part A that focuses on the design of the study and Part B that relates to the study outcomes. This instrument uses a scaling system, in which the studies are assessed using 10 criteria. Part A has a maximum total score of 65, while Part B has a maximum total score of 35, giving a total score of 100. The total score can be graded as being excellent (85-100 points), good (70-84 points), fair (55-69 points) and poor (< 55 points). A higher total score suggests that the study has an efficient design and is better at avoiding the effects of chance, various biases and confounding factors. The categories used in the CMS were formed on the basis of the Consolidated Standards of Reporting Trials statement for randomized controlled trials^[21].

RESULTS

The results of the search using the databases retrieved 297 articles. Twenty-six articles were reviewed after excluding animal and pre-clinical studies, single-patient case reports, literature reviews and articles where the original text was in a language other than English. Of the 26 articles obtained, 10 were excluded as they represented level V evidence, review studies or technical notes, resulting in a total of 16 articles that were included in this systematic review (Figure 1)^[3,13,15-17,22-33]. Of the 16 included articles, 13 studies were prospectively conducted, 2 were retrospective, and only 1 was a randomized control trial.

There were more males than females included in the studies, with a ratio of approximately 2:1. The mean age was 36.2 years (range 15-50 years) and the mean follow-up period was 30 mo (range 6-62 mo). Ten of the 16 studies focussed on the knee, 3 on the ankle, and 3 on the hip (Table 1). Some of the studies mentioned sources of funding, but none that would trigger any concerns about conflict of interests or bias. A variety of treatment algorithms were used including different drilling techniques, scaffold used, method of fixation, associated surgery and the rehabilitation protocol (Table 2).

All of the studies adopted at least one form of established patient-reported outcome measure and 9 of the 16 studies obtained patient Magnetic resonance Observation of Cartilage Repair Tissue (MOCART) scores (Tables 3 and 4). For the 10 studies looking at the knee, all reported more than one clinical outcome measure. Five used the Visual Analogue Scale (VAS), 4 used the Lysholm score and the Knee injury and Osteoarthritis Outcome Score (KOOS), 3 used the International Knee Documentation Committee (IKDC) score, 2 used the International Cartilage Repair Society (ICRS) and the Cincinnati score, and 1 used the Tegner score and Kujala patellofemoral score.

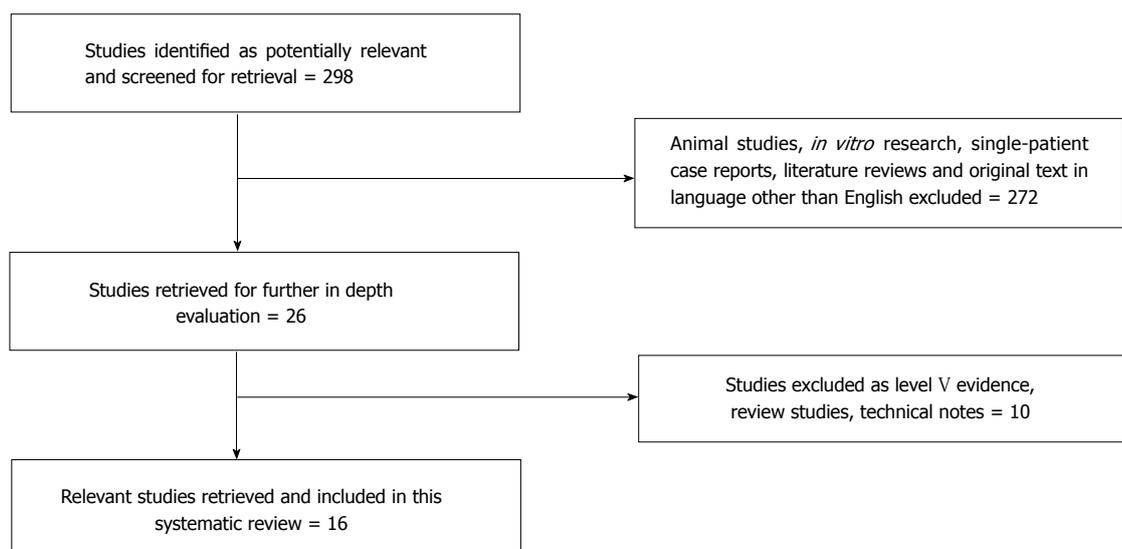


Figure 1 Illustration of the selection process for articles in this systematic review.

The three studies looking at the ankle joint used the American Orthopaedic Foot and Ankle Society (AOFAS) score and the VAS. One study also reported the Foot Function Index (FFI). Two of the hip studies reported the modified Harris Hip Score (mHHS). Four knee, four ankle and one hip studies also reported on MOCART scores. Although positive patient-reported outcomes were observed in all studies, MOCART scores did not always correlate with the patient-reported outcomes.

Kusano *et al.*^[22] found significant improvements in the IKDC and Lysholm scores, but the MOCART scores did not correlate with the positive clinical outcomes. The majority of patients displayed incomplete defect repair, damaged repair tissue, and inhomogeneous repair tissue structure, as well as subchondral lamina and subchondral bone that were not intact. The randomized control trial by Anders *et al.*^[3] assessed differences between a microfracture technique, a sutured AMIC technique, and a glued AMIC technique. In all three groups, positive patient outcomes and pain levels were observed at follow-up, with no significant differences between the groups. In assessing the magnetic resonance imaging (MRI) outcomes of patients in this study, results showed good defect filling in most patients, however homogenous repair tissue was only seen in 50% of the patients treated using the AMIC techniques, compared to 100% of the patients treated using traditional microfracture. Additionally, surface regeneration and integration of the lesion with the cartilage proved to be marginally inferior in patients that were treated using AMIC. The finding that MRI scores do not always correspond with patient-assessed outcomes is consistent with those observed in other studies. Dhollander *et al.*^[29] found favourable clinical outcome scores in patients undergoing AMIC at the patellofemoral joint but the radiological findings did not support these outcomes. All 10 patients

had subchondral lamina changes on MRI and 3 had osteophytes within 24 mo.

Does the type of scaffold, surgical technique or rehabilitation regime affect outcome?

There are three commercially available biodegradable membrane scaffolds that fill in the lesions until they are absorbed and replaced by repair tissue (Table 2). The three scaffolds are Chondro-Gide[®], Chondrotissue[®] (BioTissue, Zurich, Switzerland) and Hyalofast[™] (Fidia Advanced Biopolymers, Padua, Italy). Chondro-Gide[®] is a porcine-based membrane that is the original and most popular scaffold used in AMIC. This protein-based matrix has a bi-layer structure composed primarily of type I/III collagen. In cases where the AMIC Plus technique^[16] was implemented, a Platelet-rich plasma (PRP) gel (GPS[®] III System Advantages, Biomet) was applied to the surface of the lesion prior to the application of the membrane. Chondrotissue[®] is "sponge-like" matrix composed of polyglycolic acid treated with hyaluronan^[12,13]. In cases where Chondrotissue[®] was used, PAF was substituted with biodegradable pins^[13]. The Hyalofast[™] membrane is a partially-synthetic by-product of hyaluronic acid composed of an unstructured amalgamation of fibres. On degradation it releases hyaluronic acid into the defect site that may encourage chondrogenic differentiation of bone marrow-derived MSCs^[14]. Prior to commencing the AMIC procedure, bone marrow is aspirated from the iliac crest, and processed to obtain bone-marrow derived MSCs. This is used with autologous PRP obtained from the blood sample, and together the Hyalofast[™] membrane is immersed in this solution prior to being applied onto defect^[15]. Buda *et al.*^[15] performed the AMIC procedure on 20 patients using Hyalofast[™] membrane, and the improvements in the IKDC scores were greater than those seen with Chondro-Gide[®] membrane. The mean

Table 1 Study demographics, lesion location and grade, inclusion and exclusion criteria, and funding sources

Ref.	Treatment period	Patient numbers	Mean age (yr)	Mean follow-up in months (range)	Joint	Defect location and type	Grade of lesion	Lesion dimensions (cm ²)	Inclusions	Exclusions	Source of funding
Shetty <i>et al</i> ^[34]	4 yr	30				MFC, LFC, trochlea, patella	Grade III/IV	2-8		Malalignment of the knee exceeding 5° of valgus or varus. Generalized osteoarthritic changes in the knee	
Buda <i>et al</i> ^[15]	Apr 2006-May 2007	20 (12M, 8F)	15-50	29	Knees		Grade III/IV	Not specified		Diffuse arthritis, general medical conditions (<i>e.g.</i> , diabetes, rheumatoid arthritis etc.), haematological disorders and infections	None
Gille <i>et al</i> ^[26]	2003-2005	27 (16M, 11F)	39	37 (24-62)	Knees	Medial femoral condyle 7, lateral femoral condyle 3, patella 9, trochlea 2, femoral condyle and patella 6	Grade IV	> 1	Clinical symptomatic chondral lesions at femoral condyle, patella or trochlea	Advanced osteoarthritis, rheumatic disease, total meniscectomy, BMI > 35, deviation of mechanical axis to the affected compartment	Not specified
Dhollander <i>et al</i> ^[16]	Jan 2008-Apr 2008	5 (3M, 2F)	18-50	24 (12-24)	Knees	Patella	Grade III/IV	2 (range 1-3)	Symptomatic focal patella cartilage defects	Untreatable tibiofemoral or patellofemoral malalignment, diffuse osteoarthritis, major meniscal deficiency or other general medical conditions	Not specified
Dhollander <i>et al</i> ^[13]	2008-2009	5 (4M, 1F)	29.8	24	Knees	Right 2 (40%), left 3 (60%) medial femoral condyle (2), lateral femoral condyle (2), trochlea (1)	Grade III/IV	Median 2.3, range 1.5-5	16-40 yr, single symptomatic focal cartilage defect on femoral condyles or patellofemoral joint	Untreated tibiofemoral or patellofemoral malalignment or instability, diffuse osteoarthritis, bipolar "kissing" lesions, major meniscal deficiency and other general medical conditions	Not specified
Kusano <i>et al</i> ^[22]	Aug 2003-Jul 2006	40 (23M, 17F)	35.6	28.8 (13-51)	Knees	Full thickness chondral defect in patella (20), femoral condyle (9), osteochondral defect in femoral condyle (11)	Grade III/IV	3.87		Defects in other locations, age > 50 yr, skeletally immature	Not specified

Leunig <i>et al</i> ^[23]	Mar 2009-Dec 2010	6 (5M, 1F)	22.7	Not specified (12-30)	Hips	Femoral head 5, acetabular 1 chondral 1, osteochondral 5	Grade III/IV	> 2	Full thickness chondral lesions > 2 cm ² or osteochondral lesions > 1 cm ² with defects in weight-bearing areas of acetabulum or femoral head, irreparable by osteotomy in age < 35 yr	Patients unwilling or unable to comply with post-operative rehabilitation protocols. Systematic inflammatory arthritis, advanced arthritis involving both femur and acetabulum, or age > 35 yr	Not specified
Pascarella <i>et al</i> ^[24]	2006-2008	19 (12M, 7F)		12-36	Knees	Right knee: Femoral condyle (medial 34%, lateral 14%), patella (9%) Left knee: Femoral condyle (medial 29%, lateral 14%)	Grade III/IV	3.6	Age 18-50 yr with single lesion	Osteoarthritis, axial deviations, ligamentous injuries, complete meniscal resection, allergy to collagen membrane components	Not specified
Anders <i>et al</i> ^[21]	Jan 2004-Mar 2010	38 (Not specified)	37	19 (6-24)	Knees		Grade III/IV	3.4	Age 18-50 yr, 1-2 lesions	> 2 defects, corresponding defects, bilateral defects, signs of osteoarthritis, other general diseases, history of complete meniscectomy, mosaicplasty, treatment with cartilage specific medication, chondroplasia patallae or patellar dysplasia	None
Gille <i>et al</i> ^[28]	Not specified	57 (38M, 19F)	37.3	24	Knees	Medial condyle (32), lateral condyle (6), trochlea (4), patella (15) Grouping based on lesion size: Group A 0-3 cm ² , Group B 3-6 cm ² , Group C 6-9 cm ²	Grade III (35), Grade IV (37)	3.4 (1-12)	Age 17-61 yr	Rheumatic disease, total meniscectomy, and revision surgery	Not specified
Valderrabano <i>et al</i> ^[17]		26 (18M, 8F)	33	31 (25-54)	Ankles	Osteochondral lesions of talus		1.68	First time osteochondral lesion or failure of previous lesion	Age > 55 yr, open ankle physis	Not specified
Wiewiorski <i>et al</i> ^[25]	2008-2010	23 (16M, 7F)	34	23 (11-49)	Ankles (talus)	Osteochondral lesions of talus	Osteochondral	1.49	Single lesion with history of ankle trauma		Not specified

Dhollander <i>et al</i> ^[29]	April 2009-May 2011	10 (8M, 2F)	37.2 ± 7.1	24	Knee	Patella (8), trochlea (2)	Grade III/IV	4.2 ± 1.9	Patients aged 18-50 yr with a focal patellofemoral defect and clinical symptoms (pain, swelling, locking, giving way)	Untreatable tibio-femoral or patellofemoral mal-alignment or instability, diffuse osteoarthritis or bipolar "kissing" lesions, major meniscal deficiency and other general medical conditions (diabetes, rheumatoid arthritis)	Not specified
Mancini <i>et al</i> ^[30]	November 2004-June 2007	31	36.4 ± 10.3	60	Hip	Acetabular chondral defects	Grade III/IV	2-4	Patients 18-50 yr of age with acetabular chondral lesions with radiological Tönnis degree < 2 followed up to 5 yr	Concomitant chondral kissing lesion, systemic rheumatoid diseases, dysplasia, femoral neck axial deviations, coxa profunda, protrusio acetabuli	Not specified
Fontana <i>et al</i> ^[31]	November 2004-March 2011	55	39.1 (18 to 55)	36-60	Hip	Acetabular ± femoral head chondral defects	Grade III/IV	2-8	Patients 18-55 years of age with acetabular ± femoral head chondral lesions with radiological Tönnis degree < 2 followed up for 3-5 yr	Rheumatoid arthritis, dysplasia, axial deviation of the femoral neck, coxa profunda, protrusio acetabuli	Not specified but Girolamo is a paid consultant for Geistlich
Kubosch <i>et al</i> ^[32]	Not specified	17	38.8 ± 15.7	39.5 ± 18.4	Ankle	Osteo-chondral lesions of talus	Grade III/IV	2.4 ± 1.6	First-time diagnosis or failure of a previous operative treatment	Arthritis of the ankle joint, kissing lesions and rheumatoid arthritis	Not specified

BMI: Body mass index.

KOOS score at follow-up in this study were significantly greater than those reported by Dhollander *et al*^[16,29] using Chondro-Gide® and in Dhollander *et al*^[13] using Chondrotissue. The clinical outcomes achieved in Buda *et al*^[15]'s study were partly supported by the MOCART scores, with a majority of patients displaying complete defect repair, complete integration to surrounding cartilage, intact repair tissue surface, and iso-intense signal intensity, while other MRI measures showed poor results despite positive patient-assessed outcomes. The remainder of the studies in this review used Chondro-Gide® and resulted in patient outcomes that were posi-

tive and comparable.

Several drilling techniques were adopted in the studies. In 6 of the 16 studies, an awl was used to perforate the subchondral surface of the bone as originally described^[1]. Seven studies substituted an awl with a microdrill, with or without Kirchner wires^[23,24]. Pascarella^[24] carried out a slightly modified AMIC procedure with the intention of increasing the number of MSCs to produce healthy regenerative cartilage. Perforations were performed rather than microfractures, and the covering of the focus of the lesion with a biological collagen patch enriched with bone marrow

Table 2 Treatment algorithms

Ref.	Drilling technique	Scaffold/fixation	Associated surgery	Joint	Rehab
Buda <i>et al</i> ^[15]	No drilling	Hyalofast + PRP	3 osteotomy	Knees	NWB 4 wk, run 6 mo, RTS 12 mo
Gille <i>et al</i> ^[26]	Awl/sharp cannula	ChondroGide Fibrin glue	2 realignments, 1 capsular shift	Knees	Immobilization 1 wk, passive motion 6 wk, NWB 6 wk
Dhollander <i>et al</i> ^[16]	Microdrill	ChondroGide + PRP Sutures	3 osteotomy + 1 medial patello-femoral ligament reconstruction	Knees	NWB 2 wk, brace 0-90 for 4 wk, full ROM at 8 wk, Low impact sports 12 mo
Dhollander <i>et al</i> ^[13]	Microdrill	Chondrotissue Pin	1 osteotomy	Knees	NWB 2 wk, 0-90° 4 wk, full range 8 wk, RTS 12 mo
Kusano <i>et al</i> ^[22]	Awl	ChondroGide Suture/fibrin glue	28 osteotomy	Knees	PWB 6 wk, 0-60 4wk
Leunig <i>et al</i> ^[23]	Kirchner wire	ChondroGide, fibrin glue	3 osteoplasty, 2 femoral neck lengthening, drilling of acetabular defects	Hips	PWB 6-8 wk, passive motion 6-8 h for 6-8 wk
Pascarella <i>et al</i> ^[24]	Kirchner wire	ChondroGide Fibrin glue		Knees	
Anders <i>et al</i> ^[3]	Awl	ChondroGide Suture/fibrin glue		Knees	PWB and lymphatic draining massage 3-6 wk, FWB at 4-6 mo, RTS 3-18 mo
Gille <i>et al</i> ^[28]	Awl	ChondroGide Fibrin glue	2 patella realignments, 3 corrective osteotomies, 6 partial menisectomies, 1 ACL reconstruction	Knees	
Valderrabano <i>et al</i> ^[17]	Microdrill	ChondroGide Fibrin glue	16 osteotomy	Ankles	PWB, ROM of < 200 passive motion machine, lymphatic drainage massage 6wks, FWB 6-12 wk, Light sports 12 wk, RTS 5-6 mo
Wiewiorski <i>et al</i> ^[25]	Microdrill	ChondroGide Fibrin glue		Ankles (talus)	PWB and lymphatic draining massage 6 wk, FWB 12 wk
Dhollander <i>et al</i> ^[29]	Slow speed 1.2 mm diameter	ChondroGide Vicryl 6/0	No	Knees (Patellofemoral joint)	NWB for 2 wk, FWB at 10 wk, full range of motion at 8 wk, low impact sports 12 mo
Mancini <i>et al</i> ^[30]	Awl/sharp cannula	ChondroGide Fibrin glue	All patients had cam-type and/or pincer-type impingement, and underwent arthroscopic femoral head-neck resection arthroplasty and/or arthroscopic acetabular rim trimming and labral reattachment to the acetabular rim with suture anchors	Hips	PWB (30% of body weight) for 4 wk, impact sports 3 mo, complete RTS 6 mo
Fontana <i>et al</i> ^[31]	Awl/sharp cannula	ChondroGide Fibrin glue	All patients had cam-type and/or pincer-type impingement, and underwent arthroscopic femoral head-neck resection arthroplasty and/or arthroscopic acetabular rim trimming and labral reattachment to the acetabular rim with suture anchors	Hips	PWB for 7 wk, light sporting activities 4 wk, low impact sports 6 mo, complete RTS 12 mo
Kubosch <i>et al</i> ^[32]	Not specified	ChondroGide Fibrin glue	All patients also underwent autologous cancellous bone grafting to the site	Ankles (talus)	Ankle immobilisation for 2 wk, PWB for 6 wk
Shetty <i>et al</i> ^[34]	Microdrill	Tiseel Coltrix (atelocollagen)	-	Knees	PWB for 6 wk, gradual increase to FWB by next 6 wk

PRP: Platelet-rich plasma; ACL: Anterior cruciate ligament; PWB: Partial weight bearing; NWB: Non-weight bearing; FWB: Full weight bearing; ROM: Range of motion; RTS: Return to sport.

Table 3 Summary of patient outcome scores of the 16 reviewed studies

Ref.	Sub-groupings (Where Applicable)	Follow-up (mo)	Outcomes													
			KOOS		IKDC		VAS		ICRS		Cincinnati		Lysholm		Other	
			Pre-surgery	At follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up	Pre-surgery	At mean follow-up
Buda <i>et al</i> ^[5]		29 ± 4.1	47.1 ± 14.9	93.3 ± 6.8	32.9 ± 14.2	90.4 ± 9.2										
Gille <i>et al</i> ^[26]		48														
Dhollander <i>et al</i> ^[16]		24	41.6	71.4												
Dhollander <i>et al</i> ^[23]		24	37.6 ± 16.7	73.1 ± 25												
Kusano <i>et al</i> ^[22]	ocF	28.8 ± 1.5	44 ± 25	88 ± 9												
	cP	28.8 ± 1.5	51 ± 25	74 ± 17												
	cF	28.8 ± 1.5	45 ± 26	68 ± 14												
Leunig <i>et al</i> ^[29]		Not specified														
Pascarella <i>et al</i> ^[34]		24	30	83												
Anders <i>et al</i> ^[3]	MFx	24														
	Sutured AMIC	24														
	Glued AMIC	24														
Gille <i>et al</i> ^[28]		24														
Valderrabano <i>et al</i> ^[17]		31	7 ± 1.8	2 ± 2.1												
			5 ± 2	2 ± 2												
Wiewiorski <i>et al</i> ^[25]		23	4.8 ± 1.6	1.3 ± 2												
Dhollander <i>et al</i> ^[29]		24	44.5 ± 17.5	65.0 ± 23.3												
Mancini <i>et al</i> ^[30]	Defect < 4 cm ²	60														
Fontana <i>et al</i> ^[31]	Defect > 4 cm ²	60														
Kubosch <i>et al</i> ^[32]		39.5 ± 18.4	7.8 ± 2.1	3.2 ± 2.4												
Shetty <i>et al</i> ^[34]		48	64.7	88.2	39	78.6										

KOOS: Knee injury and Osteoarthritis Outcome Score; IKDC: International Knee Documentation Committee; VAS: Visual Analogue Scale; AOFAS: American Orthopaedic Foot and Ankle Society; ICRS: International Cartilage Repair Society; mHHS: Modified Harris Hip Score; FFI: Foot Function Index; MOCART: Magnetic resonance Observation of Cartilage Repair Tissue.

blood drawn through the knee itself. The aim of the study was simply to show that the modified AMIC procedure was a viable alternative to current surgical practices. The IKDC and Lysholm scores showed a similar trend to that observed by Kusano *et al*^[22], with the mean IKDC score increasing from 30 to 83 in 24 mo, and the mean Lysholm score increasing from 54 to 98. MRI scores showed a significant reduction of the defect area, although detailed MRI evaluations were not available. Similarly Valderrabano^[17] introduced a modified AMIC procedure that involved the addition of spongiosa bone harvested from the iliac crest to increase the number of MSCs being recruited. This graft is inserted into the lesion and the membrane placed on top. They reported significant improvement in the mean AOFAS scores from 62 to 89 for 26

Table 4 Summary of detailed magnetic resonance imaging evaluation results if provided from studies that reported Magnetic resonance Observation of Cartilage Repair Tissue scores

Scoring measure	Number and percentage of patients that achieved a particular result for each category of the MOCART scoring system															
	Buda <i>et al.</i> ^[15]	Dhollander <i>et al.</i> ^[16]	Dhollander <i>et al.</i> ^[13]	Kusano <i>et al.</i> ^[22]	Leunig <i>et al.</i> ^[23]	Valderrabano <i>et al.</i> ^[17]	Wiewiorski <i>et al.</i> ^[25]	Dhollander <i>et al.</i> ^[29]	No. of Pts.	% of Pts.	No. of Pts.	% of Pts.				
Degree of defect repair	14	0	1	3	4	9	8	2	70%	0%	19%	35%	8	35%	2	20%
Hypertrophy	4	2	2	3	0	13	12	2	20%	40%	19%	50%	12	52%	2	20%
Incomplete	2	3	2	10	0	4	3	6	10%	60%	63%	15%	3	13%	6	60%
Complete	16	4	1	8	4	9	8	4	80%	80%	50%	35%	8	35%	4	40%
Incomplete	2	0	4	4	0	9	0	2	10%	0%	25%	35%	0	0%	2	20%
Defect visible	2	1	0	4	0	8	15	4	10%	20%	25%	31%	15	65%	4	40%
Intact	14	0	1	2	3	17	15	3	70%	0%	13%	65%	15	65%	3	30%
Damaged	6	5	4	14	1	9	8	7	30%	100%	88%	35%	8	35%	7	70%
Homogeneous	6	0	0	0	1	7	6	4	30%	0%	0%	27%	6	26%	4	40%
Inhomogeneous	14	5	5	16	3	19	17	6	70%	100%	100%	73%	17	74%	6	60%
Isointense	13	0	2	1	2	4	3	1	65%	0%	6%	15%	3	13%	1	10%
Hyperintense	7	5	2	15	1	18	17	6	35%	100%	94%	69%	17	74%	6	60%
Hypointense	0	0	1	0	1	4	3	1	0%	0%	0%	15%	3	13%	3	30%
Intact	6	0	0	3	1	9	8	0	30%	0%	19%	35%	8	35%	0	0%
Not intact	14	5	5	13	3	17	15	5	70%	100%	81%	65%	15	65%	10	100%
Intact	6	0	1	4	2	3	3	1	30%	0%	25%	12%	3	13%	6	60%
Not intact	14	5	4	12	2	23	20	5	70%	100%	75%	88%	20	87%	4	40%
No	20	5	5	15	3	26	23	10	100%	100%	94%	100%	23	100%	10	100%
Yes	0	0	0	1	1	0	0	0	0%	0%	6%	0%	0	0%	0	0%
No	17	5	3	6	4	25	22	7	85%	100%	38%	96%	22	96%	7	70%
Yes	3	0	2	10	0	1	1	3	15%	40%	63%	4%	1	4%	3	30%

patients. MRI findings however showed that only 35% of participants displayed complete filling of the defect, and less than half of the participants returned to their previous level of activity. There were also slight variations depending on the region that needed to be operated upon. The study by Anders *et al.*^[3] assessed differences in efficacy and safety between a microfracture technique, a sutured AMIC technique, and a glued AMIC technique. Although the sutured AMIC group showed the greatest improvement in mean Cincinnati scores, there were no significant differences between the groups.

In more than half of the studies, additional surgery was required on at least one subject in the study. The most common additional procedure required was osteotomy and bony realignment. All patients who underwent AMIC at the hip joint underwent additional surgery, mostly for impingement. In the study carried out by Kusano *et al.*^[22] looking at the knee joint, patients treated with AMIC alone were compared with patients who had an associated procedure such as an osteotomy. No significant differences in outcomes were noted.

Post-operative rehabilitation regimes varied for the various studies, and were influenced by the location and extent of the lesion. Three studies^[3,17,25] included lymphatic drainage massage as part of their rehabilitation process. The post-operative regime generally involved a period of reduced weight-bearing that may include immobilisation of the joint, followed by a periodic increase in weight-bearing and range of motion. Full-weight bearing commenced from 6 wk to 6 mo. Return to sports periods also lacked consistency, with subjects being able to return to sports after as little as 12 wk^[17], and as much as 18 mo^[3].

Does the defect size and location, and patient factors affect outcome?

For all of the studies investigated, the AMIC procedure was carried out on subjects that had either grade III or grade IV type lesions, although the three ankle-based

Table 5 Coleman methodology scores for the 15 reviewed studies reporting on autologous matrix-induced chondrogenesis

Ref.	Coleman methodology score															Total, max = 100	
	Part A, maximum = 65						Part B, maximum = 35										
	1	2	3	4	5	6	1	2	3	4	5	6	7	8	9		
Buda <i>et al</i> ^[15]	0	4	0	10	10	5	2	2	3	3	5	4	3	3	5	5	64
Gille <i>et al</i> ^[26]	4	4	7	10	10	5	2	2	3	3	5	4	3	3	5	5	75
Dhollander <i>et al</i> ^[16]	0	4	10	10	10	5	2	2	3	3	5	0	3	0	5	5	67
Dhollander <i>et al</i> ^[13]	0	4	10	10	10	5	2	2	3	3	5	4	3	3	5	5	74
Kusano <i>et al</i> ^[22]	4	4	10	0	10	5	2	2	3	3	5	0	3	3	5	5	64
Leunig <i>et al</i> ^[23]	0	4	10	0	10	5	2	2	3	3	5	4	3	0	5	0	56
Pascarella <i>et al</i> ^[24]	0	4	10	10	0	5	0	2	3	0	5	0	3	0	5	5	52
Anders <i>et al</i> ^[3]	4	0	0	10	10	5	2	2	3	3	5	0	3	0	5	0	52
Gille <i>et al</i> ^[28]	7	4	10	0	0	0	2	2	3	3	5	0	3	0	5	5	49
Valderrabano <i>et al</i> ^[17]	0	4	10	10	10	5	2	2	3	3	5	0	3	0	5	5	67
Wiewiorski <i>et al</i> ^[25]	0	4	10	10	10	0	2	2	3	0	0	0	3	3	5	5	57
Dhollander <i>et al</i> ^[29]	0	4	10	0	10	5	2	2	3	3	5	0	3	3	5	5	60
Mancini <i>et al</i> ^[30]	4	7	0	10	5	5	2	2	3	0	5	0	3	3	5	5	59
Fontana <i>et al</i> ^[31]	7	7	0	10	5	5	2	2	3	0	5	0	3	3	5	5	62
Kubosch <i>et al</i> ^[32]	0	7	10	0	0	5	2	2	3	3	5	0	3	3	5	5	53
Shetty <i>et al</i> ^[34]	4	7	10	0	0	5	2	2	3	3	5	0	3	3	5	0	52

studies^[17,25] did not specify the grade of lesions. The studies focussed on both osteochondral and chondral defects of the joints. Although the lesions varied from 1-8 cm², the mean lesion size for all studies ranged from 1.5-3.6 cm². In the ankle based studies all AMIC procedures were conducted on the talus, and a majority of the knee based studies involved the AMIC procedure being carried out on the femoral condyle.

Kusano *et al*^[22] compared 40 defects; 11 were Osteochondral Femoral Condyle lesions (ocF), 20 were Chondral Patella lesions (cP), and nine were Chondral Femoral Condyle lesions (cF). The ocF group had the lowest mean age at 25.9, while the mean age for the other groups was just below 40. Only 36% of patients in the ocF group had an osteotomy compared with 90% in the cP group and 67% in the cF group. The cF group had a significantly smaller mean lesion size (2.3 cm²), compared with 4.2 and 4.4 cm² in the other groups. The patient outcome scores were consistent across the groups. Although the cP group reported the highest mean pre-operative scores, the ocF group showed the greatest improvement at follow-up, and the cF group showed the least improvement. As there were inconsistencies between the three groups relating to age and size of lesion, it is difficult to draw a definitive conclusion from these results. Gille *et al*^[26] followed up patients for 48 mo and failed to identify any significant effect of lesion size on Patient outcome scores. They did however find that outcomes were better for femoral condyle defects than patella defects, and the two patients who had cartilage defects greater than 8 cm² did not benefit from the procedure. Fontana *et al*^[31] compared AMIC with microfracture at the hip joint in patients undergoing impingement surgery, and only found a better five-year clinical outcome for the AMIC group for lesions greater than 4 cm².

Interestingly Fontana *et al*^[31] only found the five-

year results to be better for the AMIC group in males, and not females. Looking at the remaining studies, males generally reported higher outcome scores but showed similar levels of improvement to females after treatment. In the study carried out by Kusano *et al*^[22], the results suggested that younger patients generally experience greater improvements than older patients. Gille *et al*^[26] reported on patient outcome scores at 48 months, and failed to identify any significant effect of age, weight, gender, and previous surgery on patient outcome, but younger patients did generally display better recovery rates than older patients.

Does the outcome change with time?

Mancini *et al*^[30] and Fontana *et al*^[31] reported five-year follow-up in patients undergoing AMIC at the hip joint but all patients underwent additional impingement surgery. The authors report improved outcome scores that were achieved at six months and generally maintained till final follow-up at five-years. Gille *et al*^[26] reported on ICRS, Cincinnati, and Lysholm patient-assessed scores at 24, 36, and 48 mo for patients undergoing AMIC at the knee joint with less than 10% of patients undergoing additional procedures. Patient recovery tended to peak at 24 mo before declining. The mean Cincinnati score peaked at 74 at 24 mo, and steadily declined to 62 (36 mo) and 37 (48 mo). For all scoring systems, the patient outcomes deteriorated more rapidly once they passed the 36 mo follow-up. The randomized control trial by Anders *et al*^[3] compared a microfracture technique, a sutured AMIC technique, and a glued AMIC technique. None of the patients underwent any additional procedures. In all three groups, improvements in pain scores and patient outcomes, including Cincinnati scores, were observed at both 12 and 24 mo follow-up. Between 12 and 24 mo follow-up, 12 patients showed further

Table 6 Coleman methodology scores - mean, range and standard deviation for each section

Section score (maximum)	Mean	Range	SD
Part A (65)			
Study size	2.1	0-7	2.6
Minimum follow-up	4.5	0-7	1.7
Number of different surgical treatment included	7.3	0-10	4.3
Study design	6.3	0-10	4.8
Description of surgical technique	6.9	0-10	4.3
Post-Op management described	4.4	0-5	1.7
Total part A	31.4	21-40	5.7
Part B (35)			
Outcome measures clearly defined	1.9	0-2	0.5
Timing of outcome clearly stated	2	2	0
Use of reliable outcome criteria	3	3	0
General health measure inc.	2.2	0-3	1.3
Subjects recruited	4.7	0-5	1.2
Inv. independent of surgeon	1	0-4	1.7
Written assessment	3	3	0
Completion of assessment by patients with minimal investigator assistance	1.9	0-3	1.5
Selection criteria reported and unbiased	5	5	0
Recruitment rate reported	4.1	0-5	2
Total part B	28.9	23-35	3.9
Total, maximum = 100	60.2	49-75	7.7

improvement in Cincinnati scores, 12 showed little or no change, and 3 showed a decline.

Methodological quality assessment

CMS was used to assess the methodological quality of the studies carried out using the AMIC procedure (Tables 5 and 6). The mean CMS and standard deviation (SD) achieved was 60.7 ± 7.9 (range 49-75) out of 100. The mean CMS and standard deviation (SD) achieved in Part A was 31.8 ± 5.9 , and in Part B was 28.9 ± 4.1 .

DISCUSSION

AMIC enables the transplantation of a scaffold with MSCs in one step, avoiding the need for laboratory cell number expansion and a second procedure^[26]. In our review, 15 studies between 2003 and 2015 that used AMIC for the repair of articular cartilage defects in patients were systematically reviewed. AMIC is still a relatively new procedure and more mid-term and long-term outcomes are awaited. The mean CMS suggesting that the overall quality of the studies was fair. Studies scored poorly for number of patients, length of follow-up, study design and independence of the investigator and the surgeon. For Part A, the overall mean CMS was 31.8 out of 65 points (49%), whereas for Part B the overall mean CMS was 28.9 out of 35 (72%). This indicates that overall, the studies were more competent in defining their outcome criteria and procedures, and that greater improvements need to be made regarding study design and procedures. Although blinding of participants has ethical implications, blinding of clinicians recording the outcome measures was not practised commonly. In scoring systems that require completion by an investi-

gator, it is recommended that the investigation be carried out by an independent investigator to ensure accurate responses from the patient avoiding risk of bias through patient-investigator relationships. Several authors contributed to multiple studies included in this review introducing a risk of bias in both study design and reporting of outcomes across the studies.

The studies included in this review were not directly comparable due to differences in study design, lesions, surgical technique, follow-up and outcome measures. Although the AOFAS score was used in all three ankle studies and the mHHS in two of the three hip studies, there were no consistent scoring systems used for the knee studies. Nevertheless, a pattern of positive patient outcomes can be seen across all of the studies. Future studies should incorporate a universal method of rating patient outcomes for each joint location, allowing direct comparison of results. There also is a need to determine whether MRI assessment is a reliable tool as the studies in our review suggest that it does not necessarily correspond with patient outcome measures. Nevertheless, we recommend that all studies should continue to carry out an MRI assessment while further evidence on its relevance is sought.

Many of the studies included patients that required additional surgical procedures including osteotomies. For a patient undergoing more than one surgical procedure it would be difficult to determine the effect of each procedure in relieving pain and improving joint function. There is a distinct lack of consensus regarding post-operative management and the structure of rehabilitation programmes. Rehabilitation programs can have a significant influence on patient outcomes and recovery rates. Although it is difficult to develop a universal rehabilitation program due to the large number of variables such as patient demographics, and

lesion size and location, this needs to be considered when comparing outcomes between different studies. Due to the variation in studies it is not possible to determine if the type of scaffold, surgical technique or rehabilitation regime affect the outcome.

Limited studies suggest that femoral condyle lesions do better than patellar lesions, and osteochondral defects do better than chondral lesions. Defect sizes did not generally have an effect on the patient's outcome unless the defect was > 8 cm², in which case it had a detrimental effect on outcomes. There is limited evidence that younger patients experience greater improvements than older patients and display better recovery rates. It has been shown *in vitro* that bone marrow stem cells from older patients have reduced chondrogenic potential compared with younger patients, potentially decreasing the effectiveness of AMIC in older patient groups.

Follow-up period is an important factor in assessing the real effectiveness and reliability of the AMIC procedure. Since the treatment method is relatively new, there is a lack of long-term patient outcome data available. A longer follow-up period allows the proper assessment of long term outcomes for a procedure. Although five-year follow-up was available for two studies^[30,31], the patients had all undergone additional procedures making any improvements difficult to attribute to the AMIC procedure alone. It was demonstrated in the study conducted by Gille *et al.*^[26] and Gudas, Gudas *et al.*^[27] that declines in clinical outcomes can be observed as early as 18 to 24 mo after undergoing surgical treatment without additional procedures. Patient assessed outcomes by Gille *et al.*^[26] declined significantly between the 24 mo and 48 mo post-operative period, indicating that there may be concerns regarding durability of the repaired cartilage after undergoing the AMIC procedure. In the randomized control trial by Anders *et al.*^[3] improvements in pain scores and patient outcomes, including Cincinnati scores, were observed at 12 mo follow-up. Between 12 and 24 mo follow-up, although 12 patients showed further improvement in Cincinnati scores, 12 showed little or no change, and 3 showed a decline. This supports the observation by other studies, and their 5-year follow-up results are awaited.

The published literature reviewed suggests that AMIC in cartilage repair is a safe and effective treatment option that improves patient outcome measures and reduces pain. MRI findings however do not necessarily correspond with patient outcome measures. Most studies reported promising results, with no mention of further surgical corrections being needed in the follow-up period. Medium- and long-term results for AMIC procedures without additional surgeries are awaited. Earlier studies suggest that AMIC results may peak at around 24 mo.

The CMS results suggest that the clinical trials evaluated in this systematic review were of fair to reasonable quality; with 8 of the 15 studies achieving

total CMS scores ranging from 60 to 80. The main weaknesses across the studies were the total number of participants and the patient follow-up periods. Improvements in these areas will significantly increase the reliability of the patient outcome measures, while allowing investigators to draw more definitive conclusions. More high level studies with larger sample sizes, and extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

COMMENTS

Background

The results with autologous matrix-induced chondrogenesis (AMIC) in the literature have been variable. As there are limited studies on AMIC, variability in the type of scaffold used, the surgical procedure, defect size and location, and patient variability may all contribute to variable results. In addition, we are not aware of the longevity of these results.

Research frontiers

AMIC is a one-step procedure that brings together microfracture with a collagen matrix scaffold. There is increasing interest in AMIC as it provides a cost-effective alternative to cell-based therapies for articular cartilage repair, and it is highly autologous in nature.

Innovations and breakthroughs

The published literature reviewed suggests that AMIC in cartilage repair is a safe and effective treatment option that improves patient outcome measures and reduces pain. MRI findings however do not necessarily correspond with patient outcome measures. Most studies reported promising results, with no mention of further surgical corrections being needed in the follow-up period. Medium- and long-term results for AMIC procedures without additional surgeries are awaited.

Applications

More high level studies with larger sample sizes, and extensive and robust validated outcome measures should be conducted to evaluate the medium- and long-term effect of the AMIC procedure.

Terminology

Mesenchymal stem cells (MSCs): These cells reside in bone marrow and many adult tissues. MSCs are multipotent stromal cells capable of self-renewal and differentiation *in vitro* into a variety of cell lineages, including chondrocytes, osteoblasts, and adipocytes. They are therefore seen as an optimal regenerative cellular therapeutic for musculoskeletal regeneration.

Peer-review

This is a well-designed and written systematic review.

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Painless swollen calf muscles of a 75-year-old patient caused by bilateral venous malformations

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Abstract

A 75-year-old man presented with knee pain due to medial osteoarthritis of the knee in the orthopedic outpatient clinic. Conservative treatment was started with steroid infiltration. Besides his knee complaint reported a bilateral painless swollen calf muscle without traumatic cause, and also without any pain at night, fever or medical illness. On physical examination the soleus muscle had a swollen aspect in both calfs. The skin appeared normal without deformities and the arterial pulsations were intact. An X-ray did not show abnormalities in the tibia. Magnetic resonance imaging of the legs revealed bilateral multiple saccular intramuscular venous malformations involving the soleus muscle. Intramuscular venous malformations in skeletal muscles are rare, especially when the occurrence is bilateral. Bilateral venous malformations have the potential to be missed because of the intramuscular localization. Symptoms of intramuscular venous malformation can be often mild and overlap with non-exercise related compartment syndrome, claudication, lymphedema and post thrombotic syndrome or muscle strains.

Key words: Venous malformations; Bilateral intramuscular venous malformation; Swollen calf muscles

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Core tip: Intramuscular venous malformations involving in the skeletal muscles are rare, especially when occurrence of these lesions is bilateral. These lesions are easily missed due to intramuscular localization. We report a rare presentation of these lesions arising from the soleus muscle on both sides in a 75-year-old man, diagnosed with magnetic resonance imaging of the

legs. When the lesions are asymptomatic conservative treatment is preferred. When the appearance is symptomatic surgical resection or sclerotherapy can be an option.

Piekaar RSM, Zwitser EW, Hedeman Joosten PPA, Jansen JA. Painless swollen calf muscles of a 75-year-old patient caused by bilateral venous malformations. *World J Orthop* 2017; 8(7): 602-605 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i7/602.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i7.602>

INTRODUCTION

A vascular malformation is an aberrant morphogenetic type of blood or lymphatic vessel. The origin of vascular malformations is an abnormal embryonic development of the vascular build-up after the endothelial stage. The malformation consists of an arteriovenous, capillary, venous or lymphatic type. Also combined structures are described^[1]. This subdivision is based on the type of vessel involvement. When a lymphatic vessel is involved the anomaly is called a lymphangioma. Abnormal connections between arteries and veins will lead arteriovenous shunting with a cluster of vessels, the nidus. The most common shown type of vascular malformation is the venous malformation. These are mostly situated in the skin and subcutaneous tissues and are present at birth, although clinical manifestation will usually become apparent later in life^[2,3]. Intramuscular venous malformations on the other hand are rare especially when the occurrence is bilateral, and these have the potential to be missed because of the intramuscular localization^[1,2]. In this report we have described a patient with bilateral extensive intramuscular venous malformations involving the soleus muscles with an asymptomatic presentation.

CASE REPORT

A 75-year-old man was seen in our orthopedic outpatient clinic with osteoarthritis of the right knee. He experienced morning stiffness, pain on the medial side of his right knee after walking and he had difficulties with full flexion of his knee. Conservative treatment was started with steroid infiltration, 4 cc lidocaine mixed with 1 cc dexamethasone. Besides these complaints the patient reported a bilateral painless swollen calf muscle. The patient had noticed these swellings of the calf muscle a few years ago without any traumatic history. He had no pain at night and no fever or medical illness. The past medical history of the patient was uneventful.

On physical examination the soleus muscle was swollen on both sides. The swelling was localized on the right leg over the whole soleus muscle, 10 by 3 cm.



Figure 1 Frontal view of the lower legs. On physical examination the soleus muscle was a bit swollen on both sides, with a dimpling in both legs (right more than left).

On the left lower leg the swelling was about 3 by 3 cm over the medial part of the soleus muscle. A dimpling in both legs (right more than left) at the medial calf area was seen while standing (Figure 1). There was full strength in all lower leg muscles and the reflexes were normal on examination. The rest of the examination was unremarkable, the overlying skin appeared normal without deformities, erythema or warmth and the arterial pulsations were intact. Laboratory test results did not show any abnormalities. An X-ray did not show any bony irregularities in the tibia.

Magnetic resonance imaging (MRI) of the legs revealed bilateral multiple sacular intramuscular venous malformations involving the soleus muscle (Figure 2). There was no nidus seen on MRI so an arteriovenous form of the malformation was not plausible. Due to its asymptomatic presentation no angiogram or ultrasonography was performed to further specify the lesion. After consultation of the vascular surgeon we did not perform surgical resection or focal sclerotherapy because of the asymptomatic nature of the lesions. After explanation of the possible muscle damage from resection and because of the fact that our patient had no disabilities in daily living, we agreed upon conservative management. At three months follow up the swollen calf muscles were still asymptomatic and examination did not show any change of the venous malformations. We continued the conservative treatment focused on the osteoarthritis of the knee with good result.

DISCUSSION

Vascular anomalies are common in the general population, and the major of vascular malformations occur in the upper and lower extremities. The origin of the development of vascular malformations lies in an abnormal embryonic root thus they are present at birth, although not always evident^[1]. The precise pathogenesis is still though. These anomalies exist of an arteriovenous, capillary, venous and lymphatic type. Also combined structures are described^[1]. Venous malformations are a type of vascular malformations

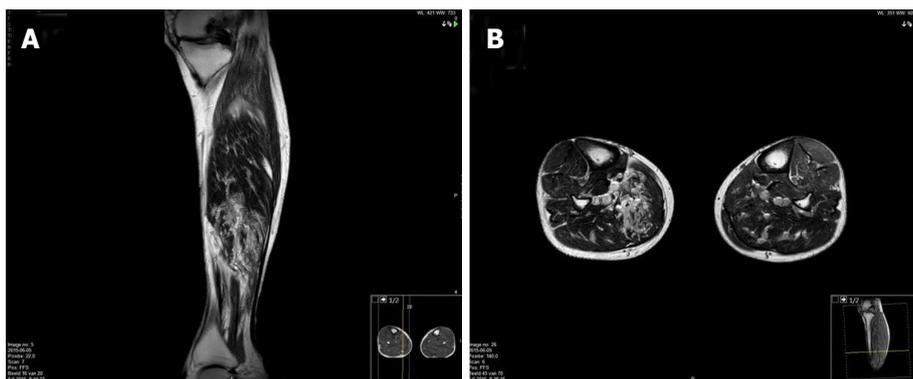


Figure 2 Magnetic resonance imaging of both legs. A: Sagittal plane magnetic resonance imaging (MRI) of both legs reveals bilateral multiple saccular intramuscular venous malformations involving the musculus soleus; B: Transverse plane MRI of both legs reveals bilateral multiple saccular intramuscular venous malformations involving the musculus soleus.

that is seen more often by changes in skin color and focal edema^[3]. These are mostly the malformations situated in the skin and subcutaneous tissues^[2]. As an uncommon cause of tumor the venous malformation can also occur in skeletal muscles of the lower extremities. Asymptomatic intramuscular venous malformations are rare, especially when the occurrence is bilateral^[1,2]. The venous malformations we presented in our patient had a bilateral appearance in both calf muscles, the soleus muscle, although the left lower extremity was less severe in comparison with the right side.

Intramuscular venous malformations can provoke contractures of the involved muscles^[4,5]. A study by Hein *et al.*^[3] shows that most of the intramuscular venous malformations are noted in youth and remain manifest during lifetime. Symptoms of intramuscular venous malformation can be often mild and overlap with non-exercise related compartment syndrome, claudication, post thrombotic syndrome or muscle strain. Other possible diagnosis of swollen lower extremities can be lymphedema with or without hyperkeratosis and papillomatosis^[6]. Besides this other vascular anomalies such as arteriovenous or lymphatic malformations can fit in the differential diagnosis of these swellings.

To determine the nature of the vascular malformation MRI is the most accurate tool and it is superior to the other modalities such as ultrasound. On MRI, venous malformations have a T1-hypointense or T1-isointense signal with a T2-hyperintense signal^[3]. In this case there were no nidi or connections between arteries and veins visible on the MRI so arteriovenous malformations were not plausible. The lymphatic system was shown without any abnormalities.

Surgical treatment for venous malformations is mostly not necessary and conservative therapy is preferred. Pain, bleeding due to lesions of the skin or cosmetic issues can make treatment indicated though after failure of nonoperative management. When the appearance is intramuscular, venous malformations can result in painful contractures of the involved

muscles. In these cases operative treatment can be necessary. The main operative treatment is surgical resection or sclerotherapy (percutaneous embolization). Percutaneous approach is the recommended treatment due to the minor connections to the normal venous system^[7]. This kind of treatment often required for larger extensive intramuscular lesions was not indicated in this instance. If sclerotherapy is impossible due to the extent or location more invasive therapy by performing excision of the lesion is possible. If surgical resection is planned it is important to visualize hidden deep truncular anomalies previously to the operation. Otherwise surgery can result in large defects with venous insufficiency and cosmetic deformities as undesirable results. The patient in our case had neither symptoms nor disabilities in daily living as a result of the intramuscular venous malformations whereby conservative treatment, focused on the osteoarthritis of the knee was chosen.

Previously some case indicated focal lesions in the muscle were presented by toe walking and a case reported the presence of extensive intramuscular venous malformation in the lower extremity as well^[4,5,8]. But, to our knowledge, a bilateral form of these intramuscular venous malformations in the soleus muscles was never reported before.

Venous malformations are the most common type of vascular anomalies. Although an asymptomatic tumor of the lower extremity can have many causes, a painless swollen calf muscle can be caused by the presence of intramuscular venous malformations. Bilateral asymptomatic appearances of these intramuscular venous malformations are rare and have the potential to be missed because of the intramuscular localization. The intramuscular localization is easily found by using MRI. Treatment is only necessary when the swelling is symptomatic.

Learning points: (1) intramuscular venous malformations in the skeletal muscles are rare, especially when the occurrence is bilateral; (2) bilateral venous malformations have the potential to be missed because

of the intramuscular localization; (3) symptoms of intramuscular venous malformation can be often mild and overlap with non-exercise related compartment syndrome, claudication, post thrombotic syndrome or muscle strain; and (4) in this case we have reported a bilateral venous malformation manifestation in calf muscles.

COMMENTS

Case characteristics

A 75-year-old man with osteoarthritis of the knee presented with asymptomatic bilateral painless swollen calf muscles, which were firstly noticed a few years ago without any previous traumatic cause.

Clinical diagnosis

Bilateral painless swollen soleus muscles, with a dimpling (right more than left) while standing.

Differential diagnosis

Non-exercise related compartment syndrome, muscle strain, claudication, lymphangioma, lymphedema, post-thrombotic syndrome or other vascular anomalies such as arteriovenous or lymphatic malformations.

Laboratory diagnosis

All laboratory test results were within the normal limits.

Imaging diagnosis

X-ray of the both legs did not show abnormalities in the bones. Magnetic resonance imaging of both legs revealed bilateral multiple saccular intramuscular venous malformations involving the musculus soleus, nidus of the arteries and the veins in an arteriovenous form of the malformation were not found.

Pathological diagnosis

Biopsy was not performed so pathological findings could not be given.

Treatment

Because of asymptomatic appearances of the bilateral swollen calf muscles conservative treatment was started in our case. Main treatment for symptomatic venous malformations is surgical resection or sclerotherapy (percutaneous embolization).

Related reports

The precise etiopathogenesis of vascular malformations is still unclear, but the origin of the development lies in an abnormal embryonic root. Venous malformations are frequently shown and are simply diagnosed when situated

in the skin or in the subcutaneous tissues. Uncommon localizations of these entities are those in the skeletal muscles. Bilateral appearances of venous intramuscular malformations in the lower extremities are commonly confused with other causes of tumor in the legs.

Term explanation

Asymptomatic bilateral intramuscular venous malformation is a rare type of vascular anomalies of which the origin lies in an abnormal embryonic development.

Experiences and lessons

Bilateral intramuscular venous malformations in the skeletal muscles are rare, with mild symptoms, and have the potential to be missed because of the intramuscular localization.

Peer-review

A straightforward, simple case report with a reasonable review of the literature. The interest is from the differential diagnosis and the concomitant other pathology of knee arthritis.

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Ultrasound diagnosis of fractures in mass casualty incidents

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Abstract

The role of point-of-care ultrasound in mass casualty incidents (MCIs) is still evolving. Occasionally, hospitals can be destroyed by disasters resulting in large number

of trauma patients. CAVEAT and FASTER ultrasound protocols, which are used in MCIs, included extremity ultrasound examination as part of them. The literature supports the use of ultrasound in diagnosing extremity fractures both in hospitals and MCIs. The most recent systematic review which was reported by Douma-den Hamer *et al* in 2016 showed that the pooled ultrasound sensitivity and specificity for detecting distal forearm fractures was 97% and 95% respectively. Nevertheless, majority of these studies were in children and they had very high heterogeneity. The portability, safety, repeatability, and cost-effectiveness of ultrasound are great advantages when treating multiply injured patients in MCIs. Its potential in managing fractures in MCIs needs to be further defined. The operator should master the technique, understand its limitations, and most importantly correlate the sonographic findings with the clinical ones to be useful. This editorial critically reviews the literature on this topic, describes its principles and techniques, and includes the author's personal learned lessons so that trauma surgeons will be encouraged to use ultrasound to diagnose fractures in their own clinical practice.

Key words: Fracture; Point-of-care ultrasound; Diagnosis; Mass casualty incidents

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Core tip: The role of point-of-care ultrasound in mass casualty incidents (MCIs) resulting in large number of trauma patients is still evolving. Radiological workup of these patients is important. The portability, safety, repeatability, and cost-effectiveness of ultrasound are great advantages in these situations. Its potential in managing fractures in MCIs is not fully defined. Its role will depend on different factors. The operator should master the technique, understand its limitations, and most importantly correlate the sonographic findings with the clinical ones.

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INTRODUCTION

New developments in technology have tremendous impact on managing trauma patients in austere conditions. Occasionally, hospitals can be destroyed or be out of function being stressed with lack of power, large number of trauma patients, and a need for rapid triage^[1-3]. Mass casualty incidents (MCIs) occur when the medical needs of injured patients exceed the available medical resources^[4,5]. Radiological workup of these patients, in this scenario, is important for accurate diagnosis and triage. So, any disaster management plan should include radiological workup as an integral part of it with full engagement of radiologists^[6]. Trauma Computed tomography (CT) scan is not available worldwide and even difficult to transport to the pre-hospital setting. In contrast, high quality portable light ultrasound machines have been used in the pre-hospital setting^[6,7]. They have rechargeable batteries that can last up to 4 h^[3]. This is a great advantage compared with CT scans and conventional heavy X-ray machines. Point-of-care ultrasound (POCUS) is noninvasive, rapid, and repeatable and can be combined with clinical examination to make critical decisions in triage and resuscitation of shocked patients^[8,9].

BASIC PHYSICS OF ULTRASOUND

Piezoelectric crystals of the ultrasound probes produce ultrasound waves and receive them. When these waves pass through body tissues, they get reflected depending on the density of the tissues. On the brightness (B) mode ultrasound images, fluids will be black, soft tissues will be grey, fibrous tissues will be white without a shadow, and bones will be bright white with a shadow. Accordingly, the cortex of long bones will be a white line with a black shadow deeper to it (Figure 1). Reverberation artifact which appears deeper to the cortical hyperdense white line occurs because ultrasound waves bounce between the transducer and the bone cortex. The white reverberation lines represent repetition of the cortical hyperdense white line as picked up by the ultrasound machine. The distance between these lines are equal^[10] (Figure 1B). This simple principle is pivotal for mastering diagnosing fractures. Fractures will appear as a complete interruption of the hyperechoic cortical line of the bone or as a cortical defect (Figures 2 and 3).

TECHNICAL CONSIDERATIONS

High frequency linear probes (10-12 MHz) have high resolution and low depth of penetration. Accordingly,

they are used for diagnosing fractures^[10,11]. It will be easy to perform POCUS on long bones using the linear probe because it gets in direct contact over the long bone (Figure 1A). The patient is asked to point at the maximum point of pain. The finger of the examiner is gently passed over the area to define the suspected area of fracture. This may not be possible in children, geriatrics and unconscious patients. It is always advised to compare the injured region with the normal side especially in children. Starting with the normal side in children will assure them and avoid the pitfall of misdiagnosing ossification centers and epiphysis as fractures^[11]. One of the major technical difficulties encountered when detecting fractures of small bones is the irregularity of the bone surface. Accordingly, air may be present between the probe and the bone. Air gives very highly echogenic reflections (white) and can cause a barrier when performing ultrasound. Adequate gel should be applied between the ultrasound probe and skin to reduce the artifacts caused by air (Figure 4). Some may even use water bath as an ultrasound transmitter to reduce the air artifact and pain while examining the patient^[11]. Ultrasound is not recommended to be done on open fractures. The diagnosis is already clinically made; this will delay the management, may cause infection, and will be very painful.

ULTRASOUND IN MCIS

The benefits of using POCUS in MCIs are numerous. Multiple injured patients may need help in austere geographical locations where radiological investigations are not available. POCUS is of great value in these circumstances. Hand-held ultrasound units have been routinely used in hospital and pre-hospital settings as a normal practice with encouraging positive results^[7,12,13]. This has increased the experience in using POCUS outside the routine hospital practice in conditions mimicking MCIs. Furthermore, POCUS has been done on patients during helicopter transportation in an unstable environment^[14]. POCUS images were transmitted through satellite technology using the principles of telemedicine by evaluating images at distant centers^[15]. Despite reduced clarity, overall accuracy in remotely detecting pericardial and peritoneal free fluid was 86%^[15]. POCUS images have even been transmitted from the International Space Station to a remote-control center located on the earth yielding acceptable image quality to make clinical decisions^[16,17]. Smartphones have been recently used in transmitting ultrasound images which is a very attractive approach in MCIs^[18].

CLINICAL APPLICATIONS

ATLS have been advocated in many countries as the accepted guidelines in the management of multiply injured patients. This includes primary physiological survey (Airway, Breathing, Circulation, Disability, and

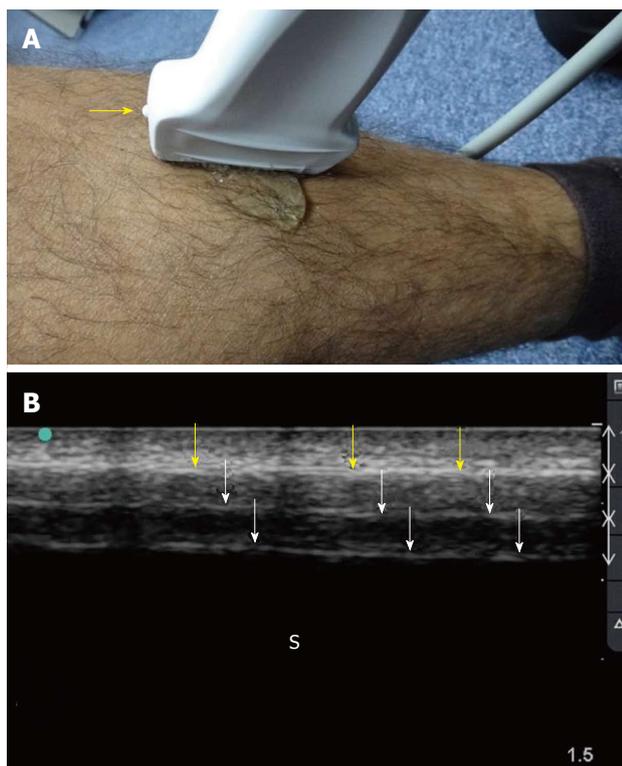


Figure 1 Ultrasound examination of the tibial shaft. A linear probe having a frequency of 10-12 MHz was used (A). The marker (yellow arrow) is pointing proximally. The plain surface of the tibia makes the examination easy. Normal ultrasound findings (B) include a hyperechoic line (yellow arrows) representing the cortical line of the bone. There are reverberation artifacts deeper to this line (white arrows). These are linear lines parallel to the cortex, having the same distance between them and decreasing in density. A black shadow is located deeper to that. S: Sonographic shadow of the shaft of the tibia. Ultrasound study was performed by Professor Fikri Abu-Zidan, Department of Surgery, Al-Ain Hospital, Al-Ain, UAE.

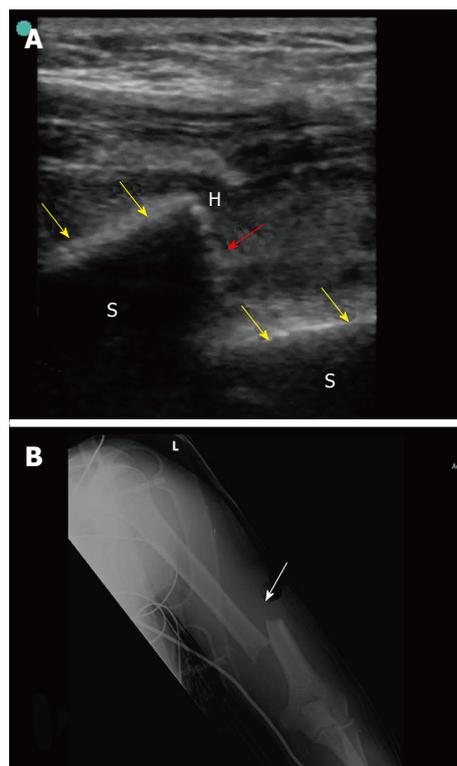


Figure 2 Point-of-care ultrasound of a 42-year-old laborer who fell from 8 meters high during work. The patient presented with pain, swelling and deformity of the left arm. He had left wrist drop. B mode point-of-care ultrasound of the humeral shaft using a linear probe having a frequency of 10-12 MHz (A) showed that the white cortical line of the humeral shaft (yellow arrows) has been interrupted by a large gap (red arrow) suggesting a displaced fracture at the shaft. X-ray of the humerus (B) confirmed the presence of a displaced fracture (white arrow). S: Sonographic shadow of the humeral shaft; H: Hematoma at the edge of the fracture. Ultrasound study was performed by Professor Fikri Abu-Zidan, Department of Surgery, Al-Ain Hospital, Al-Ain, UAE.

Exposure) for treating life-threatening conditions. This is followed by secondary survey which includes examining the patient from head to toe, front and back. POCUS has been very useful in the primary survey to define the source of shock in multiply injured patients^[19,20].

Diagnosing fractures by ultrasound should be part of the secondary survey. Certain protocols, like the CAVEAT protocol and FASTER protocol were developed to use portable ultrasound in the MCIs. They included extremity ultrasound examination in these protocols^[4,5,21]. The CAVEAT protocol (Chest, Abdomen, Vena cava, and Extremities for Acute Triage) included ultrasound extremity examination as part of the triage during the secondary survey^[4,5]. The FASTER protocol added the Extremity and Respiratory evaluation to the classical Focused Assessment Sonography for Trauma (FAST) examination^[21]. Hand held ultrasound could properly diagnose long bone fractures in military conditions^[22]. Dulchavsky *et al*^[21] used portable machines with linear probes in 95 patients who had extremity injuries (158 extremity examinations). Ninety-four percent of these patients were accurately diagnosed. Ultrasound can diagnose occult fractures that can be missed by conventional X-rays because it is very sensitive to

cortical defects^[5,23] (Figure 4).

May and Grayson^[24], in a Best Evidence Report published in 2009, critically appraised four papers. They reported that the results of using ultrasound to diagnose fractures of the wrist in children are very encouraging with high sensitivity reaching above 90%. Furthermore, they stressed the need for larger studies to prove their conclusions^[24]. A systematic review and meta-analysis, which was published in 2013, showed that ultrasound was accurate in diagnosing extremity fractures. This study searched MEDLINE and EMBASE during the period of 1965 to 2012^[25]. They included 8 studies in their final review. Six of these were in children. All studies used convenient, and not consecutive, samples. Ultrasound sensitivity for detecting extremity fractures ranged between 83% and 100%. The positive likelihood ratio ranged between 3.2 and 56.

An excellent recent systematic review and meta-analysis of high quality evaluated the diagnostic accuracy of ultrasound for distal forearm fractures^[26]. The authors searched PubMed, EMBASE and Cochrane database and included 16 studies in their final meta-analysis. Almost all studies used convenient samples but their overall quality was average to high. Majority

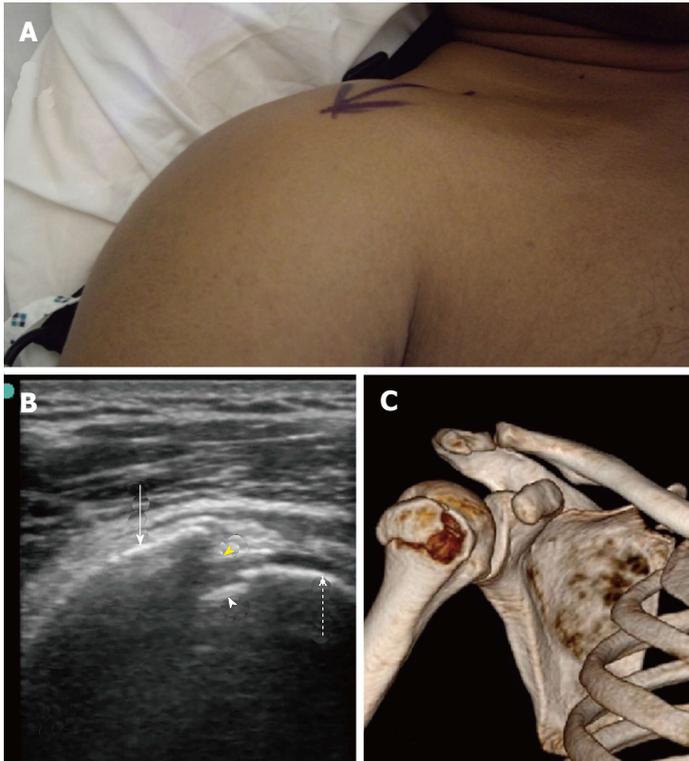


Figure 3 Point-of-care ultrasound of a 40-year-old front seat male passenger who was involved in a front impact collision with a tree. When presenting to the hospital, he had severe pain, swelling and limitation of the movement of the right shoulder (A). B mode point-of-care ultrasound of the right shoulder using a linear probe having a frequency of 10-12 MHz (B) shows that the humeral head (dashed arrow) and the greater humeral tuberosity (white arrow). There is a discontinuity of the bony line (yellow arrow head) indicating a fracture in the greater tuberosity. A small piece of fractured bone is also seen near the humeral head (white arrow head). Three-dimensional bony reconstruction of the right shoulder confirms the ultrasound findings (C). Ultrasound study was performed by Professor Fikri Abu-Zidan, Department of Surgery, Al-Ain Hospital, Al-Ain, UAE.

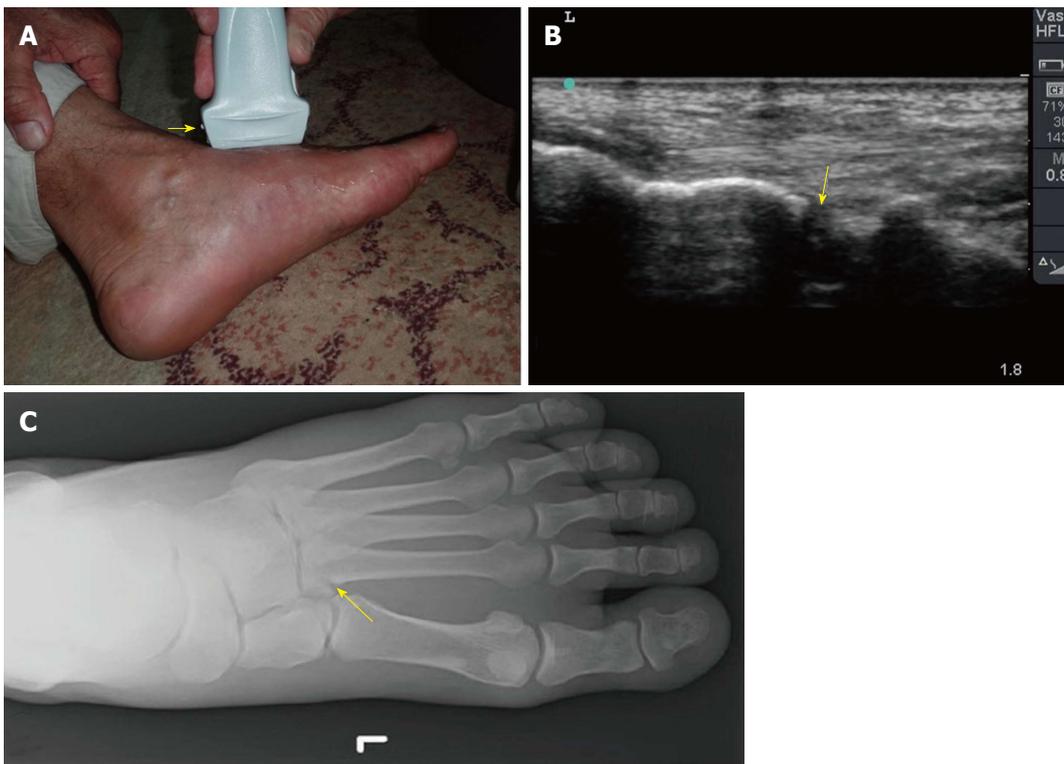


Figure 4 Point-of-care ultrasound of a 60-year-old man who twisted his left ankle and could not walk on it. He had swelling of the left foot with maximum tenderness on the base of second metatarsal bone (A). The yellow arrow indicates the marker of linear probe which is shown on the left side of the screen while the groove on the other side is shown on the right side of the screen. B mode images of the previous patient showed a cortical defect (yellow arrow) at the base of the second metatarsal bone suggestive of a fracture (B). Plain X-ray of the foot confirmed these findings (C). Ultrasound study was performed by Professor Fikri Abu-Zidan, Department of Surgery, Al-Ain Hospital, Al-Ain, UAE.

were in children. The pooled ultrasound sensitivity and specificity for detecting distal forearm fractures were 97% and 95% respectively. The positive likelihood

ratio was 20. Nevertheless, the heterogeneity of the sensitivity and specificity of the studies was very high (82% and 87%) with a very significant p value from the

chi-squared test ($P < 0.0001$).

POCUS TRAINING

The ultrasound guidelines for the American College of Emergency Physicians advocates the diagnosis of fractures by emergency physicians^[11]. According to the CAVEAT protocol, extremity assessment by ultrasound is one of the most difficult skills to be achieved^[4]. The results of ultrasound depend on three main factors: (1) training and experience of the operator; (2) quality of the machine; and (3) the studied region of the patient^[27]. Operators' experience in ultrasound varies tremendously which may dramatically affect its results^[28,29]. This is important when defining the role of ultrasound in MCIs. In principle, POCUS training should be incorporated into the surgical and emergency physicians training. Ultrasound training should include understanding the basic physics, instrumentation and image interpretation^[30,31]. Different methods have been used to achieve that including human models, patients, video clips, cadavers, simulation technology, and animal models^[29,32-34].

PERSONAL VIEW

Although the discussed principles in this article look easy, I find it occasionally difficult to diagnose very minor fractures. The main reason is that it takes time to do a full screening especially for minor fractures in seriously injured patients. This is a limitation which has been acknowledged by others^[6]. There is no doubt that POCUS is very useful to early diagnose fractures of long bone as they may cause shock. It is questionable whether diagnosing small bone fracture will have a long-term advantage on these patients.

Twenty-five years ago, no one would have imagined the place that POCUS will take in managing multiple trauma patients. The role of POCUS in MCIs in austere conditions is still evolving. Its potential is not yet fully defined. Its role in managing fractures will depend on different factors. The operator should master the technique, understand its limitations, and most importantly correlate the sonographic findings with the clinical ones. No doubt that portability, safety, repeatability, and cost-effectiveness of ultrasound are great advantages when treating multiply injured patients in MCIs. The technology is there but it is our duty to define its real value.

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Postoperative deep shoulder infections following rotator cuff repair

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Abstract

Rotator cuff repair (RCR) is one of the most commonly

performed surgical procedures in orthopaedic surgery. The reported incidence of deep soft-tissue infections after RCR ranges between 0.3% and 1.9%. Deep shoulder infection after RCR appears uncommon, but the actual incidence may be higher as many cases may go unreported. Clinical presentation may include increasing shoulder pain and stiffness, high temperature, local erythema, swelling, warmth, and fibrinous exudate. Generalized fatigue and signs of sepsis may be present in severe cases. Varying clinical presentation coupled with a low index of suspicion may result in delayed diagnosis. Laboratory findings include high erythrocyte sedimentation rate and C-reactive protein level, and, rarely, abnormal peripheral blood leucocyte count. Aspiration of glenohumeral joint synovial fluid with analysis of cell count, gram staining and culture should be performed in all patients suspected with deep shoulder infection after RCR. The most commonly isolated pathogens are *Propionibacterium acnes*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*. Management of a deep soft-tissue infection of the shoulder after RCR involves surgical debridement with lavage and long-term intravenous antibiotic treatment based on the pathogen identified. Although deep shoulder infection after RCR is usually successfully treated, complications of this condition can be devastating. Prolonged course of intravenous antibiotic treatment, extensive soft-tissue destruction and adhesions may result in substantially diminished functional outcomes.

Key words: Rotator cuff repair; Deep shoulder infection; Shoulder surgery; Postoperative complication

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Core tip: Rotator cuff repair (RCR) has become one of the most frequently performed orthopaedic procedures during the last two decades. Paralleling the exponential increase in the number of RCRs, uncommon complications such as postoperative deep shoulder infections may be seen more frequently. Patients who are suspected to have a post-RCR infection require a thorough diagnostic evaluation, including clinical signs and symptoms, laboratory workups

and cultures. Although appropriate management of this condition with surgical debridement and lavage, and long-term IV antibiotics usually results in eradication of the infection, complications can be disabling and functional outcomes poor. The majority of the patients with deep infections after RCR report unsatisfactory outcomes with permanent functional limitations.

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INTRODUCTION

Rotator cuff pathology is one of the most commonly encountered orthopaedic problems, with an estimated prevalence of 17% to 35% including asymptomatic patients^[1]. In symptomatic patients, rotator cuff repair (RCR) usually provides good to excellent clinical outcomes^[1-4]. As a result, RCR has become one of the most frequently performed orthopaedic procedures during the last two decades^[5,6]. Paralleling the exponential increase in the number of RCRs, associated complications such as postoperative deep shoulder infections may be seen more frequently^[7]. Published literature indicates that the incidence of deep shoulder infection after open or mini-open RCR ranges between approximately 0.3% and 1.9%, and the condition is more common in male patients^[7-9]. While the rate of infection is generally thought to be lower after arthroscopic RCR, current high level evidence supporting this assertion is limited. In a recently published retrospective study including 3294 all-arthroscopic RCRs, Pauzenberger *et al.*^[10] reported an infection rate of 0.85%. In another retrospective case series, Vopat *et al.*^[11] studied the effects of surgical technique on infection rate. Out of 1824 RCRs performed by a single surgeon, 14 had an early deep postoperative shoulder infection that required surgical irrigation and debridement. Of these 14 patients who developed deep infections, primary RCR surgery was performed arthroscopically in only three of them, while 11 patients received open or mini-open repairs. The authors stated that "The most important finding in this study was that patients with non-arthroscopic RCR (open/mini open surgeries) had a greater risk [odds ratio (OR) = 8.63, $P < 0.001$] of infection compared with patients who had an all-arthroscopic RCR". It must be noted that all the available data in the literature consists of retrospective case series and that the patient records were reviewed based on follow-up notes or a re-operation registry for debridement^[7-11]. Hence, the actual incidence of infection may be higher, as many cases may go unreported due to patients choosing to seek treatment

at different institutions than where the primary repair had been performed.

RISK FACTORS

Risk factors for the development of suppurative infections of the shoulder joint can be summarized under three main categories: Anatomic, patient-related, and surgical technique or operating room (OR) environment-related risk factors.

Anatomic risk factors

The axillary area has been shown to provide an enriched colonization environment for various bacteria due to the presence of numerous sebaceous glands and hair follicles^[12-14]. Surgical incisions and entry portals for open, mini-open, and arthroscopic RCR are near the axilla, which may increase the possibility of inadvertent transmission of colonized microorganisms into the joint during surgery. Furthermore, precautions, such as clipping the axillary hair or preparing axillary skin with various solutions have not been proven to be successful in reducing infection rates or bacterial load^[15,16].

Patient-related risk factors

There are various patient characteristics that can adversely affect the body's defense against infections, including diabetes mellitus, immunosuppression, chronic diseases, advanced age, smoking, intravenous drug use, malnutrition, obesity, kidney and/or liver failure, and malignancies^[13,17,18]. In a retrospective comparative study from Chen *et al.*^[18], three out of 30 (10%) type I diabetic patients developed infections following RCR. However, no patients in the non-diabetic group had infections after RCR. Pauzenberger *et al.*^[10] found that age over 60 was an independent risk factor for post-RCR infections. In addition to systemic conditions, local factors, such as previous shoulder surgery and local corticosteroid injections, may also increase the risk of deep shoulder infection after RCR^[19,20].

Pauzenberger *et al.*^[10] indicated that males are more prone to infection after RCR. The authors showed that out of 28 patients with deep infections after arthroscopic RCR, 27 (96.4%) were male and only 1 (3.6%) was female (OR = 21.41, $P = 0.003$). Likewise, Vopat *et al.*^[11] reported that 92% of the patients in the infected group after RCR were male, compared to 58% of the control group patients who did not develop infections after RCR (OR = 9.52, $P = 0.042$). Although more male patients undergo RCR than female patients, this difference does not appear to be large enough to explain the significant difference in infection rates between men and women^[5]. Interestingly, there is evidence in the literature showing that *Propionibacterium acnes*' superficial skin colonization rate around arthroscopy portal sites was 81.6% in male patients and 46.1% in female patients^[21]. This colonization rate difference between men and women may be attributed

to the significantly higher serum testosterone levels in the male population vs the female population^[21,22].

Risk factors related to surgical technique and operating room environment

The risk of postoperative deep shoulder infection appears to be higher in open or mini-open RCR techniques compared with arthroscopic techniques^[1,11]. It is conceivable that the likelihood of bacterial contamination increases as the operation time and the size of the surgical incision increases. Another point worth considering is that open or mini-open RCR techniques have been performed much longer than arthroscopic repair techniques, which have only been performed for the last few decades. This fact, along with the improvement in disinfection and OR safety protocols, may have also influenced the decrease in infection rates for arthroscopic techniques^[23,24]. Nonetheless, there can be differences in the incidence of infection between various arthroscopic procedures. Yeraniosian *et al.*^[17] reported that out of 165820 arthroscopic shoulder surgeries, 450 required additional surgery due to infections. The authors have noted that the incidence of infection was highest after RCR (0.29%) when compared with other arthroscopic procedures ($P < 0.01$). This finding underlines the significance of RCR as a procedure that increases the risk of infection, even when performed arthroscopically.

DIAGNOSIS

Clinical presentation

At the early stages, patients with deep infections after RCR usually present with increasing shoulder pain, stiffness, and, in some cases, loss of previously achieved postoperative range of motion (ROM)^[1,11,25-27]. There may be noticeable fibrinous exudate or pus drainage from the surgical wound and/or arthroscopy portals, with local swelling, erythema, and warmth around the shoulder joint^[7,8]. However, systemic signs and symptoms, such as fever, chills, low blood pressure, and generalized fatigue, are not common but they may be seen when there is a delay in presentation or when patients have immunosuppressive diseases.

Laboratory findings

Diagnostic lab workups to rule out or confirm deep shoulder infection after RCR include standard peripheral white blood cell (WBC) count with differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels. Peripheral WBC count is usually within normal limits; however, ESR and CRP levels can be elevated. ESR and CRP levels are sensitive but not specific markers for deep shoulder infection. Athwal *et al.*^[8] studied 39 cases of deep shoulder infections after RCR and detected an elevated WBC count in only five patients (approximately 13%); ESR was available for 30 cases and was elevated in 18 cases (60%). The authors

checked CRP levels in 10 cases, and was elevated in five of them (50%). Kwon *et al.*^[7] reported similar results in a study including 14 patients with deep shoulder infections after RCR. In this study, the WBC count was measured in 10 patients, and nine of them had normal levels, averaging $7.6 \times 10^3/\mu\text{L}$ (range, $4.9\text{-}10.8 \times 10^3/\mu\text{L}$). The ESR was measured in eight patients and found to be elevated at least two-fold in seven patients (mean ESR value, $69 \text{ mm/h} \pm 32 \text{ mm/h}$). CRP was measured for two patients, and both were found to be increased, measuring 1.1 mg/dL and 7.7 mg/dL (normal, $< 0.8 \text{ mg/dL}$).

Glenohumeral joint aspiration and analysis with a cell count should be routinely performed in all patients presenting with a suspected deep shoulder infection. Aspirated fluid should also be examined microscopically for crystals, and a gram stain must be performed. As in most cases of septic arthritis, analysis of infected shoulder joint aspiration usually reveals a WBC count above 50000/ μL , with more than 75% polymorphonuclear leukocytes. These values indicate a deep infection of the shoulder, even if the gram stain returns negative and crystals are detected in the joint fluid. Aspiration fluid should be cultured in all cases, regardless of the results of cell count and the microscopic fluid analysis. Even though joint aspiration and synovial fluid analysis should be part of standard diagnostic work up for every case with a suspected joint infection, such data from patients with a reported deep shoulder infection after RCR is lacking in the literature.

Causative microorganisms

The most commonly isolated pathogens are, not surprisingly, the main species in sebaceous areas of normal skin flora, including *Propionibacterium acnes*, coagulase-negative *Staphylococci* (e.g., *Staphylococcus epidermidis*), and *Staphylococcus aureus*^[7-9,13]. However, infections due to various other microorganisms, such as *Corynebacterium* species, *Proteus mirabilis*, *Enterococcus faecalis*, *Peptostreptococcus magnus*, *Bacillus* species, *Streptococcus viridans*, *Actinomyces* species, and poly-microbial culture results, were also reported (Table 1)^[7-10,27].

Shoulder surgeons have recently focused on *Propionibacterium acnes* as a causative agent in many cases of deep shoulder infections after arthroscopic and open shoulder procedures. *P. acnes* is an anaerobic gram-positive bacillus densely colonized in the dermal skin layers around the head and shoulders. Despite routine preoperative antibiotic prophylaxis and skin preparation in shoulder arthroscopy, the rate of surgical site deep tissue inoculation with *P. acnes* can be as high as 19.6%^[21]. Furthermore, these patients were also found to have positive *P. acnes* superficial skin colonization that may indicate contamination by means of surgical instruments^[21]. Interestingly, Pauzenberger *et al.*^[10] reported that although administration of prophylactic antibiotics reduced the rate of infection

Table 1 Summary of reported microorganisms that were isolated from the patients with deep shoulder infections following rotator cuff repair in various retrospective case-series studies

Ref.	Patient No.	No. of isolated organisms	<i>P. acnes</i>	<i>S. aureus</i>	Coagulase-negative Staph ¹	Other microorganisms
Kwon <i>et al</i> ^[7]	14 (11 mono, 3 poly-microbial)	19	7	4	6	2
Athwal <i>et al</i> ^[8]	38 (39 shoulders: 33 mono, 6 poly-microbial)	45	20	8	12	(<i>Proteus mirabilis</i> and <i>Enterococcus faecalis</i>) 5 (<i>Corynebacterium species</i> × 2, <i>Peptostreptococcus magnus</i> , <i>Bacillus species</i> , <i>Streptococcus viridans</i>) 1 (<i>Peptostreptococcus</i>)
Settecerri <i>et al</i> ^[9]	16 (15 mono, 1 poly-microbial)	15	6	4	4	1 (<i>Peptostreptococcus</i>)
Pauzenberger <i>et al</i> ^[10]	28 (mono-microbial isolation in 23 patients)	23	8	2	12	1 (<i>Actinomyces species</i>)
Mirzayan <i>et al</i> ^[27]	13 (7 mono, 3 poly-microbial, 3 no growth)	15	3	5	5	2 (<i>Diphtheroids</i> and <i>Streptococcal species</i>)

¹Coagulase-negative *Staphylococci* include but not limited to *S. epidermitis*, *S. saprophyticus* and *S. hominis* (Courtesy of University of Manitoba, Section of Orthopaedic Surgery, Pan Am Clinic, Winnipeg, Manitoba, Canada).

from 1.54% to 0.28% ($P < 0.001$), there was no significant reduction in the rate of infections due to *P. acnes*. Further research is needed to study the correlation between superficial skin colonization and deep surgical tissue inoculation with *P. acnes* and postoperative deep shoulder infections following RCR.

Imaging

Radiographic evaluation in patients with deep shoulder infections after RCR is rarely necessary and usually reveals normal findings, particularly in acute cases. In subacute or delayed cases, ultrasonography and magnetic resonance imaging (MRI) with an intravenous contrast agent may be valuable to detect abscess formation around the shoulder joint or to identify complications, such as osteomyelitis^[13].

In rare cases, when the joint aspiration and culture results remain negative but the patient has clinical symptoms of infection, an indium 111-labeled WBC scan can be considered. Although this imaging modality might be helpful in localizing inflammation, it does not clearly distinguish between infectious and noninfectious inflammatory processes. Furthermore, reported sensitivity of indium 111-labeled WBC scans for the diagnosis of infectious conditions ranges from 60% to 100%, and specificity ranges from 69% to 92%^[28].

MANAGEMENT

Deep soft-tissue infections of the shoulder after RCR require a thorough and meticulous management that involves surgical debridement with copious lavage and long-term intravenous (IV) antibiotic treatment. Although this approach is universally accepted, the literature mostly provides evidence regarding open debridement due to the fact that the great majority of published studies are retrospective case series including patients who had either open RCRs or arthroscopically-assisted mini-open RCRs^[7-9,11,27]. However, studies indicate that arthroscopic RCRs have increased by

600%, while open repairs have increased by only 34% during the time interval between 1996 and 2006^[5]. It is highly possible that the percentage of arthroscopic RCRs have increased even further since 2006 compared with open repairs, as arthroscopic RCR has become the procedure of choice for the surgical treatment of rotator cuff pathologies. Hence, arthroscopic debridement and lavage needs to be emphasized as the primary surgical procedure to address acute deep shoulder infections after RCR.

Arthroscopic lavage and debridement

Any antibiotic treatment prior to surgery should be discontinued at least five to seven days before surgery. The importance of withholding lavage and IV antibiotics until obtaining cultures from the pus and debrided deep tissues cannot be overemphasized. In general, after the operative site is prepared and draped, incisions along the infected portals are made, and the pus from deeper tissues is drained through these portals. Cultures are then taken from the drained pus, and the swabs are used to obtain deep tissue cultures through the portals (Figure 1). It is advisable to start with a dry arthroscopy of the glenohumeral joint to achieve a better visualization of the infection and to obtain more tissues for culturing before the joint is washed (Figure 2). The glenohumeral joint and the previously repaired rotator cuff is assessed intraoperatively following the initial lavage. Ideally, all the suture material and anchors are removed, and the joint is washed profusely using a minimum of 10 L of fluid, with the last liter containing 100000 units of bacitracin^[27]. Although there could be variations in approach among individual surgeons, a re-repair of the rotator cuff during the same arthroscopic debridement and lavage procedure is not suggested before completing a long-term IV antibiotic therapy and confirming that the infection has been eradicated. In selected patients, based on intraoperative assessment, the sutures and anchors can be retained if the infection is not extensive and there is no loosening of the re-



Figure 1 Drainage from an infected arthroscopy portal immediately before the arthroscopic debridement and lavage. After anesthesia the patient is positioned and the shoulder is draped. An incision is made through the infected portal and cultures are taken from the draining pus. Additional deep tissue cultures are sent during the arthroscopic debridement (Courtesy of University of Manitoba, Section of Orthopaedic Surgery, Pan Am Clinic, Winnipeg, Manitoba, Canada).

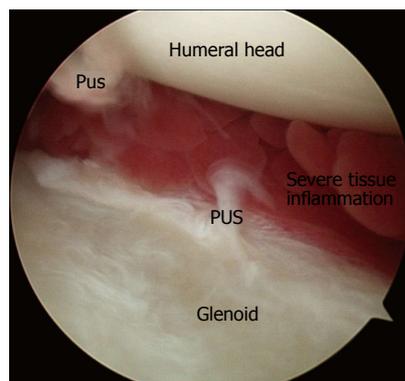


Figure 2 Arthroscopic view of the glenohumeral joint space from a patient with deep shoulder infection after rotator cuff repair. It is possible to visualize the pus and severe tissue inflammation before the irrigation (Courtesy of University of Manitoba, Section of Orthopaedic Surgery, Pan Am Clinic, Winnipeg, Manitoba, Canada).

paired cuff tissue.

Open debridement and lavage

Deep infection usually involves the surgical wound and forms a tract that connects the deep tissues to the superficial layers of the surgical incision. Hence, open surgical debridement and lavage is the mainstay of treatment in patients who had open RCR as the initial procedure. Athwal *et al*^[8] treated 39 patients with post-RCR deep shoulder infections by means of an open irrigation and debridement (30 patients), and a combined arthroscopic and open debridement (nine patients). They reported that a mean of 3.3 surgical debridements were necessary for eradicating the infection. Between surgical debridements, the wound was left open and packed with sterile gauze in 18 shoulders and closed over a drain in 21. They used antibiotic-laden cement beads in five patients. In a series including 16 patients with deep infections after an open RCR, Settecerrri *et al*^[9] did an average of 3.5 open debridements (range two to eight debridements), and the wound was left open and packed with sterile gauze between the procedures. Other studies report a similar treatment approach to deep shoulder infection after open RCR^[7,27].

This evidence shows a tendency for multiple open debridement and lavage procedures in patients with deep infections after open RCR. Furthermore, leaving the wound open and packed with sterile gauze between debridements may also mean extended hospital stays for these patients that can negatively influence their quality of life and increase the economic burden on the healthcare system. Of note, patients with deep shoulder infections who underwent arthroscopic RCR as the initial procedure should also be treated with open debridement and lavage if complications such as osteomyelitis, abscess formation, or tissue necrosis exist.

Intravenous antibiotic therapy and infection follow-up

It is imperative to approach post-RCR deep shoulder infection as septic arthritis and to consider IV antibiotic treatment for a minimum of 4 to 6 wk to successfully eradicate the infection and to minimize the risk of complications, such as osteomyelitis, that may occur with a higher incidence due to the suture anchors placed in the humeral head. The antibiotic should be chosen based on the culture and susceptibility results and after a consultation with the infectious disease specialist who will be involved in the patient's management through the course of the initial treatment and the follow-up. A peripherally inserted central catheter must be placed and managed appropriately by regular flushing with normal saline between antibiotic doses to maintain patency. Depending on the causative microorganism and the patient's response to the initial treatment, IV antibiotic treatment can be supplemented or extended by oral antibiotics, as supported in the literature^[7-9].

The assessment of therapeutic response and follow-up of infection is mainly done by clinically evaluating the patient and monitoring infection markers, such as ESR and CRP. The duration of antibiotic treatment and the confirmation of infection eradication requires shared decision making between the orthopaedic surgeon and the infectious disease specialist.

COMPLICATIONS AND OUTCOMES

Deep infections of the shoulder after RCR are usually successfully eradicated with debridement and lavage, and long-term IV antibiotics^[7-9]. Nevertheless, devastating complications, such as osteomyelitis, abscess formation, post-infectious glenohumeral arthritis, and insufficient soft tissue coverage can be encountered, and functional outcomes may be far less than optimal. Kwon *et al*^[7] reported a 67% dissatisfaction rate in a group of 12 patients treated for deep infection after RCR, with a mean UCLA score of 23.6 (excellent and good ≥ 28 , fair and poor ≤ 27). Among these patients,

two needed rotational muscle flaps due to insufficient deltoid tissue after repeated open debridements. Athwal *et al.*^[8] reported a complication rate of 32% during the medical and surgical treatment of deep infection after RCR. Their series included one patient who required arthrodesis and two patients who underwent shoulder arthroplasty due to glenohumeral arthrosis within 66 mo of eradicating the deep infection. Mirzayan *et al.*^[27] studied 13 patients with chronic deep infections following open RCR. Seven patients had osteomyelitis of the humeral head, two had osteomyelitis of the humeral head and the glenoid, two had osteomyelitis of the clavicle and the acromion, and two had no osteomyelitis but had a subdeltoid abscess. Seven patients required a rotational flap to allow for joint coverage. The results of the Simple Shoulder Test in this study revealed that only three patients could lift a one-pound weight (0.5 kg) and none could lift an eight-pound weight (3.6 kg) to shoulder level without bending the elbow. Eight patients could throw underhand; however, only one could throw overhead.

Although these studies clearly indicate that outcomes after an infected open or mini-open rotator cuff repair can be permanently disabling, no studies to date have reported the effects of deep infections after arthroscopic RCRs on functional outcomes.

CONCLUSION

Deep shoulder infections after rotator cuff repair are not frequently encountered. Patients who are suspected to have a post-RCR infection require a thorough diagnostic evaluation, including clinical signs and symptoms, laboratory workups and cultures. Although appropriate management of this condition with surgical debridement and lavage, and long-term IV antibiotics usually results in eradication of the infection, complications can be disabling and functional outcomes poor. Abscess formation, osteomyelitis, post-infectious glenohumeral arthritis, and loss of the soft tissue envelope are among the most devastating complications resulting from post-RCR deep infections. The majority of the patients with deep infections after RCR report unsatisfactory outcomes with permanent functional limitations.

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Synthesis of evidence for the treatment of intersection syndrome

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Abstract

Intersection syndrome is a rare sports overuse injury occurring through friction at the intersection of the first and second compartment of the forearm. Differential diagnosis must be carefully made, especially from De Quervain tendosynovitis. Clinical examination provides with the necessary information for diagnosis, still magnetic resonance imaging scans and ultrasonography may assist in diagnosis. Treatment consists mainly of rest, use of a thumb spica splint, analgetic and oral nonsteroidal anti-inflammatory drugs and after 2-3 wk progressive stretching and muscle strengthening. Should symptoms persist beyond this time, corticosteroid injections adjacent to the site of injury may be useful. In refractory cases, surgical intervention is warranted.

Key words: Intersection syndrome; Overuse injury; Wrist pain; Differential diagnosis; Treatment

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Core tip: In this review, current aspects of clinical and imaging diagnosis, as well as therapeutic approach of intersection syndrome, are outlined. This overuse syndrome which may provokes significant wrist pain and disability, is associated with repetitive wrist flexion and extension and compressive forces applied to the wrist and is common in sports such as rowing, canoeing, skiing, weight lifting and racket sports. Conservative treatment is generally an efficient therapeutic approach and includes means such as rest, cryotherapy, immobilization through splinting, medication with non-steroid anti-inflammatory and corticoid drugs as well as individualized rehabilitation program incorporating progressive stretching and muscle

strengthening exercises. Future research is proposed to select larger samples if possible and utilize the frank value of imaging studies such as magnetic resonance imaging scans or ultrasonography as well as optimal therapeutic strategies for every individual suffering from this syndrome.

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INTRODUCTION

Although the first report of the IS took place by Velpeau in 1841, Dobyys in 1978 was the first who introduced this term^[1,2]. Intersection syndrome (IS) which has been alternatively named peritendinitis crepitans, crossover syndrome, adventitial bursitis, subcutaneous perimyositis with abductor pollicis longus syndrome and bugaboo forearm^[3-5] is a rare inflammatory condition, usually reported as an overuse injury resulting from friction between two compartments each wrapped in its own sheath. The dorsal or first musculotendinous unit/compartment contains the abductor pollicis longus and the extensor pollicis brevis while the second compartment includes the extensor carpi radialis longus and extensor carpi radialis brevis^[6]. These two compartments intercept at an angle of 60 degrees^[7]. Montechiarelllo *et al*^[11], specifically report that friction occurs between the muscle bellies of the first compartment and the tendon sheaths of the second compartment. Intersection syndrome has been also reported to result from stenosis and entrapment of the second compartment, although it has been supported that it is not clear which is the etiology of this pathology^[5].

Draghi and Bortolotto^[8] report that there is also an intersection more distally where the extensor pollicis longus intersects with the second compartment. Friction may occur at that site as well, resulting in intersection syndrome^[9-11]. Furthermore, the second compartment may also be not in a single sheath but each tendon may be in its own sheath^[4,12]. The flexor retinaculum has also been attributed a possibly important role in the pathogenesis of IS^[13].

Overall incidence ranges from 0.2% to 0.37% in various studies^[14]. IS occurs through repetitive wrist flexion and extension and compressive forces applied to the wrist^[15], affects mainly the dominant hand, and onset has been pinpointed specifically when beginning a new sport^[15]. This nosologic entity is reported in sports such as rowing, canoeing, horseback riding, skiing, weight training or racket sports, activities associated with repetitive wrist extension^[16,17]. In a study including 42 skiers, prevalence was estimated as high as 11.9%



Figure 1 Area of pain and tenderness to palpation in intersection syndrome.

in the first two days^[18]. In another study, incidence reached 2% in tennis players^[11] whilst in a study of 8000 patients with arm or hand pain, occurrence was found to reach only 0.37%^[19].

In this review current aspects of clinical and imaging diagnosis as well as the therapeutic approach of IS are outlined.

CLINICAL EXAMINATION

Clinical examination reveals usually pain 4-8 cm proximally to radial styloid and swelling in the radial aspect of the wrist and forearm^[20] (Figure 1). Localized redness and tenderness to palpation over the site of swelling are two other typical clinical signs^[20]. Pain in movement is observed specifically in ulnar deviation and wrist extension. Crepitus in palpation during flexion and extension of the wrist may also be present^[1,17].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis from similar pathologies is of paramount importance, due to its different strategy in treatment (Table 1). Differential diagnosis should mainly be made from De Quervain Syndrome (DQS)^[3]. Other pathologies such as scaphoid fractures, osteoarthritis of the first metacarpal joint, ganglion cysts, Wartenberg syndrome wrist ligament sprains, and muscle strains maybe also confused with IS and should be early diagnosed and properly treated^[1,6]. In DQS pain is localized distally to the dorsal interphalageal joint of the thumb, in the first dorsal compartment that consists of the abductor pollicis longus and the extensor pollicis brevis. Finkelstein test in this case is considered pathognomonic^[21]. In IS, on the contrary, pain is identified 4-8 cm proximally to the radial styloid. The method of application of the test is important since it is a pathognomonic test guiding diagnosis. It is described as grasping the thumb within the fingers forming a fist and deviating the wrist in an ulnar direction. Still, the original description by Finkelstein reports that the patient's thumb is grasped with abduction of the wrist taking place in an ulnar direction, resulting in

Table 1 Differential diagnosis of radial wrist pain^[1,3,6]

Intersection syndrome
Tendonitis De Quervain
Scaphoid fractures
Osteoarthritis of the first metacarpal joint
Ganglion cysts
Wartenberg syndrome
Wrist ligament sprains
Muscle strains
Soft tissue neoplasms

intense pain over the styloid^[21]. Differentiating DQS from intersection syndrome is significant since in DQS earlier surgical intervention is recommended by some experts^[22].

IMAGING STUDIES

Although clinical diagnosis is usually sufficient, imaging studies offer a more certain diagnosis and clarify complicated injuries^[11].

Ultrasound imaging provides reliable and “first-line” diagnosis in the study of IS, while magnetic resonance imaging (MRI) studies are retrospective studies^[1]. It is important to note that the utility of the ultrasound in diagnosing IS is of value and even more important in research studies. Through ultrasound imaging, details in the anatomy of the region may be observed, that may explain symptoms or guide treatment. In the study by Draghi and Bortolotto^[8], valuable information was derived. The study can be considered of significant value since it took place over 5 years and included 1131 patients with hand and wrist pathology. It was reported that tendons may be coated in one sheath or individual sheaths and a second location of an intersection was underlined. This information may be beneficial in both research and clinical level. For instance, a more detailed anatomy or pathologic anatomy may elucidate the mechanics of injury and healing. It may also result in improved effectiveness in injection therapy, by targeting the intended site.

Clinical examination may be accompanied by axial MRI^[3]. de Lima *et al.*^[4], studied through MRI scans the anatomy of the forearm around the intersection area, before and after tenography. The authors of this study concluded that MRI may be a useful noninvasive method for the evaluation of wrist pain. In T2 weighted fat suppressed fast spin echo axial MRI, peritendinous and subcutaneous edema concentrically both proximally and distally of the intersection site) or even synovial effusion are depicted in the presence of intersection syndrome pathology^[6,7] Lee *et al.*^[9], in a review of intersection injury studied through MRI, identified also tendinosis and subcutaneous and muscle edema as abnormalities related to this overuse syndrome.

Of note, although imaging studies may be useful in identifying and confirming IS, is reported that 70% of cases can be found through appropriate history

taking^[23].

TREATMENT

It is common ground that the fundamental element for the recuperation of an overuse injury is informing the patient of the steps he or she may follow to assist in healing. Patient education thus is important in IS and understanding of the mechanism of injury will aid in conceiving how to protect and progressively rehabilitate the wrist back to its normal daily activities^[24].

In the first phase, the proposed main line of action consists of rest, use of oral nonsteroidal anti-inflammatory medication, cryotherapy, elevation, and compression. Although inflammation is necessary for the proper cascade of healing of the site of injury, reduction to some extent of inflammation to result in the reduction of pain is necessary in order to eliminate disabling symptoms as soon as possible^[3]. The second phase of rehabilitation consists of the gradual restoration of function of the upper extremity to former daily activities. This phase lasts 4-6 wk and consists of progressive stretching and mobilization of relevant joints that is the wrist, elbow joint, metacarpophalangeal and phalangophalangeal joints and other structures such as musculature, tendons, and fascia. Strength training should be initiated carefully to avoid relapse of symptoms. The performance of daily life activities is a part of training, in order to reach full functional rehabilitation. The general rule of increasing parameters such as intensity, repetition, or distance per week, has been shown to be a beneficial rule of thumb for runners^[20].

Immobilization through splinting is proposed in the literature^[20]. Immobilization of the wrist as well as the thumb has been proposed, with a thumb spica splint, strapping or use of a cock up wire-splint^[3]. The anatomical position of immobilization is 20 degrees of extension of the wrist. The duration of immobilization in research studies extends from 2-3 wk^[20,23].

Persistence of symptoms after 2-3 wk, leads to the consideration of a second line of available treatment procedures available^[21]. A percentage of 60% has been reported to heal solely through conservative management^[18]. Corticosteroid injections may alleviate pain and reduce inflammation^[25]. Injections may be administered adjacent to the maximally tender areas solely, providing relief after 10 d^[3].

Resolving to surgical intervention is very effective but is offered only to patients not responding to conservative treatment. Operative management consists of Abductor Pollicis Longus (APL) and Extensor Pollicis Brevis (EPB) tenosynovectomy and fasciotomy, and debridement of the bursa so as to result in release compression at the crossover site^[17,18] while post-operatively immobility using plaster forearm splint is recommended for ten days. Return to full activity is permitted from at least 12 wk^[26].

Williams *et al.*^[27], described the decompression of the

muscle belly of the swollen by overuse muscles. They performed an incision at the site of maximum swelling, aiming at decompression of the extensors beneath. This incision is performed 3-4 cm proximal to the incision for De Quervain tenosynovitis. It may take place by local anesthesia, by bypassing superficial layers to reach the tendon and fascia of the APL and EPB. In 11 patients, mostly rowing athletes presenting with overuse syndrome of the extensors of the wrist, this technique was performed. Return to light training was achieved from the first day post-surgery and return to training 10 d later. No return of symptoms was reported even 4 mo following operation^[27].

Another therapeutic approach was proposed by Grundberg and Reagan^[5]. According to the authors pathology relates mainly to Extensor Carpi Radialis Brevis (ECRB) and Extensor Carpi Radialis Longus (ECRL) who are responsible for the more proximal than the De Quervain localization of pain. This decompression of the second extensor compartment is thought to resolve symptoms of the syndrome. This technique was performed to 13 patients with IS of a duration from 4 mo to 5 years, where conservative treatment had failed. In two patients a surgical approach was implemented more proximally to the tendon of the carpal extensors which rendered unsatisfactory results. In line incision of the carpal extensors was performed with a direction centrally towards the area of the marked edema. Release of ECRL and ECRB within the second dorsal compartment after dissecting the deep fascia achieved reduction of symptoms in all patients ten months on average, postoperatively. All patients returned to their former employment^[5].

DISCUSSION

Up to this day, there is a debate whether IS is a tendinosis, thus a chronic tendon degeneration with the absence of inflammation or a peritenosynovitis, involving an inflammatory process across the tendon sheaths^[28,29]. Furthermore, as reported above the site of injury in IS is also debatable, since it may occur at two different intersections of the second compartment with the abductor extensor longus and extensor pollicis brevis or more distally with the extensor pollicis longus alone.

The establishment of diagnosis of this pathology is based mainly on thorough clinical examination and should be achieved early in order to avoid functional impairment of the affected hand and devastating consequences for patients and especially these interfering with athletic activity. Differential diagnosis includes several nosologic entities which provoke wrist pain and mainly De Quervain Syndrome^[1,3,26].

Treatment includes mainly conservative therapeutic strategies such as rest, immobilization with a thumb spica splint, analgetic and non-steroid anti-inflammatory drugs (NSAIDS) and after 2-3 wk progressive stretching and muscle strengthening. Injection therapy using

drugs such as using 2 mL of 1% of lidocaine with beta-methasone, is another conservative therapeutic option which is proposed when symptoms persist more than few weeks of immobilization^[25]. Still, major adverse events that may take place and represent a percentage of 5,8%, have to be discussed with the patient. These range from a simple ecchymosis which may occur to as much as a devastating tendon rupture^[25].

As conservative treatment is generally an efficient therapeutic approach for IS, surgical management is warranted only for refractory cases and is followed with good results^[5,17,18,27].

CONCLUSION

Intersection syndrome is not a clearly understudied syndrome. The etiology, site of injury, histologic underlying changes are still debatable. Moreover, the extent of the utility of imaging studies in diagnosis is still not entirely clear. Adding to the necessity of further elucidating all aspects of the syndrome, every possible way of studying the syndrome is proposed. The utility of imaging in research as a means of studying histology and anatomy is supported as well as the need to conduct studies with larger samples in order to study the injury in depth.

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Retrospective Study

Ponseti method treatment of neglected idiopathic clubfoot: Preliminary results of a multi-center study in Nigeria

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data from the International Clubfoot Registry. Patients agreed to be a part of the registry at the commencement of treatment by written consent.

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Abstract

AIM

To evaluate the effectiveness of the Ponseti method for initial correction of neglected clubfoot cases in multiple centers throughout Nigeria.

METHODS

Patient charts were reviewed through the International Clubfoot Registry for 12 different Ponseti clubfoot treatment centers and 328 clubfeet (225 patients) met inclusion criteria. All patients were treated by the method described by Ponseti including manipulation and casting with percutaneous Achilles tenotomy as needed.

RESULTS

A painless plantigrade foot was obtained in 255 feet (78%) without the need for extensive soft tissue release and/or bony procedures.

CONCLUSION

We conclude that the Ponseti method is a safe, effective and low-cost treatment for initial correction of neglected idiopathic clubfoot presenting after walking age. Long-term follow-up will be required to assess outcomes.

Key words: Ponseti method; Neglected clubfoot; Nigeria; Walking age

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Core tip: This is a retrospective study to evaluate the efficacy of the Ponseti method for initial correction of untreated, idiopathic clubfoot in patients above one year of age. The rate of initial correction to a painless, plantigrade foot without the need for soft tissue release was 78% in 255 evaluated clubfeet from 12 treatment centers in Nigeria. The Ponseti method, a non-operative treatment method involving serial manipulation and casting, is useful and effective for initial correction of clubfoot, even after walking age.

Adegbehingbe OO, Adetiloye AJ, Adewole L, Ajodo DU, Bello N, Esan O, Hoover AC, Ior J, Lasebikan O, Ojo O, Olasinde A, Songden D, Morcuende JA. Ponseti method treatment of neglected idiopathic clubfoot: Preliminary results of a multi-center study in Nigeria. *World J Orthop* 2017; 8(8): 624-630 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i8/624.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i8.624>

INTRODUCTION

Idiopathic clubfoot is the most common musculoskeletal congenital birth defect, affecting between 1 and 7 births in every 1000^[1]. Left untreated, clubfoot may lead to pain, disability, discrimination, and hardship throughout the person's life. This is especially a problem in developing countries like Nigeria where 70% of the

population lives below the poverty line and has limited access to treatment. Although Nigeria has around half the population of the United States at about 180 million, it is estimated that the prevalence of clubfoot is at least three to five times higher than in the United States. This high prevalence is mainly a result of the number of people living with neglected clubfoot, defined as clubfoot that has not been treated before walking age^[2,3].

For many years in Nigeria and around the world, soft tissue release or extensive bony surgery were seen as the only options for the full correction of clubfoot. In the past two decades, the minimally invasive Ponseti method has been proven and accepted as the worldwide gold standard for treatment of clubfoot based on its success in both the short term and long term^[4]. Introduced in Nigeria in 2009, the Ponseti method is a safe, effective, and economical option for many patients who cannot afford an extensive surgery. The method involves skilled serial manipulation and plaster casting as well as a percutaneous Achilles tenotomy (PAT) to completely correct the deformity. After the correction is complete, the child wears a foot abduction brace at night for a few years to prevent relapse^[5-7].

There are few studies on the effectiveness of the Ponseti method for patients over age 1, but the early evidence has been promising. Studies in Brazil, Nepal, India and Ethiopia reported that use of the Ponseti method allowed for avoidance of soft tissue release in 66%-92% of cases above one year of age^[8-16].

The purpose of this study was to evaluate the effectiveness of the Ponseti method for initial correction of neglected clubfoot cases in multiple centers throughout Nigeria.

MATERIALS AND METHODS

The accepted definition of neglected clubfoot is true idiopathic clubfoot that has not been treated before walking age. In this study, age one will be used as representative of walking age. Through July 2015, 1137 clubfoot cases from 2010-2015 were recorded from Ponseti treatment centers in Nigeria into the International Clubfoot Registry with patient permission. Patient charts were reviewed through the registry. Two hundred and twenty-five patients (328 clubfeet) from 12 different centers (Figure 1) met inclusion criteria and are profiled in Table 1. Patients were excluded if they were younger than 1 year of age, had non-idiopathic clubfoot (syndromic, neuromuscular, etc.) or had other treatment prior to Ponseti method.

Treatment at all 12 centers, including casting and percutaneous Achilles tenotomy as necessary, was performed by orthopaedic surgeons who were properly trained in the technique according to Ponseti^[5-7]. Casts were changed at intervals of 7-10 d if possible but up to every 14 d depending on the ability of the patient to reach the clinic and pay for the treatment. All patients were treated on an outpatient basis although two of the twelve centers, including 18 total patients, performed

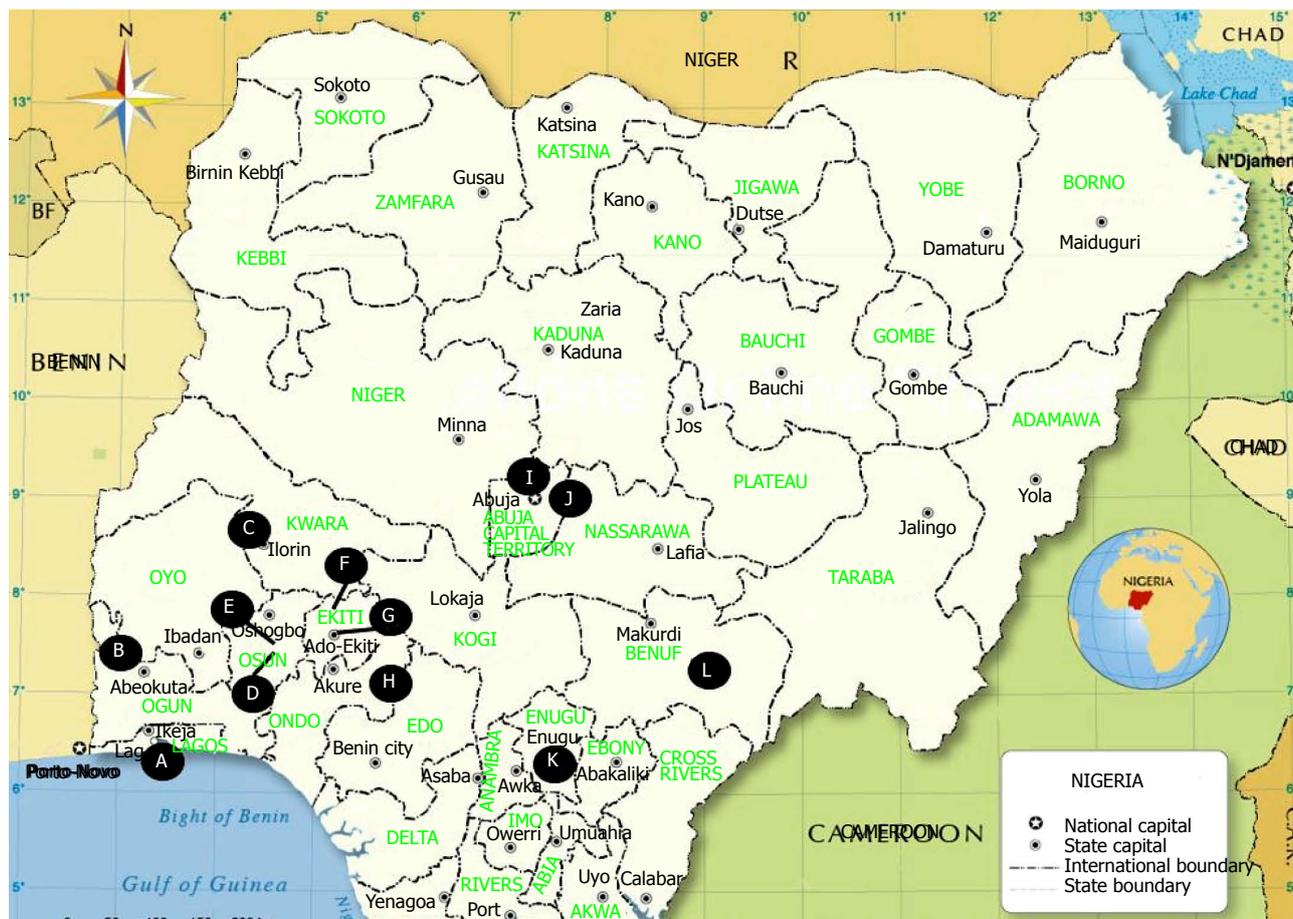


Figure 1 Map of clubfoot clinic sites. A: LASUCOM; B: FMC Abeokuta; C: University of Ilorin; D: Obafemi Awolowo University; E: Wesley Guild Hospital Ilesha; F: FMC Ido-Ekiti; G: Ekiti St Teaching Hospital; H: FMC Owo; I: Gwarinpa GH; J: FMC Keffi; K: NOH Enugu; L: NKST-Mkar, Benue.

Table 1 Phenotypic characteristics n (%)	
	Cases
Female	94 (42)
Male	131 (58)
Bilateral	103 (46)
Right	66 (29)
Left	56 (25)
Age 1-2 yr	147 (65)
Age 3-9 yr	59 (26)
Age ≥ 10 yr	19 (9)

tenotomies in the operating theatre for optimal sterility. Although tendon transfer can be considered part of the Ponseti protocol, one of the main objectives of this study is to show that neglected clubfoot can be corrected non-operatively as that is most beneficial in the low resource setting. Therefore in this study, tendon transfer will be considered failure in treatment along with tendoachilles lengthening and major soft tissue release.

After completion of serial casting, correction was maintained with a foot abduction brace at night or in rare cases when braces were not available, with encouragement of active play (walking, running, etc.). Abduction braces were generally crafted by each hospital's orthotics department or local cobblers working

with the orthopaedic surgeons.

In the newborn population, Pirani and Dimeglio scoring systems are generally used to assess the severity and characteristics of a clubfoot. These systems have been validated and are useful for comparing the quality of correction^[17,18]. However, these have not been validated for the neglected population and no system exists yet for the qualification of neglected clubfoot^[19].

RESULTS

The study population consisted of 225 patients, 131 (58.2%) were male, and the clubfoot was bilateral in 103 cases (46%). One hundred and forty-seven patients were age 1 or 2, 59 were between the ages of 3 and 9, and 19 patients were age 10 to 16.

Of 328 neglected clubfeet studied, 255 feet (78%) achieved initial correction, a completely plantigrade foot, without soft tissue release or other surgical intervention besides PAT. Of the 73 other feet, 47 were lost to follow up mid-treatment and 26 of the feet were converted to Achilles tendon lengthening, tendon transfer procedures, or major soft tissue release.

A profile of the total number of casts required for complete correction and the PAT rates based on age group is shown in Table 2. A distribution of the number

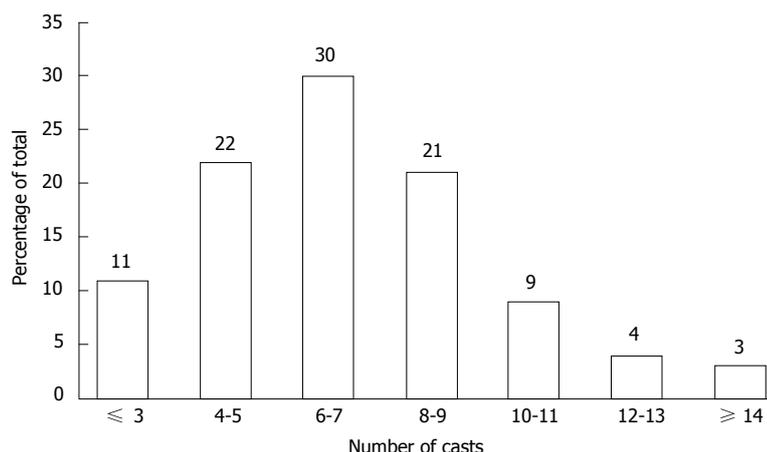


Figure 2 Number of casts required for correction.

Table 2 Number of casts and tenotomy rate

	Total	Age 1-2 yr	Age 3-9 yr	Age 10-16 yr
Mean casts ¹ , n (range)	6.84 (3-20)	6.71 (3-20)	7.03 (4-17)	7.43 (4-13)
Tenotomy rate	51%	42%	53%	60%

¹Between groups ANOVA *P*-value = 0.78.

of casts required across all age groups is shown in Figure 2. The average number of casts necessary for correction was 6.84, ranging from 6.71 casts/foot for 1 and 2 year olds up to 7.43 casts/foot for those above age 10. Analysis of variance between the groups shows no statistically significant difference ($P = 0.78$). The overall rate of percutaneous Achilles tenotomy was 51% and also tended to increase with patient age from 42% in the youngest age group to 60% in the oldest. There were no failures of PAT's reported.

DISCUSSION

Neglected clubfoot is a serious problem in developing nations where a significant number of children born with the deformity do not receive immediate treatment. It is common for parents to delay treatment due to cost, lack of transportation or limited availability of proper care. Frequently, children do not present until around the start of school age at 4 or 5 because of increased interaction with peers and social pressures to fit in. Neglected clubfoot can cause significant physical, psychological and financial burden to the child and the family. Adults with untreated clubfoot may experience significant pain and disability, be unable to work, and have difficulty performing daily activities of living.

Historically, neglected clubfoot has been treated with bony surgery and extensive soft tissue release. These techniques are difficult, costly, have substantial complication rates, and they are rarely feasible in the healthcare settings of developing nations^[20-23].

Our study has shown that the Ponseti method is

effective in the initial correction of neglected clubfoot and reduction of the need for surgical treatment beyond percutaneous tenotomy. Its suitability at the clinical level is imperative for use in developing countries like Nigeria, where operating room access comes at a premium. Our results are similar to multiple recent studies on Ponseti treatment of neglected clubfoot cases, shown in Table 3.

Ponseti *et al*^[5] described successful results from Brazil after Ponseti treatment in 17 children (24 feet) with an average age at presentation of 3.9 (1.2-9.0). A full correction was achieved in 16 feet (67%) without the need for extensive surgery and it was found that those who eventually needed surgery ended up with a lesser surgical intervention. Six of the patients had recurrence, and the best results were achieved in the youngest group.

In Nepal, Ponseti *et al*^[6] reported the use of Ponseti treatment in neglected cases between the age of 1 and 6. In 260 feet, 83% were able to avoid any surgery besides PAT. Similar to our study, with a broader range of ages and larger study group, they found a wider range of casts were necessary to achieve full correction.

Spiegel *et al*^[9] in India had 37 neglected clubfoot patients (55 clubfeet) with a mean age of presentation of 2 (1-3) years. After a Ponseti trial, 4 patients (6 feet) were considered unfit for Ponseti treatment and had a posteromedial release, 4 patients (4 feet) relapsed and had tibialis tendon transfer and 3 patients (4 feet) required tendoachilles lengthening to obtain adequate dorsiflexion.

In Ethiopia, Khan *et al*^[11] found that in 22 neglected clubfoot patients (32 feet), an open tendoachilles lengthening was required for 5 patients (7 feet) plus posterior capsulotomy in 3 additional patients (4 feet). Correction was achieved for the remaining 14 patients (21 feet) with the Ponseti method and PAT alone.

In our study, 78% of 328 feet achieved correction without major surgery. Some factors, such as time between casts, were variable between the 12 different treatment centers because of the socioeconomic differences between the regions of Nigeria. In a survey of

Table 3 Published results on correction of neglected clubfoot

	Brazil, 2007	Nepal, 2009	India, 2012	Ethiopia, 2014	Present study
Total number of feet	24	260	55	32	328
M/F	12/5	120/51	7/30	5/17	131/94
Mean casts, <i>n</i> (range)	9 (7-12)	7 (4-14)	10 (6-12)	8 (6-10)	7 (3-20)
Successful correction without surgery	67%	83%	71%	66%	78%

the providers at each center, reportedly patients who were wealthier or in more urban areas were more likely to have casts changed slightly more frequently, 7-8 d as opposed to 13-14. PAT's were performed under local anesthesia in clinics at 10 sites and in the operating theatre at 2 sites (18 study patients) for better infection control and sterile instruments.

If the number of casts required for correction can serve as a proxy for the severity of a clubfoot, neglected clubfoot can be described simply as a more severe form of idiopathic clubfoot in a newborn. The average number of casts required in newborns is around 5 with a correction rate around 90%^[4]. In our study and review of the literature, casts required for neglected cases is between 7 and 10 with successful correction rates from 66%-83%. The Ponseti method is nearly as successful on neglected clubfoot as in newborns at preventing the need for surgical intervention.

The phenotypic characteristics for cases in our study were similar to the reported rates of incidence of congenital idiopathic clubfoot in the literature^[24-27]. Fifty-eight percent of patients in our study population were male, consistent with the evidence that males are twice as likely to be affected. Also, in concordance with the evidence that half of cases occur bilaterally, 46% of our cases were bilateral and 54% were unilateral. This is significant because there has not been profound gender or laterality bias in presentation of neglected cases. Therefore, these factors do not seem to affect parents' willingness to seek treatment for their children before age 1.

One intriguing finding in our study is that the percutaneous Achilles tenotomy rate seems to be lower than in much of the literature^[5-11]. There are a few unique factors that could be causing this finding. The first is that there was considerable variability in rate of tenotomy between different centers. Costs for sterile equipment, local anesthetic and time required may be causing some providers to increase the number of casts to achieve necessary dorsiflexion rather than performing a PAT. It is also possible that some of the cases treated were actually positional equinovarus deformity rather than true talipes equinovarus, and did not require tenotomy. General guidelines for the Ponseti method recommend that a clubfoot achieve 15° of dorsiflexion to be considered corrected^[22]. More research into the tenotomy rate for neglected clubfoot worldwide and for all idiopathic clubfoot in Nigeria would be encouraged.

Our study has some potential limitations. During the course of treatment, 47 patients were lost to follow

up. In the setting of a developing country, patients are often lost to follow-up because of socioeconomic factors such as costs, transportation, and lack of social support and behavioral factors such as feeling improved function mid-treatment and knowledge deficit about duration of treatment^[24]. Data collection was variable between centers so 32 neglected clubfoot patients had to be excluded from the initial study population because there was not enough treatment data. If more data could be recorded, research into the feasibility of Pirani and Dimeglio scoring for neglected clubfoot would be very helpful and could aid providers in guiding their manipulation and casting to each individual. The current algorithm for Ponseti treatment of neglected clubfoot is provided in Figure 3.

In conclusion, this study has shown that the Ponseti method can be effectively used to correct neglected clubfoot in children older than walking age. If the method is performed properly, it will significantly reduce the need for bony surgery or major soft tissue release.

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This study was made possible by the creation of the Nigerian Sustainable Clubfoot Childcare Program (NS CCP), a nonprofit organization established to be a leader and model for clubfoot treatment throughout Africa. The NSCCP combines physicians, parents, and clubfoot advocates in efforts to increase public awareness, especially among local healthcare workers such as midwives. It also helps organize Ponseti trainings for orthopaedic surgeons and collaboration between those who are treating clubfoot frequently. It was the collaboration of the physicians who are part of the NSCCP that led this study and shows the benefit the Ponseti method has on neglected clubfoot in Nigeria.

COMMENTS

Background

Clubfoot is the most common musculoskeletal birth defect and left untreated, can result in lifelong disability and hardship. The Ponseti method involving serial manipulation and casting has become the gold standard in treatment of clubfoot. In low resource and developing countries, neglected clubfoot, or clubfoot that is untreated by one year of age, is a significant problem because of limited access to healthcare. In this study, the authors evaluated the efficacy of the Ponseti method in treating neglected clubfoot in 12 centers in Nigeria.

Research frontiers

Currently, there is very little literature on the effectiveness of the Ponseti method in clubfoot patients over age one. The current studies are on small populations

Algorithm No. 3
Management of idiopathic clubfoot
Patient walking

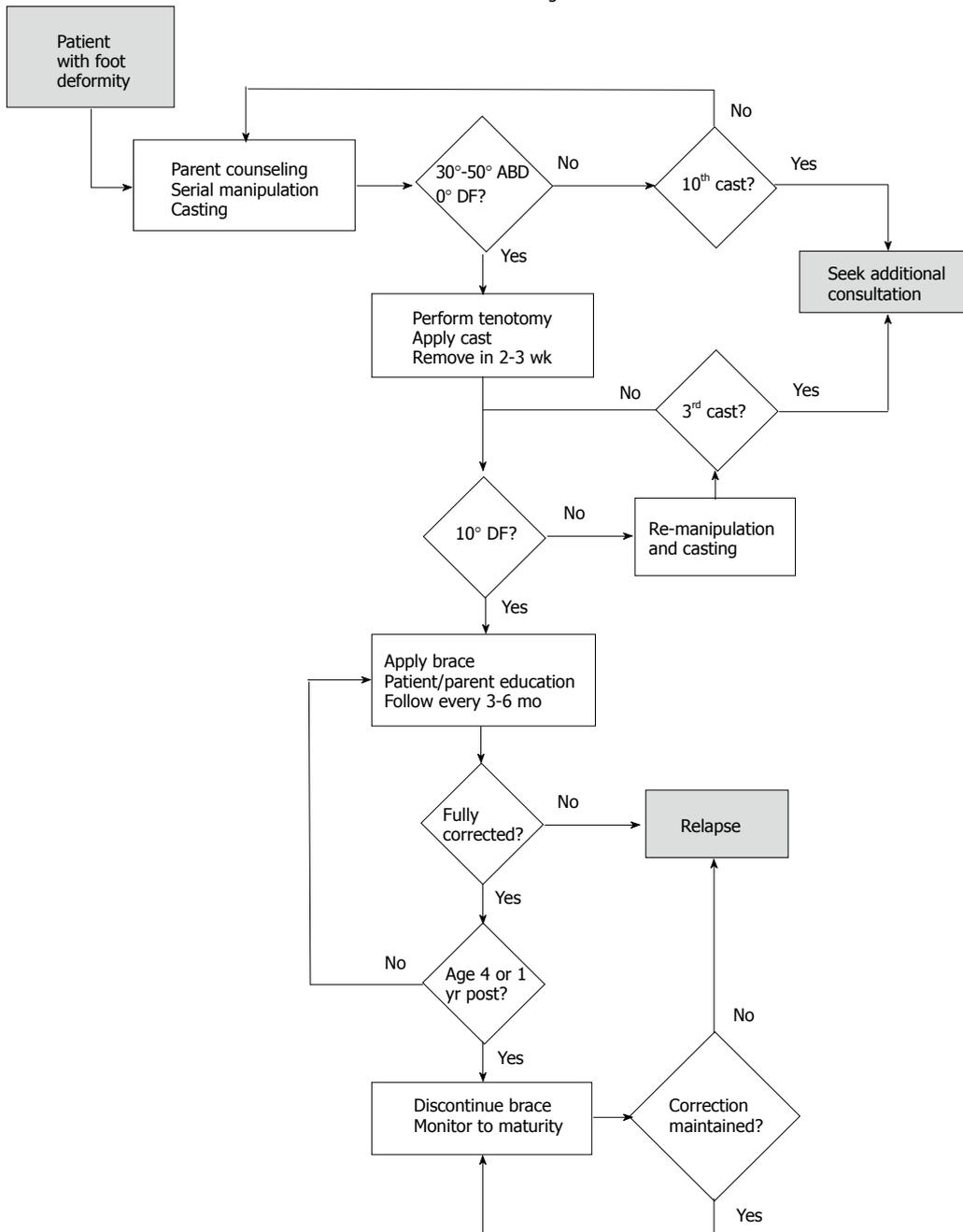


Figure 3 Neglected clubfoot treatment algorithm. Adapted form Ref. [29].

but have shown significant success.

Innovations and breakthroughs

In this study, the Ponseti method was successful in the initial correction of 78% of neglected clubfeet. These results are in concurrence with previous, smaller studies which showed similar correction rates.

Applications

This study suggests that providers throughout the world who are treating neglected clubfoot should begin with the Ponseti method as it can be performed at low cost and is highly effective.

Terminology

PAT: Percutaneous achilles tenotomy - minimally invasive procedure involving

the nicking of the heel cord in order to achieve maximal stretching in the final phase of treatment.

Peer-review

The paper is interesting and emphasizing the statement that Ponseti method can be effectively used to correct neglected clubfoot in children older than walking age, and significantly reduce the need for bony surgery or major soft tissue release.

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Observational Study

Functional outcomes of traumatic and non-traumatic rotator cuff tears after arthroscopic repair

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Abstract**AIM**

To compare the functional outcomes of traumatic and non-traumatic rotator cuff tears after arthroscopic repair.

METHODS

Eighty-seven patients with rotator cuff tears following arthroscopic treatment were divided into traumatic and non-traumatic tear groups. Postoperative muscle strength and outcomes using the modified University of California, Los Angeles score were evaluated. Sex, age, affected limb and dominant limb were correlated between groups. Muscle strength of the repaired and unaffected shoulders was compared. Rotator cuff injury size was measured.

RESULTS

Of the 87 patients who underwent rotator cuff repairs, 35 had traumatic tears and 52 had non-traumatic tears. In patients with non-traumatic tears, the average age was 59 years, 74.5% were female, 96.1% were right-hand dominant and 92.3% had their dominant shoulder affected. Patients with traumatic tears were 59.5 years

old on average, 51.4% were female, 91.4% were right-hand dominant and 88.5% had their dominant shoulder affected. No difference existed in the mean modified University of California, Los Angeles score between patients with traumatic tears (33.7) compared with those with non-traumatic tears (32.8). No strength differences were observed between groups: The strength difference between the non-affected and affected sides was 1.21 kg in the non-traumatic group and 1.39 kg in the traumatic group ($P = 0.576$), while the strength ratio between the non-affected/affected sides was 0.805 in the non-traumatic group and 0.729 in the traumatic group ($P = 0.224$).

CONCLUSION

The functional results of traumatic rotator cuff repairs are similar to non-traumatic tears. Both outcomes are satisfactory.

Key words: Rotator cuff; Shoulder pain; Arthroscopy; Tendon injuries; Orthopedics

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Core tip: The causes of rotator cuff tears are multifactorial. It is believed that degeneration is essential, and most tears are slow and progressive. In contrast, acute tears can occur after trauma. Acute tears generally have better functional and pain outcomes compared with chronic injuries. The aim of this study is to compare shoulder functional outcomes after arthroscopic rotator cuff repair of traumatic and non-traumatic tears. Outcomes will be evaluated using the modified University of California, Los Angeles score and muscle strength measurements.

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INTRODUCTION

Rotator cuff injuries are very common, ranging from 5%-39%. They are the leading cause of shoulder pain, and have a high prevalence in the aging population^[1]. They can cause intense shoulder pain, functional limitation and decreased quality of life^[2-7]. It is extremely important to understand these injuries to treat them appropriately, as it is likely that every physician, not just orthopedic surgeons, will encounter this pathology.

The rotator cuff is a group of muscles that cover the humeral head and plays an important role in the strength, mobility and stability of the shoulder by fixing the humeral head to the glenoid. The rotator cuff consists of four muscles: Subscapularis, supraspinatus,

infraspinatus and teres minor. The tendons of these muscles merge with the joint capsule. Around the shoulder joint and between the tendons of the rotator cuff muscles and the fibrous joint capsule, bursa reduces the friction of the tendons that pass over bone or other areas of resistance^[8].

In general, the treatment for rotator cuff tears should be clinical, even in cases in which anatomic changes are also present^[9]. However, in cases of rotator cuff failures, surgical treatment is indicated^[4]. Rotator cuff repairs can be performed through either arthroscopic or open approaches. Arthroscopic surgery is performed through micro incisions and preserves the deltoid muscle insertion, theoretically permitting early rehabilitation and a lower risk of iatrogenic injuries or complications from deltoid healing.

The causes of rotator cuff tears are multifactorial. However, it is believed that degeneration is an essential factor, as this leads to a high rate of non-healing or failures, which range from 10%-94%^[10-17]. In most cases, rotator cuff tears are slow and progressive injuries, occurring after a relatively long period of symptoms. However, acute tears can also occur secondary to trauma. This mechanism has been found to have better functional and pain outcomes than chronic injuries.

We therefore decided to compare functional outcomes after arthroscopic rotator cuff repairs of those patients who sustained traumatic rotator cuff tears, and those without traumatic etiologies. This may help us understand the post-surgical function of these patients, and support clinical decision making.

MATERIALS AND METHODS

This is a retrospective study of 87 adult patients with rotator cuff injuries treated arthroscopically at the Hospital Ortopédico de Belo Horizonte. Most of them were operated from June to December 2014, and the others were retrospectively selected by medical records. All patients were informed about the objectives of this protocol and signed a consent form agreeing to participate in the study. The study was approved by the National Ethics Committee on Research.

The average patient follow-up was 43 mo (range 24-72 mo). Lesions were characterized clinically and with magnetic resonance imaging, and the criteria for surgery was determined after a discussion meeting.

The traumatic rotator cuff tear group was defined^[18] by trauma followed by acute shoulder pain associated with impaired active range of motion of the affected limb. This trauma can be a cause of a medial rotation or lateral force with the arm adducted or abducted, a ventral, medial or caudal passive draw force, an axial compressive force toward the cranial and ventral or ventromedial direction or secondary to a shoulder dislocation. It was expected that the patient did not have any pain before the trauma. In all cases, fractures were excluded using anteroposterior, lateral and axillary radiographs of the affected shoulder. In this group,

surgeries were performed within six months after the traumatic event.

For the non-traumatic rotator cuff injury group, inclusion criteria were a chronic history of shoulder pain with pre-existing limited shoulder function. Acromioclavicular osteoarthritis and osteophytes of the acromion are also commonly observed.

Exclusion criteria included: Bilateral lesions, previous surgery in the affected limb, patients that required other upper extremity surgical procedures after the rotator cuff repair and any condition that would interfere with the evaluation of long term outcomes, such as rheumatoid arthritis or fractures. Patient demographics of interest included sex, age, affected limb, dominant limb and mechanism of injury (traumatic or non-traumatic).

All patients were evaluated 24 mo after surgery, since most cases of re-rupture occur before two years after surgery^[19-21]. In patients who were selected retrospectively, we used the evaluations performed within 24 mo. The primary outcome was modified University of California, Los Angeles (UCLA) score validated for the Portuguese language, which takes into account pain, function, range of motion, strength and patient satisfaction^[22,23].

The modified UCLA scale is scored out of a total of 35 points. Subsections include: Pain (10 points), function (10 points), active forward flexion range of motion (5 points), a manual strength test for forward flexion (5 points) and patient satisfaction (5 points). Outcomes according to this scale are as follows: 34-35 points correspond to excellent results, 28-33 good, 21-27 satisfactory and 0-20 poor^[23]. No minimum clinically important difference has been reported using this scale^[24]. The modified UCLA scale can be easily applied, and allows for effective clinical tracking. It is also one of the only patient satisfaction scales that are validated for the Portuguese language^[22].

Arm strength was measured with the patient positioned in orthostasis, with the upper limb in 90 degrees of elevation and angled 30 degrees anteriorly, corresponding to the abduction axis in the scapular plane^[25]. We used a dynamometer that consisted of a household scale with a maximum capacity of 20 kg (Performance Plus, Performance Plus Ind. E Com. Ltda., Rio de Janeiro - RJ, Brazil). One end of the dynamometer was fixed to a fabric strap wrapped around the distal end of the forearm that was maintained in full pronation^[26]. The other end of the dynamometer was secured to the scale's spring and attached to a nylon rope whose length reached the foot of the patient. The other end of the rope was secured with a handle attached to the patient's footwear. This setup allowed for force measurements with a fixed point (foot). The patient was asked to exert the maximum possible strength during upper limb elevation for 5 s. The final reading at the end of this period was used to represent limb strength^[27]. We avoided placing the bracelet on the wrist or hand, where local muscle activity could

confound our measurements. Avoiding this positioning also helped to keep the patient's trunk upright, avoiding compensation with lateral tilt. Muscle strength of the injured shoulder was compared with the unaffected side, and correlated with rotator cuff injury size.

Surgical technique

All patients received general anesthesia and a brachial plexus block. They were positioned in the lateral decubitus position with a vertical and longitudinal traction of 5 kg fixed to the affected arm. The arthroscope was introduced through a posterior portal positioned 2 cm medial and 2 cm below the posterolateral edge of the acromion. The joint was evaluated for degenerative or inflammatory changes, which were treated with synovectomy and debridement through an anterior portal along the top edge of the subscapularis muscle with a shaver blade. When the rotator cuff tendon injury was observed, a monofilament was introduced to demarcate the injury site, making it easy to locate during subacromial view.

Subacromial view was performed through the same posterior portal. The arthroscope was introduced into the subacromial space and a bursectomy was performed with the shaver blade introduced through a lateral portal.

The rotator cuff injury was repaired using 5 mm titanium suture anchors placed into the anatomic neck of the humerus. It was made single row repair with Revo knots. When the subacromial space was found to be pathologically decreased, an acromioplasty was performed as well. All arthroscopic portals were closed using monofilament suture.

Patients were immobilized postoperatively in a Velpeau sling (Mercur, Santa Cruz do Sul - RS, Brazil) for 6 wk. Sutures were removed 10-14 d after surgery. Patients were encouraged to start pendulous movements and elbow, wrist and hand range of motion immediately after surgery. Active motion was only permitted 6 wk after surgery, following evidence of restored strength and proprioception. It was used the same physical therapy protocol in both groups.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician. A *P*-value < 0.05 was considered significant. Our confidence interval was 95%. A paired Student's *t*-test was used to compare outcomes between affected and unaffected shoulders. This test was selected because the same subject contributes to the experimental and control sample.

We used an analysis of variance (ANOVA) to compare subjects with and without a traumatic injury to the strength ratio of the affected and unaffected shoulder. The ANOVA was also to compare mean age, UCLA-modified score and strength differences between the affected and unaffected shoulders. The two-proportion equality test (χ^2 test) was used to compare the sex distribution of traumatic vs non-traumatic rotator cuff

Table 1 Sex distribution of patients with traumatic *vs* non-traumatic rotator cuff tears *n* (%)

Trauma	No	Yes	<i>P</i> -value
Female	38 (74.5)	18 (51.4)	0.027
Male	13 (25.5)	17 (48.6)	

Table 2 Average ages of patients with traumatic *vs* non-traumatic rotator cuff tears

Age	Trauma	
	No	Yes
Mean	59	59.5
Median	60	62
Standard deviation	8.4	9.7
Coefficient of variation	14%	16%
Minimum	40	42
Maximum	75	76
Patients	51	35
Confidence interval	2.3	3.2
<i>P</i> -value	0.799	

tears.

RESULTS

The clinical and functional data of 87 patients who underwent a rotator cuff repair were analyzed. Thirty-five had traumatic tears and 52 had non-traumatic tears. Both groups were treated using the same surgical technique. The mean follow-up was 43 mo (24-72 mo). Women composed 74.5% of non-traumatic rotator cuff tears, compared with 51.4% of traumatic tears. This difference in sex distribution was significant (*P* < 0.05, Table 1).

The average age of the non-traumatic group was 59 years, compared with 59.5 years in the traumatic group (Table 2). In the traumatic group, 91.4% were right-hand dominant and 88.5% had their dominant limb affected. In the non-traumatic group, 96.1% were right-hand dominant and 92.3% had their dominant limb affected. There was no difference in mean modified UCLA score between the non-traumatic (33.7) and the traumatic (32.8) groups (Table 3). The strength difference between the non-affected and affected sides was 1.21 kg in the non-traumatic group and 1.39 kg in the traumatic group (*P* = 0.576, Table 4).

There was no difference in the affected/non-affected strength ratio, which was 0.805 in the non-traumatic group and 0.729 in the traumatic group (Table 5). Significant differences were observed in the mean strength of the affected shoulder after surgery, which was 4.76 kg compared with 6.04 kg in the uninjured shoulder (Table 6). Tear size was 2.49 cm on average. It was 2.254 cm (range 1.0-5.4 cm) in the non-traumatic group and 2.84 cm (range 1.0-5.2 cm) in the traumatic group.

DISCUSSION

Rotator cuff injuries are multifactorial, and can include

Table 3 Modified University of California, Los Angeles scores of patients with traumatic *vs* non-traumatic rotator cuff tears

UCLA	Trauma	
	No	Yes
Mean	33.7	32.8
Median	35	35
Standard deviation	3.9	4.5
Coefficient of variation	12%	14%
Minimum	12	17
Maximum	35	35
Patients	51	35
Confidence interval	1.1	1.5
<i>P</i> -value	0.337	

UCLA: University of California, Los Angeles.

Table 4 Strength ratios between unaffected-affected shoulders of patients with traumatic *vs* non-traumatic rotator cuff tears

Unaffected-affected	Trauma	
	No	Yes
Mean	1.21	1.39
Median	1	1
Standard deviation	1.42	1.49
Coefficient of variation	117%	107%
Minimum	-1.5	-0.5
Maximum	6	4.5
Patients	51	35
Confidence interval	0.39	0.49
<i>P</i> -value	0.576	

degeneration because of age and microtrauma. Other factors that can increase the likelihood of a rotator cuff tear include smoking, hypercholesterolemia and genetics^[28]. The pathophysiology of rotator cuff tears is more complex than previously believed. The mechanisms behind rotator cuff injury and healing have a direct impact on treatment and recovery.

One common mechanism of rotator cuff injury is direct trauma to the tendon. Another mechanism is gradual tendon degeneration with age, predisposing the rotator cuff to tears. A widely held theory regarding rotator cuff injuries is the vascular theory, in which lesions occur because of hypovascularization near the rotator cuff's insertion on the humerus. In general, the injury process is of a multifactorial origin^[29].

Of the various factors that contribute to rotator cuff tears, such as trauma, subacromial impingement and hypovascularization, the most important is the aging process^[30]. Aging is a major prognostic indicator of tendon degeneration^[31]. The vast majority of rotator cuff ruptures occur in middle-aged and older patients^[32,33]. Previous studies have shown that the prevalence of rotator cuff injuries increases with age, reaching 50% by the 8th decade of life^[31].

Clinically, it is difficult to differentiate between patients whose rotator cuff injuries originate traumatically from those that have some degenerative component, as there is no way to know what degree of tendon degeneration occurred prior to the inciting

Table 5 Affected/unaffected shoulder strength ratio between patients with traumatic and non-traumatic rotator cuff tears

Strength ratio	Trauma	
	No	Yes
Mean	0.805	0.729
Median	0.833	0.857
Standard deviation	0.257	0.32
Coefficient of variation	32%	44%
Minimum	0.143	0
Maximum	1.6	1.083
Patients	51	35
Confidence interval	0.071	0.106
P-value	0.224	

trauma. This is especially important as a significant part of the population has some degree of asymptomatic tendon degeneration^[3]. Several authors^[18,34-36] proposed methods to differentiate between these two types of tears. However, there remains no established protocol. Therefore, because of the difficulty in differentiating between these two groups, we focused our analysis purely on those lesions that were diagnosed following trauma, rather than were determined to be of a purely traumatic origin. This may also provide greater clinical applicability to our findings.

In this study, the average age of the traumatic group was similar to the non-traumatic group. In the literature^[37-39] there is greater age heterogeneity in studies that identify trauma as a causal factor in rotator cuff injuries (mean age 34.2-56.1 years). This may be because of the variability in the selection criteria for assigning patients to a "purely traumatic tear" group. Studies that examine degenerative injuries have greater homogeneity (mean age 54.1-62.6 years).

In our study, most patients with degenerative tears were female (74.5%), while those with traumatic tears were more balanced (51.4% female). This is consistent with other reports that show a higher percentage of males with traumatic injuries^[37,38,40-42].

The average modified UCLA scale in this study was 33.7 in the non-traumatic group and 32.8 in the traumatic group. These results are similar to those found in the literature^[37,38,43]. As a score of 28-33 points is considered good, the non-traumatic group had a slightly higher score than the traumatic group. We expected to find better functional outcomes in patients with traumatic rotator cuff repairs, as the healing capacity of these patients is higher. These results therefore disproved our hypothesis.

Rotator cuff repairs lead to improved muscle strength and range of motion compared with preoperative measurements^[38,39,44,45]. This was one reason why we did not collect preoperative patient data. We observed that postoperative strength was reduced in the surgical shoulder compared with the unaffected side after a mean follow-up of 43 mo. Tear etiology did not impact strength recovery after rotator cuff repair compared with the uninjured limb.

Table 6 Affected vs unaffected shoulder strength

Strength	Affected side	Unaffected side
Mean	4.76	6.04
Median	5	6
Standard deviation	2.38	2.06
Coefficient of variation	50%	34%
Minimum	0	1
Maximum	11.5	12.5
Patients	86	86
Confidence interval	0.5	0.44
P-value	< 0.001	

Several factors influence the outcomes of rotator cuff repairs, including: Sex, duration of symptoms, and abduction and external rotation strength^[23,46]. However, in our study we could not identify any variable that was predictive of functional outcome.

In the patients in our study with traumatic rotator cuff repairs, it was likely that many already had tendon degeneration, characterized by reduced cellular activity, collagen disorganization, fibroblast apoptosis and decreased extracellular matrix synthesis^[29]. Chronic rotator cuff tears in older adults have a low healing potential and a high recurrence risk, even if treated surgically. This can be explained by degenerative changes in the tendon margin, even in cases with fatty infiltration below grade 2 on Goutallier scale. If these injuries had occurred in younger patients with acute and smaller injuries, the healing potential could be better because of low levels of apoptosis, fibrocartilaginous metaplasia and high rates of neoangiogenesis. The traumatic group could get better results in comparison with the non-traumatic group^[28].

Braune *et al*^[39] in 2003 compared range of motion and patient satisfaction after rotator cuff repairs after traumatic or non-traumatic tears. The traumatic group produced better postoperative results. However, in this study the average age was significantly lower in the traumatic group (mean 34.1 years) than in the non-traumatic (mean 54.1 years) group, as one of the inclusion criteria for the traumatic group was an age younger than 50 years.

The rotator cuff prevents degenerative processes, as it permits the formation of a closed joint space and participates in cartilage nutrition^[47]. A hypothesis as to why our findings were equivocal between traumatic and non-traumatic tears is that patients with traumatic tears may wait a relatively long period of time to seek medical aid. A diagnostic failure in primary medical care^[37] may also compromise treatment outcomes, as there may already be degenerative changes at the time of surgery. The late diagnosis of traumatic injuries can lead to surgical complications and poor results^[37,38,44]. Compared with early repairs (< 3 wk), traumatic rotator cuff tears have better functional results compared with delayed repairs (> 3 wk). Late treatment is associated with reduced tendon elasticity, increased repair tension, muscle atrophy and fatty degeneration. Increased repair

tension leads to a lower rate of healing and decreased viscoelastic properties. Further, injuries resulting from trauma are large or massive (> 2 tendons)^[37], which has a worse prognosis compared with minor injuries. Other authors^[37,45] found that the outcomes of early repairs are better than late repairs, although exact time cutoffs have not been defined.

In our study we obtained good results in both groups as rated by the modified UCLA scale. These findings support arthroscopic rotator cuff repairs of either traumatic or non-traumatic injuries. Limitations to our study include: A small sample ($n = 87$), our muscle strength measurement method, and the use of only one functional score.

The functional results of the arthroscopic rotator cuff repair of traumatic tears are equivocal to those measured after non-traumatic tears. Both groups display adequate overall results.

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COMMENTS

Background

Rotator cuff injuries are the leading cause of shoulder pain, and can cause functional limitation and decreased quality of life. The causes of rotator cuff tears are multifactorial. It is believed that degeneration is essential, and most tears are slow and progressive. In contrast, acute tears can occur after trauma. The aim of this study is to compare shoulder functional outcomes after arthroscopic rotator cuff repair of traumatic and non-traumatic tears.

Research frontiers

Surgical treatment of rotator cuff tears is currently widely performed, since the prevalence of this disease is up to 39% in the population, increasing with age. The research hotspot is to evaluate the functional outcomes after arthroscopic rotator cuff repair in patients with traumatic and non-traumatic injuries. This may help to understand the post-surgical function of these patients, and support clinical decision making.

Innovations and breakthroughs

Chronic rotator cuff tears in older adults have a low healing potential and a high recurrence risk, even if treated surgically. Because of the higher healing capacity of patients with traumatic rotator cuff repairs, it was expected that this group of patients would have better functional outcomes. In previous data, traumatic tears had better postoperative results (range of motion and patient satisfaction) than non-traumatic tears, but the average age was significantly lower in the traumatic group than in the non-traumatic group, as one of the inclusion criteria for the traumatic group was an age younger than 50 years. In this study, the average age of the traumatic group was similar to the non-traumatic group, and the functional outcomes were similar in both groups. In this study, there was a higher percentage of males with traumatic injuries in comparison with non-traumatic injuries, and a good result in modified University of California, Los Angeles (UCLA) scale evaluation in both groups. These results are similar to those found in the literature.

Applications

The functional results of the arthroscopic rotator cuff repair are similar in traumatic and non-traumatic tears, with adequate overall results in both groups. These findings support arthroscopic rotator cuff repairs of either traumatic or non-traumatic injuries.

Terminology

The rotator cuff is a group of four tendons (subscapularis, supraspinatus, infraspinatus and teres minor) that cover the humeral head and plays an important role in the strength, mobility and stability of the shoulder by fixing the humeral head to the glenoid. The treatment for rotator cuff tears should be clinical or surgical. When surgical treatment is indicated, rotator cuff repairs can be performed through either arthroscopic or open approaches. Arthroscopic surgery is performed through micro incisions and preserves the deltoid muscle insertion.

Peer-review

The primary outcome was modified UCLA score validated for the Portuguese language, which takes into account pain, function, range of motion, strength and patient satisfaction.

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Ipsilateral femur and tibia fractures in pediatric patients: A systematic review

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Abstract

AIM

To better understand how pediatric floating knee injuries are managed after the wide spread use of new orthopaedic technology.

METHODS

We searched EMBASE, COCHRANE and MEDLINE computerized literature databases from the earliest date available in the databases to February 2017 using the following search term including variants and pleural counterparts: Pediatric floating knee. All studies were thoroughly reviewed by multiple authors. Reference lists from all articles were scrutinized to identify any additional studies of interest. A final database of individual patients was assembled from the literature. Univariate and multivariate statistical tests were applied to the assembled database to assess differences in outcomes.

RESULTS

The English language literature contains series with a total of 97 pediatric patients who sustained floating knee injuries. Patients averaged 9.3 years of age and were mostly male (73). Approximately 25% of the fractures were open injuries, more tibia (27) than femur (10). Over 75% of the fractures of both the tibia and the femur involved the diaphysis. More than half (52) of the patients were treated non-operatively for both fractures. As a sequela of the injury 32 (33%) patients were left with a limb length discrepancy, 24 (25%) patients had lengthening of the injured limb at follow up, while 8 (8%) had shortening of the affected limb. Infection developed in 9 patients and 3 had premature physal closure. Younger patients were more likely to be treated non-operatively ($P < 0.001$) and patients treated with operative intervention had statistically significant shorter hospital length of stays ($P = 0.001$).

CONCLUSION

Given the predominance of non-operative management

in published studies, the available literature is not clinically relevant since the popularization of internal fixation for pediatric long-bone fractures

Key words: Pediatrics; Femur; Tibia; Fracture; Floating knee

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Core tip: Advances in orthopaedic technology and implants have dramatically changed the management of femur and tibia fractures in children, when treated in isolation. No current day study, however, has examined the effects of this advancement on the higher energy pediatric floating knee injury. This systematic review indicates a gap in the literature and the need for further investigation.

Anari JB, Neuwirth AL, Horn BD, Baldwin KD. Ipsilateral femur and tibia fractures in pediatric patients: A systematic review. *World J Orthop* 2017; 8(8): 638-643 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i8/638.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i8.638>

INTRODUCTION

Isolated femur and tibia fractures are a frequent occurrence in the pediatric age group; these two diagnoses account for 2 of the 4 most frequent pediatric orthopaedic injuries requiring hospitalization^[1]. In 1997 pediatric orthopaedic trauma accounted for 84000 in-patient hospital admissions, 43.2% of which was accounted for by tibia (21.5%) and femur (21.7%) fractures^[2]. Although these two fractures occur often in the pediatric population their prevalence in the ipsilateral limb, resulting in a floating knee, is a rare event, generally resulting from a high energy mechanism^[3]. Literature on ipsilateral tibia and femur fractures (floating knee) has primarily focused on the adult patient population leaving the optimal treatment of pediatric patients undefined.

Two unique classifications systems exist to describe these fracture patterns. Letts *et al*^[3] in 1986 first grouped these fractures by region of fracture in the bone as well as whether the fracture was open or closed. The Letts-Vincent pediatric floating knee classification system is as follows: Type A-both fractures diaphyseal and closed; type B-both fractures closed with one diaphyseal and one metaphyseal fracture; type C-both fractures closed with one diaphyseal and epiphyseal fracture; type D-one fracture is open; and type E-both fractures are open^[3]. The Bohn-Durbin classification system, published in 1991, is the other classification system for pediatric floating knee injuries. It has 3 types: Type 1-double shaft pattern; type 2-juxta-articular pattern; and type 3-epiphyseal component^[4]. Neither classification system however

provides therapeutic guidance or offers prognostic value.

Given the rare nature of the injury pattern, limited data exist in the literature. No published series includes more than 30 patients and no manuscript on pediatric floating knee injuries (excluding case reports) has been published in the English language literature in over a decade. Neither large prospective studies nor aggregate data reviews have been performed to further elucidate the best classification system or treatment algorithm for pediatric floating knee injuries. The objective of this study is to synthesize the literature and to identify factors associated with both good and poor outcomes of these complex pediatric injuries in order improve care of this high energy fracture pattern.

MATERIALS AND METHODS

We searched EMBASE, COCHRANE and MEDLINE computerized literature databases from the earliest possible date to February 2017 using the search term "pediatric floating knee". Reference lists from all articles were scrutinized to identify any additional studies of interest. All studies were thoroughly reviewed and included in the study if they met the following criteria: (1) written in English language; (2) had a level I, II, III, IV, or V study design classified by "Journal of Bone and Joint Surgery" criteria; (3) articles had patient information listed within article; and (4) patient age under 18 years old. Two authors performed the initial search (Jason B Anari, Alexander L Neuwirth) and three authors (Jason B Anari, Alexander L Neuwirth, Keith D Baldwin) independently reviewed the references of the qualifying papers and selected those studies that fit based on the aforementioned criteria. In the final phase of review, full text review, no disagreement occurred regarding which studies would be included. Univariate and multivariate statistical tests were applied to the assembled database to assess differences in outcomes.

When assessing for nonunion and malunion we applied the criteria previously described by Bohn and Durbin^[4]. Malunion of the femur required the following criteria: 30° anterior, 15° valgus, 5° posterior or varus, or more than 2 cm of shortening. Malunion of the tibia is defined by angulation greater than 5° in any plane or more than 1 cm of shortening. Rotational nonunions were defined as more than 20° of external rotation or any internal rotation compared to the contralateral side. Nonunion was defined as the absence of bridging callus and persistent fracture lines beyond 4 mo.

Classification of the open fractures was based on the classification published by Gustilo *et al*^[5] in 1984. Limb length discrepancies were diagnosed by clinical exam and measured on scanograms. Length of stay was determined by the number of days following admission until discharge to home, rehab, or another non-hospital facility. Infections included any fracture or wound requiring irrigation and debridement or treatment with antibiotics. Any additional operations performed on the

Table 1 Patient demographics and characteristics

Characteristics	n (%)
No. of patients	97
Age (yr)	9.3
Follow up (mo)	39.99
Open fracture	48
Tibia	27
Gustillo Anderson 1	5 (18.52)
Gustillo Anderson 2	11 (40.74)
Gustillo Anderson 3a	7 (25.92)
Gustillo Anderson 3b	2 (7.41)
Gustillo Anderson 3c	2 (7.41)
Femur	10
Gustillo Anderson 1	4 (40.00)
Gustillo Anderson 2	2 (20.00)
Gustillo Anderson 3a	2 (20.00)
Gustillo Anderson 3b	1 (10.00)
Gustillo Anderson 3c	1 (10.00)
Not specified	11
Fracture pattern	
Tibia	97
Diaphysis	75 (77.32)
Metaphysis	9 (9.28)
Epiphysis	13 (13.40)
Femur	97
Diaphysis	73 (75.26)
Metaphysis	15 (15.46)
Epiphysis	9 (9.28)
Management	
ORIF femur and non-operative tibia	14
ORIF tibia and non-operative femur	12
ORIF tibia and femur	19
Non-operative tibia and femur	52

ORIF: Open reduction internal fixation.

floating extremity were included under 2nd procedures.

We identified 5 articles from MEDLINE, 4 articles from EMBASE, all of which were duplicates, and zero articles from COCHRANE. Initially, articles were eliminated based on title relevance. Articles were then eliminated by abstract for failing to meet inclusion criteria. We finally reviewed the full text of the remaining 6 papers and 1 was eliminated for meeting exclusion criteria. References from the remaining 5 papers were evaluated and 1 additional study was identified that met inclusion criteria leaving us with 6 articles for the systematic review: Four case series and 2 case reports.

Data on 97 patients were then collected from the 6 articles that met inclusion criteria (Table 1). The average age of patients presenting with a floating knee injury was 9.3 years old. The male to female ratio was approximately 3:1. The majority of open fractures occurred in the tibia (27/48), with most injuries being Gustilo-Anderson grade 2. Seventy-five percent of the fractures for both the tibia (75/97) and the femur (73/97) occurred in the diaphysis. Over half (52/97) of the patients with floating knee injuries had both fractures definitively treated non-operatively with casting and/or traction. Average follow-up was 39.99 mo.

Table 2 Complications

Characteristics	n (%)
Limb length discrepancy	32
Overgrowth	24 (75.00)
Undergrowth	8 (25.00)
Non-union	7
Femur	3 (42.86)
Tibia	4 (57.14)
Mal-union	20
Femur	11 (55.00)
Tibia	9 (45.00)
Infection	9
2 nd surgery	13
Premature physeal closure	3

Univariate *P* values were calculated on the basis of independent sample *t*-tests in cases of continuous variables, and Pearsons χ^2 and Fisher's exact tests were used to calculate differences in dichotomous or categorical outcomes. All statistics were calculated using SPSS version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

In the assembled literature, 32 patients (33%) had limb length discrepancies at their final post-operative visit (Table 2). The majority of these were lengthening of the injured limb, presumably from overgrowth (24/32). Eight patients had shortening of the injured limb, most likely from healing in a shortened position, since only 3 patients with a floating knee experience premature physeal closure. Infection occurred in 9/97 patients. Thirteen patients required additional surgery after initial treatment of the floating knee injury. The two most prevalent additional procedures were osteotomy (4) for angulation or limb length discrepancy and revision fixation (4). Infections, which were mostly superficial pin track infections, also included deep space infections (more commonly involving the tibia than the femur). Femoral nonunion and malunion occurred in 3 and 11 patients, respectively. Tibial nonunion occurred in 4 patients, while malunion was present in 9.

Univariate analysis in Table 3 shows that younger children were more likely to be treated non-operatively than their adolescent counterparts ($P < 0.001$). Patients who were treated operatively for either their femur fracture, tibia fracture, or both had statistically significant shorter length of stays ($P = 0.001$). When evaluating length of stay in patients older or younger 10 years of age, this trend is accentuated. No association was noted between management of injury and resultant limb length discrepancy for either undergrowth or overgrowth.

DISCUSSION

Ipsilateral fractures of the tibia and femur in the pediatric patient are rare injuries. There is not a consensus

Table 3 Univariate analysis

Characteristics	mean	P
Age (yr)		< 0.001
ORIF femur and non-operative tibia	11.47	
ORIF tibia and non-operative femur	10.07	
ORIF tibia and femur	11.45	
Non-operative tibia and femur	7.7	
Length of stay (d)		0.001
ORIF femur and non-operative tibia	27.26	
ORIF tibia and non-operative femur	100.86	
ORIF tibia and femur	18	
Non-operative tibia and femur	37.35	
Limb length discrepancy overgrowth (mm)		0.372
ORIF femur and non-operative tibia	1.37	
ORIF tibia and non-operative femur	1.9	
ORIF tibia and femur	2.27	
Non-operative tibia and femur	2.81	
Limb length discrepancy undergrowth (mm)		0.514
ORIF femur and non-operative tibia	1.2	
ORIF tibia and non-operative femur	6	
ORIF tibia and femur	2.7	
Non-operative tibia and femur	2.75	

ORIF: Open reduction internal fixation.

regarding treatment of this fracture pattern in children and adolescents, and optimal treatment remains controversial. Historically, however, pediatric floating knee injuries have been treated non-operatively with traction and casting.

In 1975, Blake *et al*^[6] reported one of the first case series on adult and pediatric patients with ipsilateral tibia and femur fractures. They noted the floating knee injury pattern to be associated with high-energy mechanisms of injury as well as to have a high rate of nonunion and malunion. Blake *et al*^[6] treated most of the floating knee injuries with skeletal traction and casting, however they concluded that emerging techniques of osteosynthesis would alter the treatment options.

In 1986, Letts *et al*^[3] reported on floating knee injuries in children. Over an 11-year period they treated 15 patients with ipsilateral tibia and femur fractures. Letts acknowledged the difficulty in treating this fracture pattern and recognized the complications associated with non-operative modalities such as casting and traction alone. Ultimately, Letts *et al*^[3] concluded that at least one of the two fractures should be rigidly fixed when treating pediatric patients with floating knee injuries.

The largest collection of pediatric patients with ipsilateral tibia and femur fractures is Bohn *et al*^[4]'s published case series from 1991. These authors were the first to suggest a treatment algorithm based on patient age, and they created their own classification system in an attempt to guide treatment by fracture type. For patients under 10 years of age they suggested a short leg cast for the tibia fracture and 90°-90° femoral-pin traction (with subsequent conversion to a hip spica cast at 4 wk) for the femur. In adolescent patients they recommended operative treatment of

the femur fracture and non-operative treatment of the tibia fracture. The authors additionally identified general indications for operative treatment for each fracture. Severe head trauma, adolescent patient, severe soft tissue injury and inability to maintain reduction were indications for surgical treatment of the femur while severe soft tissue injury and inability to maintain reduction were indications for the tibia^[4]. Importantly, given the risk of limb length discrepancy and deformity, the concept of longitudinal follow up until skeletal maturity was raised by Bohn and Durbin in their article

In 2000, Yue *et al*^[7] reported another large case series of pediatric patients with floating knee injuries. The authors claimed that the rate of limb deformity and limb length discrepancy were decreased when fracture patterns were treated with operative intervention^[7]. They recommended that all patients with floating knee injuries, regardless of age, be treated with operative fixation of the femoral fracture. The most recently published case series from Arslan *et al*^[8] in 2003 reiterates the importance of operative fixation for patients with floating knee injuries independent of age. The authors additionally comment on the inadequacy of the Bohn and Durbin as well as the Letts classification systems in directing treatment plans for patients with floating knee injuries.

Ipsilateral fractures of the tibia and femur are rare but severe injuries in children and adolescents. They often result from a high-energy mechanism of injury. The literature currently available to the practicing orthopaedic surgeon is of limited value given the historic nature of the studies and available treatment strategies at the time of investigation. The articles reviewed, however, do demonstrate a high complication rate in the treatment of these injuries. The advent of newer techniques for treating long bone fractures in children and adolescents (such as flexible elastic nailing and submuscular plating) allow for surgeons to achieve relative stability in diaphyseal long bone fractures through minimally invasive approaches. In addition there are multiple techniques now available for reduction and stabilization of pediatric physeal and juxta-articular fractures. Long bone injuries in children and adolescents are now less frequently treated with traction and casting in the United States. Surgical fixation of isolated length-stable pediatric tibia and femur fractures allows for quicker mobilization, discharge from in-patient care, and return to school as well as activities of daily living (Figure 1)^[9].

This study has limitations, which were largely due to the weakness of member studies. The studies were all uncontrolled, and many were small heterogeneous case series. This type of literature severely limits the conclusions one can draw. Many modern techniques, which are available today, were not evaluated in many of the member studies. However, our study has value in that it identifies the gap in the literature, and synthesizes the available outcomes so that the pediatric



Figure 1 A floating knee injury in a pediatric patient. A: AP of the right proximal femur showing an oblique diaphyseal fracture with a butterfly fragment; B: AP of the midshaft right femur confirming the oblique diaphyseal fracture; C: AP of the right tibia showing an oblique diaphyseal fracture; D: Lateral of the right tibia confirming the oblique diaphyseal fracture (E) AP and (F) lateral of the right femur and (G) AP and (H) lateral of the right tibia at 12 wk with osseous union of both diaphyseal fractures.

orthopedic surgeon can counsel the patient with this rare injury.

The available literature on this uncommon injury is sorely lacking. The series available for review are comprised of heterogeneous treatments, which are largely non-operative. Many school-age children with long bone fractures are now treated with internal fixation that provides relative or absolute stability of these fractures. New studies are needed to see if this approach is beneficial for pediatric floating knee injuries. A study evaluating current technology with consistent use of a single classification system that helps direct treatment will better elucidate how Pediatric Orthopaedic surgeons should manage this highly complex and often severe pediatric injury.

COMMENTS

Background

Historically pediatric patients who had injuries of both the femur and tibia were treated in traction and casting for weeks in the hospital.

Research frontiers

Open reduction and internal fixation has become more commonplace for pediatric long-bone fracture management given the advancement in orthopaedic technology.

Innovations and breakthroughs

Flexible nails for the femur and the tibia as well as adolescent intramedullary rods have changed the management of pediatric long bone fractures in isolation. No one is yet to comment on this technology in the setting of the more severe floating knee injury in pediatric patients.

Application

Mobilizing patients soon leads to improved patient satisfaction, shorter hospital

stays, less costly time away from work, and overall better outcomes. Using this technology to get children back home and to school sooner and parents to work is beneficial to the hospital, the healthcare system, the patient, and the parents.

Terminology

Floating knee-injuries to both the femur and tibia resulting in the knee joint not being connected to either long bone.

Peer-review

Well-organized paper.

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Femoral positioning influences ipsi-and contralateral anterior cruciate ligament rupture following its reconstruction: Systematic review and meta-analysis

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Abstract

AIM

To systematically review the incidence of ipsilateral graft re-rupture and contralateral anterior cruciate ligament (ACL) rupture following its reconstruction, with special attention to the femoral drilling technique.

METHODS

Systematic review and meta-analysis of high-level prospective studies searched in MEDLINE database following PRISMA statement. The rate of ipsilateral graft re-rupture and contralateral rupture in patients submitted to either transtibial (TT) technique (isometric) or anteromedial (AM) technique (anatomic) was compared.

RESULTS

Eleven studies met the criteria and were included in final analysis. Reconstructions using the AM technique had a similar chance of contralateral ACL rupture when compared to the chance of ipsilateral graft failure (OR = 1.08, $P = 0.746$). In reconstructions using TT technique, the chance of contralateral ACL rupture was approximately 1.5 times higher than ipsilateral graft failure (OR = 1.49, $P = 0.048$). Incidence of contralateral lesions were similar among the techniques TT (7.4%) and AM (7.0%) ($P = 0.963$), but a trend could be noticed with a lower incidence of lesion in the ipsilateral limb when using the TT technique (4.9%) compared to the AM technique (6.5%) ($P = 0.081$).

CONCLUSION

ACL reconstruction by TT technique leads to lower incidence of graft re-injury than contralateral ACL lesion. There is no difference between the chance of re-injury after AM technique and the chance of contralateral ACL lesion (native ligament) with either technique.

Key words: Anterior cruciate ligament; Anterior cruciate ligament reconstruction; Arthroscopy; Graft survival

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Core tip: There is no convincing evidence that anatomic reconstruction leads to better clinical outcomes than transtibial (TT) reconstruction. Moreover, data suggests that it could lead to an increased risk of graft re-rupture. We found that anterior cruciate ligament (ACL) reconstruction by TT technique led to lower incidence of graft re-rupture than contralateral ACL lesion. The chance of graft re-rupture after anteromedial (AM) technique was the same of contralateral ACL lesion. There was no difference between contralateral lesion after both techniques and re-rupture after AM technique, what could mean that re-rupture chance after AM technique is indeed closer to normal knee, and, in fact, it is the TT technique's re-tear incidence that is lower than it should be.

de Campos GC, Teixeira PEP, Castro A, Alves Junior WM. Femoral positioning influences ipsi- and contralateral anterior cruciate ligament rupture following its reconstruction: Systematic review and meta-analysis. *World J Orthop* 2017; 8(8): 644-650 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i8/644.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i8.644>

INTRODUCTION

Optimal reconstruction technique for an anterior cruciate ligament (ACL) tear still on debate. In the last fifteen years literature has shown a significant shift in trends regarding graft positioning^[1]. The "isometric" femoral graft positioning, made through the tibial tunnel (transtibial technique) and very popular during the last two decades of the twentieth century, is gradually being loathed^[2]. Since the introduction of the anterior cruciate anatomic reconstruction concept^[3], the pursuit of the ideal graft positioning has led to the so-called "anatomic" single-bundle reconstruction techniques, which can be accomplished by either by an anteromedial approach^[4,5] as well as an outside-in femoral drilling^[6].

Despite the plethora of anatomical and biomechanical studies suggesting incorrect graft positioning and inadequate knee rotational stability with transtibial (TT) femoral drilling technique, there is no convincing evidence that anatomic reconstruction leads to better clinical outcomes^[7]. Moreover, recent data suggests that the anteromedial (AM) technique for femoral drilling

could lead to an increased risk of graft re-rupture^[8].

We hypothesized that the increased risk of graft re-rupture observed in anatomical reconstructions could in fact represent an approximation to the "normal knee" ACL rupture risk, that could be represented by the risk of contralateral knee lesion. This also would explain the odd finding that there is a higher incidence of contralateral knee ACL lesion when compared to graft re-lesion following ACL reconstruction by isometric technique^[9].

Therefore, the aim of this study is to systematically review the incidence of ipsilateral graft re-rupture and contralateral ACL rupture following ACL reconstruction, with special attention to the femoral drilling technique.

MATERIALS AND METHODS

Systematic review and meta-analysis of studies including patients submitted to ACL reconstruction, registered at PROSPERO under the number CRD 42015019336. PRISMA statement guidelines were followed for conducting and reporting meta-analysis data.

Literature review

On September 13, 2015, a systematic literature search of the MEDLINE database was performed independently by two of the authors (Gustavo Constantino de Campos and Paulo Eduardo Portes Teixeira) using the following terms: "Anterior cruciate ligament" AND "contralateral" AND "reconstruction" AND "follow-up". The initial search yielded 189 results. Eligibility criteria were original studies that included adult patients submitted to ACL reconstruction, in English language. Title and abstract evaluation suggested 156 articles for full text revision. Studies were excluded if did not specifically described drilling technique for ACL femoral tunnel confection, did not report the incidence of ipsilateral graft failure and incidence of contralateral ACL lesion during follow-up, if they were experimental studies (biomechanics or animal), if patients were submitted to revision surgery, double bundle or multiple ligaments reconstruction, or graft selection comprising allograft, artificial devices or harvested from contralateral knee. Risk of bias was minimized including only grade I to III prospective studies with a minimum of 75% of patients at final follow-up.

From the 156 articles reviewed, 145 articles were excluded, resulting in 11 articles for final analysis^[10-20]. The references of the remaining eleven articles were reviewed with no additional studies for inclusion identified. These 11 studies provided the data for the present analysis. Literature review is summarized in Figure 1.

Data extraction

Extracted data included type of study, evidence level, patient demographics, follow-up duration, loss of follow-up, surgical technique, graft choice, ACL graft re-lesion

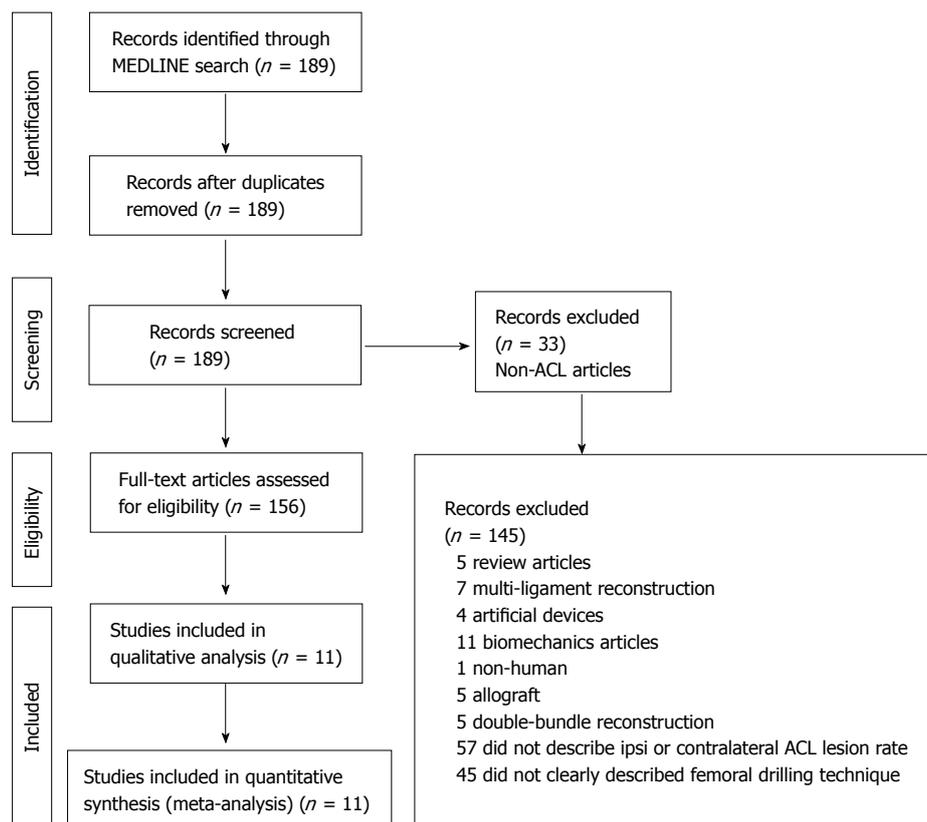


Figure 1 Prisma flow diagram. ACL: Anterior cruciate ligament.

incidence and contralateral ACL rupture incidence. Data were extracted by two authors independently (GCC and PEPT). Discrepancies were resolved by consensus.

Statistical analysis

A meta-analysis of the incidence of contralateral vs ipsilateral lesions to each of surgical techniques (AM and TT) was performed by "Comprehensive Meta-Analysis software version 3.3.070". The heterogeneity of variances between studies was examined by χ^2 test for heterogeneity and I^2 statistics (proportion of the total variance due to heterogeneity) and χ^2 (effect size variance between studies)^[21,22]. When a significant heterogeneity was observed between studies, the combined effects across studies were analyzed by random effects model. When there was no significant heterogeneity between studies, these effects were analyzed using fixed effects model^[22].

The estimate of the pooled effect (pooled odds ratio) between studies was calculated using the Mantel-Haenszel method (MH OR). Publication biases were analyzed by the asymmetry in the Begg and Mazumdar's funnel plot^[23]. Additionally, an association analysis between the surgical technique used (AM or TT) and the incidence of total ipsilateral and contralateral lesions of all publications was performed using χ^2 2 × 2 test statistic in SPSS 18.0 software (SPSS Inc., Chicago, United States).

The chance of injury occurrence was calculated by OR

using simple logistic regression in which was considered the sum of the number of events (contralateral or ipsilateral lesions) and the sum of the number of cases of all publications that have used the technique AM or TT separately. The significance level (α) used for all analyzes was 5% ($P < 0.05$).

RESULTS

Follow-up

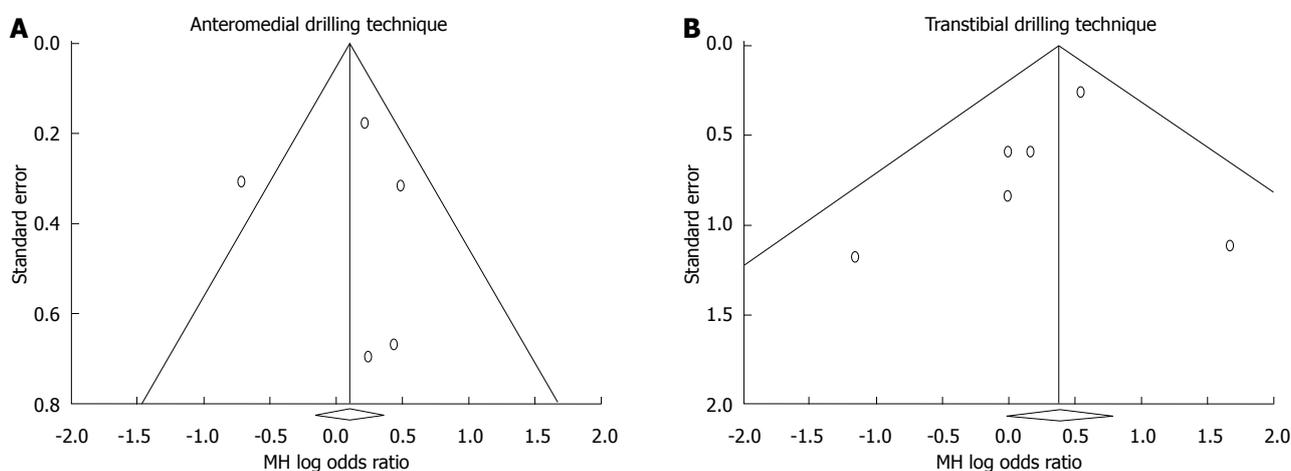
All studies had a minimum of 2 years of follow-up after ACL reconstruction. The duration of follow-up's ranged from 2 to 15 years. Data concerning the incidence of lesions were based on the total amount of individuals who have completed 100% of follow-up for each study. The percentage of individuals who completed the follow-up in each study ranged from 75% to 98% (Table 1).

Quality evaluation and potential biases

Study quality was assessed as recommended by previous studies^[23,24]. Of the eleven studies included in this meta-analysis, 6 (55%) were classified as level of evidence 1, 3 (27%) with level of evidence 2 and 2 (18%) with evidence of Level 3 (Table 1). The potential bias across studies were evaluated by Begg and Mazumdar's funnel plot for the incidence of contralateral and ipsilateral lesions in each of the AM and TT techniques, which were predominantly symmetrical, suggesting lack of significant biases in the publications

Table 1 Data of the studies *n* (%)

Author	Year	Evidence level	No. of initial patients	No. of patients included in follow-up	Follow-up (yr)	No. of contralateral injuries	No. of Ipsilaterais injuries
Anteromedial drilling technique							
Webb	2013	3	200	181 (91)	15	19 (10.5)	35 (19.3)
Shelbourne	2009	2	1820	1415 (78)	14	75 (5.3)	61 (4.3)
Pinczewsky	2007	2	180	178 (99)	10	29 (16.3)	19 (10.7)
Sajovic	2006	1	64	61 (95)	5	5 (8.2)	4 (6.6)
Shaieb	2002	1	82	70 (85)	2	6 (8.6)	4 (5.7)
Total	-	-	2346	1905 (81)	-	134 (7.0)	123 (6.5)
Transtibial drilling technique							
Barenius	2014	1	164	134 (82)	14.1	6 (4.5)	6 (4.5)
Webster	2014	3	750	561 (75)	4.8	42 (7.5)	25 (4.5)
Holm	2010	1	72	57 (79)	10	7 (12.3)	6 (10.5)
Keays	2007	2	62	62 (100)	6	5 (8.1)	1 (1.6)
Drogset	2005	1	41	38 (93)	2	1 (2.6)	3 (7.9)
Aune	2001	1	72	64 (89)	2	3 (4.7)	3 (4.7)
Total	-	-	1161	916 (79)	-	64 (7.4)	44 (4.9)

**Figure 2** Funnel plot for the incidence of contralateral and ipsilateral lesions in each of the anteromedial (A) and transtibial (B) techniques included in the meta-analysis. MH: Mantel-Haenszel.

included in the meta-analysis (Figure 2).

Incidence of ipsilateral vs contralateral rupture

After the meta-analysis and combining the data, it was observed that ACL reconstructions using the AM technique had a similar chance of contralateral ACL rupture when compared to the chance of ipsilateral graft failure (MH OR = 1.08, 95%CI: 0.67 to 1.75, $P = 0.746$; Figure 3). However, after reconstructions using the TT technique, the chance of contralateral ACL rupture was approximately 1.5 times higher than the chance of ipsilateral graft failure (MH OR = 1.49, 95%CI: 1.00 to 2.21, $P = 0.048$, Figure 3). There was no heterogeneity of variances between studies using the TT technique ($I^2 = 0.0\%$, $\chi^2 = 0.0$, $P = 0.517$, Figure 3).

Nevertheless, those who used AM technique showed significant heterogeneity of variances ($I^2 = 56.9\%$, $\chi^2 = 0.151$, $P = 0.054$, Figure 3). Finally, from the publications included in the present meta-analysis (Table 1), no differences in the incidence of contralateral lesions were identified among the techniques TT (7.4%)

and AM (7.0%) (OR = 0.99, 95%CI: 0.73 to 1.35, $P = 0.963$). But a trend could be noticed with a lower incidence of lesion in the ipsilateral limb when using the TT technique (4.9%) compared to the AM technique (6.5%) (OR = 0.73, 95%CI: 0.51 to 1.04, $P = 0.081$).

DISCUSSION

The present study found no difference between the risk of an ipsilateral graft re-rupture and a contralateral ACL rupture in individuals operated with the AM technique. There was also no difference in the risk of a contralateral ACL rupture when comparing both techniques (7%). However, the present analysis found a lower rate of ipsilateral graft re-rupture in patients operated with TT technique (4.9%; $P = 0.048$). This is the first analysis focusing the influence of femoral drilling technique over the graft failure and contralateral ACL lesion after ACL reconstruction.

Ipsilateral graft re-lesion is, for obvious reasons, an undesirable event, occurring in 1.8%^[14] to 10.4%^[25]

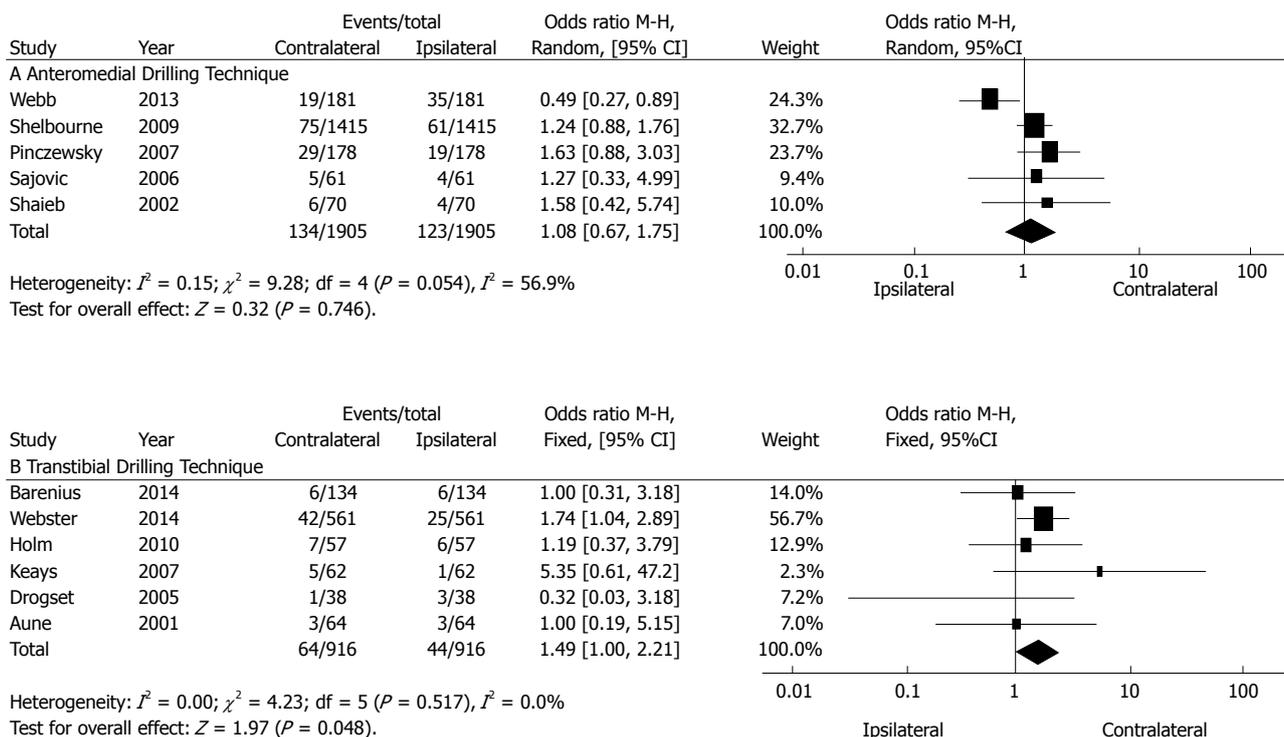


Figure 3 Results of individual studies along with a Forest plot that graphically displays the point estimates on a common scale surrounded by the 95%CI (indicated by the horizontal lines). The diamond represents the pooled effect between studies. M-H: Mantel-Haenszel; df: Degrees of freedom.

of ACL reconstructed patients during the follow-up. Literature shows higher rates of contralateral ACL lesions than ipsilateral graft failure after ACL reconstruction^[9]. An explanation to this finding could be inadequate rehabilitation^[16] or even the assumption that the neoligament would be stronger than the original ACL^[16]. Some authors attribute such finding to the protective role of the uninjured limb that renders it more suitable to lesion^[26].

However, recent studies found a decrease in graft in situ forces when positioned in more vertical locations (isometric position), indicating that the femoral tunnel drilled through transtibial approach will result in a more vertical graft with in situ force lower than the in situ force found in the native ACL^[27-29]. Therefore, the lower graft failure rates found in TT reconstruction could be because the neoligament simply is not submitted to the physiological forces that occur in the "normal" knee. With that in mind, one could speculate that it is not the AM technique that presents a higher failure rate, but the TT graft failure rate that is lower than it should be.

Anatomic ACL reconstruction results in graft inclination angle closer to the native ACL inclination angle and graft force and knee anterior laxity closer to those of the native knee^[29]. It is our understanding that this could be the explanation to the findings of the present analysis, since we found same risk of contralateral ACL rupture ("normal" knee) for both techniques, with no difference for graft failure in the AM group (7%), and lower incidence of ipsilateral graft failure in TT group (4.9%, $P = 0.048$).

It is fundamental, thus, to provide information regarding femoral drilling technique when discussing ipsi or contralateral lesions rates during follow-up. Most of studies just focus on the graft choice and patient demographics. The vast majority of studies initially included in our analysis did not adequately describe the ACL reconstruction technique used. This is in accordance to van Eck *et al*^[30], who examined 74 studies that claimed to use "anatomic technique" for ACL reconstruction and found a gross under-reporting of specific operative technique data.

Rahr-Wagner *et al*^[8] found increased risk of revision in patients undergone to ACL reconstruction with femoral drilling through AM portal when compared to TT technique in the Danish Knee Ligament Reconstruction Register. They explained this finding as a result of a learning curve due to the introduction of a new and more complex technique. The higher force over the more anatomically placed grafts could be a more accurate explanation.

Our results indicate that the increased risk is in fact an approximation to the expected failure rate of the normal knee, that could be represented by the rate of contralateral ACL lesion. van Eck *et al*^[31] found that the majority of graft failures following anatomic ACL reconstruction occurred between six and nine months postoperatively, precisely the commonly recommended period for return to sports. Although there has been a transition toward the "anatomic" reconstruction over the last decades, rehabilitation protocols still the same. Maybe the higher forces over the graft could alter the

time frame for complete graft healing and maturation. More studies are needed on that matter.

In another point of view, one can argue that, since there is no convincing data on the superiority of anatomic technique regarding clinical outcomes, it would be better to choose a technique with a lower rate of graft failure (TT technique). This question will only be answered as longer follow-up of anatomic reconstruction series successfully demonstrates better clinical outcomes and lower evolution to osteoarthritis.

We acknowledge that this meta-analysis has strengths and limitations. One limitation is the lack of demographic data, such as age, gender, body mass index and level of activity. Post-operative rehabilitation protocols were not analyzed or even considered. We acknowledge the importance of rehabilitation data. However, meta-analysis was performed comparing two groups operated by the same authors, therefore subjected to same rehabilitation protocols. Also, we did not include anatomic reconstruction by out-in femoral drilling technique. We chose to use only AM technique to standardize our analysis.

In addition, we were not able to show the data on direct comparison between AM and TT techniques on graft failure and contralateral ACL rupture. To perform this comparison and present it in a meta-analysis format, the comparison effect between techniques would have to be presented individually in each study selected for this meta-analysis. All selected studies for this review were independent and presented only intra-technical comparisons. Although we performed an exploratory analysis to test the differences between the incidences of graft failure and contralateral ACL rupture among AM and TT techniques, it could be biased. This issue is still a gap in the literature and more clinical studies are needed to conduct future meta-analyses to clarify the subject. The major strength is the rigorous criteria used. We only included studies that reported both ipsi- and contralateral failure information, thus ensuring proper comparison when performing the meta-analysis. Moreover, we only included high quality prospective studies with high level of evidence and loss of follow-up lower than 25%.

The ACL reconstruction by transtibial technique leads to lower incidence of graft re-injury than contralateral ACL lesion. There is no difference between the chance of re-injury after anteromedial technique and the chance of contralateral ACL lesion (native ligament).

COMMENTS

Background

Optimal reconstruction technique for an anterior cruciate ligament (ACL) tear still on debate. Evidence regarding the influence of graft femoral positioning over ipsilateral graft re-lesion and contralateral rupture following ACL reconstruction is conflicting.

Research frontiers

Since the introduction of the anterior cruciate anatomic reconstruction concept, the pursuit of the ideal graft positioning has led to the so-called "anatomic"

single-bundle reconstruction techniques. However, despite the plethora of anatomical and biomechanical studies suggesting incorrect graft positioning and inadequate knee rotational stability with transtibial (TT) femoral drilling technique, there is no convincing evidence that anatomic reconstruction leads to better clinical outcomes. Moreover, recent data suggests that the anteromedial (AM) technique for femoral drilling could lead to an increased risk of graft re-rupture.

Innovations and breakthroughs

This is the first analysis focusing the influence of femoral drilling technique over the graft failure and contralateral ACL lesion after ACL reconstruction. The authors found that ACL reconstruction by TT technique led to lower incidence of graft re-injury than contralateral ACL lesion. There was no difference between the chance of re-injury after AM technique and the chance of contralateral ACL lesion (native ligament) with any technique.

Applications

The increased risk of graft re-rupture observed in anatomical reconstructions could in fact represent an approximation to the "normal knee" ACL rupture risk, that could be represented by the risk of contralateral knee lesion. The lower graft failure rates found in TT reconstruction could be because the neoligament simply is not submitted to the physiological forces that occur in the "normal" knee. With that in mind, one could speculate that it is not the AM technique that presents a higher failure rate, but it is the TT graft failure rate that is lower than it should be, probably due to incorrect femoral positioning.

Terminology

Transtibial technique refers to an anterior cruciate ligament reconstruction technique in which the femoral tunnel is created with a drill inserted through a tibial tunnel previously drilled. It leads to a non-anatomic positioning of the femoral tunnel, searching for an isometric position of the femoral tunnel. In the anteromedial portal technique, the femoral tunnel is created with a drill inserted through the arthroscopic anteromedial portal, which makes it possible to create the femoral tunnel in its anatomic position.

Peer-review

This is a very nice paper, it is well written with very interesting results and conclusions.

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Open wound management of esophagocutaneous fistula in unstable cervical spine after corpectomy and multilevel laminectomy: A case report and review of the literature

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Abstract

A 67-year-old female patient developed an esophagocutaneous fistula 4 mo after C4 and C5 partial corpectomy. Plain radiograph and computed tomography (CT) scan of cervical spine showed inferior screws pullout with plate migration that caused the esophageal perforation. Management included removal of anterior hardware, revision C4-5 corpectomy, iliac crest strut autograft and halo orthosis immobilization. The fistula was treated using antibiotics and a 10-french gauge rubber tube for daily irrigation and Penrose drain. At 3 mo, the esophagocutaneous fistula healed and the patient resumed oral feeding. Six months follow-up CT scan showed sound fusion with graft incorporation. At two-year follow-up, patient denied any neck pain or dysphagia. This case report presents a successful outcome of a conservative open wound management without attempted repair. The importance of this case report is to highlight this treatment method that may be considered in such a rare complication particularly if surgical repair failed.

Key words: Wound management; Esophagocutaneous fistula

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Core tip: Esophageal perforation and subsequent fistulization is a known complication following anterior cervical spine surgery. As part of the treatment of this complication, hardware removal is commonly required. The majority of the literature advises against conservative treatment of esophageal injury due to the associated morbidity and mortality.

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INTRODUCTION

Anterior cervical spine discectomy and corpectomy are reliable with good outcomes for the treatment of neck pain with radiculopathy or myelopathy. The incidence of esophageal perforation in anterior cervical spine surgery is 0.2% to 0.4%. High mortality rates up to 20% have been reported with injury even when the patient is treated within the first 24 h. This increases to 50% when treatment is further delayed. In rare circumstances with delayed diagnosis, esophagocutaneous fistulous tract may form and presents with discharge of food particles from the surgical wound. As with most infections involving orthopedic implants, management involves hardware removal, debridement of soft tissues and culture specific antibiotic^[1-4]. The objective of this case report is to present a successful open wound management without attempted repair of a patient with an esophagocutaneous fistula.

CASE REPORT

A 67-year-old female patient was hospitalized at the authors' institution for left distal femur fracture that was treated with open reduction and internal fixation. During her postoperative stay, it was noted that food particles were draining from an anterior cervical wound. Patient had a history of two previous cervical spine surgeries, both performed at other institutions. The first was a C4-6 posterior laminectomy without fusion, performed eight years prior to this hospitalization. The second surgery was performed 4 mo prior to her admission to the authors' institution. It consisted of C4 and C5 partial corpectomy with insertion of a polyetheretherketone (PEEK) cage and C3-6 anterior cervical instrumentation.

The spine service was consulted and plain radiograph demonstrated inferior screws pullout with plate migration (Figure 1). Computed tomography (CT) scan showed subcutaneous air tracking along the neck soft tissues. General surgery and otolaryngology were consulted and an esophagram (Figure 2) revealed ingested oral contrast tracking along the right subcutaneous tissues of the neck confirming perforation of the esophagus at the level of the inferior screws with fistulization through the anterior surgical wound. Blood work showed normal white cell count 8000 (normal 4500-10000), decreased prealbumin 6.1 mg/dL (normal 17-34) and serum iron level 15 mg/dL (normal 50-212) that confirmed malnutrition.

The patient's oral intake was suspended and a



Figure 1 Lateral plain radiograph showed inferior screws pullout and anterior displacement of the plate.

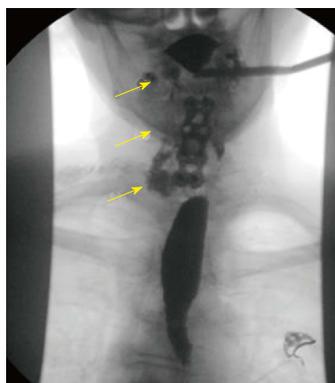


Figure 2 Anteroposterior fluoroscopic image of esophagram showed extravasated contrast material tracking along the right side of the neck (arrows).

nasogastric tube placed to facilitate feeding. The patient was taken to the operating room and underwent removal of the anterior hardware, drainage of cervical abscess, revision C4-5 corpectomy, C3-C6 fusion using tricortical iliac crest strut autograft and halo vest immobilization. The wound was left open and managed by the general surgery and otolaryngology services. One week after the revision cervical fusion, the patient was taken to the operating room by general surgery for irrigation and debridement, insertion of a 10 French gauge rubber tube for irrigation and Penrose drain. The wound was irrigated *via* the rubber tube two times daily with a dilute hydrogen peroxide solution. The patient was placed on ceftriaxone and flagyl for 6 wk as cultures grew polymicrobial mouth flora.

The halo vest removed at 3 mo. The fistulous tract healed at 3 mo and patient resumed oral feeding. Six months follow-up CT scan showed graft incorporation (Figure 3). At two years follow up, patient denied any neck pain or dysphagia and plain radiograph showed maintenance of the cervical spine alignment (Figure 4).

DISCUSSION

The incidence of esophageal perforation after anterior cervical spine surgery is 0.2% to 0.4% and may present

Table 1 Cases reported in the literature

Ref.	No of patients with perforation	Time of diagnosis	Management	Outcome
Zhong <i>et al</i> ^[11]	6	Early postoperative	Wound debrided in 3 patients, implant removed and primary suture of perforation in 2 patients	5 healed 1 died due to pneumonia
Ardon <i>et al</i> ^[3]	4	Early postoperative in 3 patients	Hardware removed with primary suture of the perforation in 2 patients and in one of these an additional sternocleidomastoid myoplasty was done	3 healed 1 patient died due to systemic complication, indirectly related to the perforation
Yin <i>et al</i> ^[4]	1	3 yr after surgery	Emergency tracheostomy, hardware removal, abscess drainage and infected tissue debridement	Healed
Jamjoom <i>et al</i> ^[27]	1	Early postoperative	No definite perforation detected at reoperation, pharyngocutaneous fistula formed subsequently No attempted repair	Fistula recurred twice soon after resumption of oral feeding
Orlando <i>et al</i> ^[9]	5	2 during surgery 2 early postoperative 6 mo postoperative in 1	Hardware removal in 2 Hardware retained in 1 No hardware inserted in 2	All healed
Sun <i>et al</i> ^[10]	5	1 during surgery 4 early postoperative	Esophagus repaired in 4 Hardware removal in 2 Esophagus repaired in 4 reinforcement with a sternocleidomastoid muscle flap in 1 patient	All healed
Balmaseda <i>et al</i> ^[20]	1	Early postoperative	Hardware retained No repair	Healed
Ji <i>et al</i> ^[21]	1	Early postoperative	Hardware retained repaired and reinforced with sternocleidomastoid flap Recurrent esophageal leakage 2 d after the repair Wound reopened and a continuous irrigation and drainage system used	Healed



Figure 3 Computed tomography scan sagittal reformat showed incorporation of the iliac crest strut graft.



Figure 4 Lateral cervical spine plain radiograph at 2-year follow-up showed incorporation of the iliac crest strut graft with maintenance of the cervical spine alignment.

intraoperatively or in the postoperative period^[1-5]. Graft dislodgment, prominent hardware or migration can result in chronic pressure on the esophagus, which leads to ischemic tissue breakdown^[4,6,7]. It has been reported that 50% of esophageal fistulas occur at C5-6 level instrumentation. At this anatomic landmark, known as Lannier’s triangle, the pharynx transitions to the esophagus and the posterior esophageal mucosa is extremely thin and covered only by fascia^[8-11].

Patients with delayed esophageal injury commonly present with surgical wound infection, odynophagia (pain

on swallowing) and dysphagia^[1,4,12,13]. When esophageal injury is suspected, contrast swallow studies may reveal extravasation of the contrast material and CT scan may demonstrate subcutaneous air. The patient in the current report had loose hardware, prior corpectomy and presented with food particles draining from an anterior cervical wound, which is pathognomonic for esophageal fistula.

Treatment strategies for esophageal perforation and fistula are debated (Table 1). The majority of

publications recommended surgical repair of esophageal injury due to the associated morbidity and mortality^[1,3,4,7,9,10,14-19]. However, some have reported successful conservative management^[20,21]. The key aspects of the treatment strategy include: Anterior hardware removal, posterior fusion for patients in whom primary fusion has not yet occurred, primary closure of the esophageal perforation, and intravenous antibiotics. The patient in the current report was treated with anterior hardware removal and revision interbody fusion with iliac crest tricortical autograft. Patient's prior multilevel laminectomy rendered the cervical spine unstable after anterior hardware removal. In the setting of esophageal perforation and active infection re-instrumentation of the anterior cervical spine was not possible. Commonly a posterior cervical instrumentation and fusion would be the approach considered. The patient presented in the current study had an increased risk of postoperative posterior cervical spine surgical wound infection related to the existing anterior wound infection and malnutrition. Furthermore, the previous multilevel wide posterior laminectomy would have made the posterior cervical approach challenging with increased risk of dural tear and spinal cord injury. Given those risks associated with a posterior approach in this patient, the authors opted to use a halo vest immobilization postoperatively for cervical stabilization in place of posterior instrumentation. The esophageal perforation and fistulous tract in this patient successfully resolved without attempted repair by two times daily wound irrigation through a rubber tubing and Penrose drain.

In conclusion, the current report shows that this complication can be successfully treated with open wound management. This highlights the value of wound management for such a rare complication that could be considered after failed surgical repair of esophageal injury.

COMMENTS

Case characteristics

A 67-year-old female patient presented with food particles draining from an anterior cervical wound. Patient had a history of two previous cervical spine surgeries; the first was a C4-6 posterior laminectomy without fusion, performed eight years prior current presentation. The second surgery was performed 4 mo prior to her admission to the authors' institution. It consisted of C4 and C5 partial corpectomy with insertion of a PEEK cage and C3-6 anterior cervical instrumentation.

Clinical diagnosis

Esophagus perforation with fistulization through the anterior surgical wound.

Laboratory diagnosis

Blood work showed normal white cell count 8000 (normal 4500-10000), decreased prealbumin 6.1 mg/dL (normal 17-34) and serum iron level 15 mcg/dL (normal 50-212) that confirmed malnutrition.

Imaging diagnosis

Plain radiograph demonstrated inferior screws pullout with plate migration.

Computed tomography (CT) scan showed subcutaneous air tracking along the neck soft tissues. Esophagram revealed ingested oral contrast tracking along the right subcutaneous tissues of the neck.

Treatment

Management included suspended oral intake, a nasogastric tube feeding, removal of anterior hardware, revision C4-5 corpectomy, iliac crest strut autograft and halo orthosis immobilization. The wound left opened and a 10-french gauge rubber tube was placed for daily irrigation. The patient was placed on ceftriaxone and flagyl for 6 wk.

Related reports

The majority of publications recommended surgical repair of esophageal injury due to the associated morbidity and mortality. However, some have reported successful conservative management.

Term explanation

Fifty percent of esophageal fistulas occur at C5-6 level instrumentation. At this anatomic landmark, known as Lannier's triangle, the pharynx transitions to the esophagus and the posterior esophageal mucosa is extremely thin and covered only by fascia.

Experiences and lessons

When esophageal injury is suspected, contrast swallow studies may reveal extravasation of the contrast material and CT scan may demonstrate subcutaneous air. The current report shows that this complication can be successfully treated with open wound management.

Peer-review

Text well written and easily comprehensible with clear figures.

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Bennett's fracture associated with fracture of Trapezium - A rare injury of first carpo-metacarpal joint

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Author contributions: Goyal T conducted the study and compiled the report.

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Abstract

Association of fracture of trapezium with Bennett's

fracture is very rare and makes reduction and stabilisation more difficult. We are reporting a rare case of Bennett's fracture with fracture of the trapezium and subluxation of the carpo-metacarpal joint (CMC) joint. The patient was a 47-year-old school teacher who fell from his motorbike on his outstretched right dominant hand. Radiographs and computed tomography showed fracture of the trapezium with subluxation of the CMC joint, associated with Bennett's fracture. Open reduction and internal fixation was carried out. Trapezium was reduced first and secured with a 2 mm diameter screw. Bennett's fracture was then reduced and fixed with two per-cutaneously placed Kirchner's wires. CMC was stabilised with per-cutaneous Kirchner's wires. Latest follow up at 12 mo showed a healed fracture with good reduction of the CMC joint. Clinically patient had no pain and normal extension, abduction and opposition of the thumb. QuickDASH score was 3.9/100. Thus, fracture of trapezium associated with a Bennett's fracture is a rare injury and if ignored it may lead to poor results. This injury is more challenging to manage than an isolated Bennett's fracture as anatomical reduction of the trapezium with reduction of the first CMC is needed. Fracture of the trapezium should be fixed first as this will provide a stable base for reduction of the Bennett's fracture.

Key words: Bennett's fracture; Carpo-metacarpal joint; Trapezium

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Core tip: Association of fracture of the trapezium with Bennett's fracture is very rare and makes reduction and stabilisation more difficult. We are reporting a rare case of Bennett's fracture with fracture of the trapezium and subluxation of the carpo-metacarpal joint (CMC) joint, and describing a technique for successful reduction and stabilisation of these fractures. Trapezium should be reduced first and secured with a 2 mm diameter screw. Bennett's fracture should then be reduced and fixed with two per-cutaneously placed Kirchner's wires. CMC should

be stabilised with per-cutaneous Kirchner's wires. This is expected to result in good functional outcomes.

Goyal T. Bennett's fracture associated with fracture of Trapezium - A rare injury of first carpo-metacarpal joint. *World J Orthop* 2017; 8(8): 656-659 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i8/656.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i8.656>

INTRODUCTION

Bennett's fracture typically involves an intra-articular fracture of the base of the first metacarpal with dislocation of the carpo-metacarpal joint (CMC). This represents avulsion of the attachment of the volar oblique ligament. Most common mechanism is fall on hand with thumb in abduction or extension. Fractures of the trapezium are rare and accounts for only 3%-5% of carpal fractures^[1,2]. Association of fracture of trapezium with a Bennett's fracture is very rare. Presence of fracture of trapezium makes reduction and stabilisation of the Bennett's fracture more challenging. High degree of clinical suspicion is necessary as CMC injuries may be a result of indirect force resulting in little swelling^[3]. Neglected or untreated injuries may lead to degenerative changes of the CMC joint resulting in pain during grip and pinch.

We are reporting a case of Bennett's fracture with fracture of the trapezium and disruption of CMC joint. This is an extremely rare injury and only a few cases have been mentioned in literature before^[4-7]. Open reduction and internal fixation was carried out and clinical and radiological outcomes were good at 6 mo of follow up.

CASE REPORT

The patient was a 47-year-old school teacher who fell from his motorbike on his outstretched right hand. He was right hand dominant. Radiographs showed fracture of the trapezium with subluxation of the CMC joint, associated with Bennett's fracture (Figure 1).

Patient was operated five days after the injury under general anaesthesia. Fracture site was approached using a curved incision beginning at the dorso-radial border of the first metacarpal bone, curving along the junction of the palmar and dorsal skin, to the distal wrist crease. Base of the first metacarpal was recognised which helped in identification of the CMC joint and the trapezium. Trapezium was reduced first and secured with a 0.045-inch Kirchner wire (Figure 2). A 2 mm diameter screw was used to secure the fracture. Bennett's fracture was reduced and fixed with two per-cutaneously inserted 0.045-inch Kirchner's wires (Figure 3). The CMC joint was further stabilised with a per-cutaneously inserted 0.045-inch Kirchner's



Figure 1 Preoperative radiograph showing the Bennett's fracture with fracture of the trapezium.



Figure 2 Intraoperative photograph showing the surgical approach, fixation of the capitellum with screw and reduction of the carpo-metacarpal joint.

wire. Limb was put in a thumb spica cast.

Sutures were removed at 10 d followed by removal of Kirchner wires at 3 wk. Cast was continued for a total of 8 wk after the surgery. Range of motion and gripping exercises were begun after the cast was removed.

Latest follow up at 12 mo showed no fracture lines, with good reduction of the CMC joint. Clinically patient had no pain and normal extension, abduction and opposition of the thumb (Figure 4). Stress testing of the CMC revealed normal ligaments. QuickDASH score was 3.9/100^[8].

DISCUSSION

Most probable mechanism of Bennett's fracture with fracture of the trapezium is axial loading of a partially flexed metacarpal bone. Axial loading in a flexed thumb may initially result in a Bennett's type fracture due to bony avulsion of the anterior oblique ligament. This Bennett's fragment represents the ulnar-volar part of the base of the metacarpal and has strong capsulo-ligamentous attachments. If the Bennett's fragment is small and axial loading continues, trapezium will be impacted between the remaining part of metacarpal base and the radial styloid resulting in a vertically split or

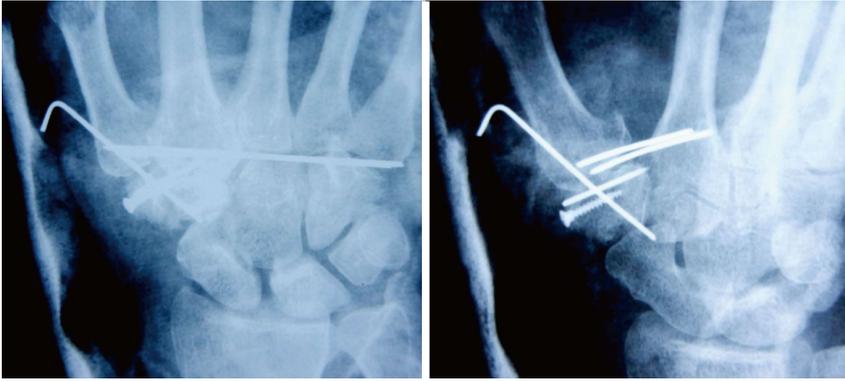


Figure 3 Postoperative radiograph showing reduction of fracture fragments and the carpo-metacarpal joint.



Figure 4 Clinico-radiological follow-up at 6 mo. A: Radiograph at 6 mo follow up showing a healed fracture with maintainance of joint reduction; B: Clinical photograph showing good range of motion.

comminuted fracture of the trapezium. An alternative mechanism of injury could be a hyper-abduction shearing force on the first web-space. This can be seen commonly if a person suffers deceleration injury while holding a handlebar, resulting a commissural shearing force on the first web-space. This may also occur if a person falls on the radial side of the hand with thumb in abduction, so that the first web-space suffers a commissural force.

Stable reduction of the CMC joint and restoring congruity of the articular surface is the goal of treatment^[9,10]. Residual subluxation of the joint or intra-articular displacement of more than 4 mm may lead to poor functional outcomes^[11].

Fractures of carpal bones of hand, and subluxations

of CMCs may be overlooked as soft tissue injuries unless specifically looked for. This will result in poor functional outcomes in long-term follow-up. The type of views imaged or quality of the radiographs may frequently contribute to a missed diagnosis. Appropriate true antero-posterior and lateral radiographs of CMC joint should be insisted. Special views such as Bett view is useful, in which the hand is pronated approximately 20°-30° and the imaging beam is directed obliquely at 15° in a distal to proximal direction, centered over the trapeziometacarpal joint. Computed tomography is a useful imaging modality to study complex fractures of the hand and provides better anatomical details.

Injuries to the CMC joint should be carefully searched

for in patients with intra-articular fractures of the trapezium. These may be associated with the Bennett's fracture, as in this case, or with purely ligamentous injury to the CMC joint. McGuigan and Culp reported 11 patients with intra-articular fractures of the trapezium, four of which were associated with the Bennett's fracture^[4]. Three of these fractures were initially unnoticed. All these patients had good clinical outcomes with open reduction and internal fixation in terms of range of motion, pain and patient satisfaction.

In this case the Bennett's fracture was associated with the vertically split fracture of the trapezium. These fractures require open reduction and internal fixation in order to control reduction of both these fractures. The fracture of trapezium was fixed first with a K wire and a screw to provide a stable platform for reduction of the Bennett's fracture. Bennett's fracture was then fixed with K wires. This gave excellent results at follow up.

Thus, fracture of trapezium associated with a Bennett's fracture is a rare injury and if ignored it may lead to poor results. Fracture of the trapezium should be fixed first as this will provide a stable base for reduction of the Bennett's fracture.

COMMENTS

Case characteristics

This was a rare case of carpal injuries.

Clinical diagnosis

Bennett's fracture dislocation with fracture of Trapezium.

Differential diagnosis

Bennett's fracture dislocation.

Imaging diagnosis

Plain radiographs and computed tomography scan confirmed the diagnosis

Treatment

The fracture of trapezium was fixed first with a K wire and a screw to provide a stable platform for reduction of the Bennett's fracture which was then fixed with K wires.

Experiences and lessons

This is a rare injury and if missed may make the reduction and stabilisation of Bennett's fracture dislocation difficult.

Peer-review

This is generally a good paper.

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Clinical applications of advanced magnetic resonance imaging techniques for arthritis evaluation

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Abstract

Magnetic resonance imaging (MRI) has allowed a comprehensive evaluation of articular disease, increasing the detection of early cartilage involvement, bone erosions, and edema in soft tissue and bone marrow compared to other imaging techniques. In the era of functional imaging, new advanced MRI sequences are being successfully applied for articular evaluation in cases of inflammatory, infectious, and degenerative arthropathies. Diffusion weighted imaging, new fat suppression techniques such as DIXON, dynamic contrast enhanced-MRI, and specific T2 mapping cartilage sequences allow a better understanding of the physiopathological processes that underlie these different arthropathies. They provide valuable quantitative information that aids in their differentiation and can be used as potential biomarkers of articular disease course and treatment response.

Key words: Magnetic resonance imaging; Joint; Diffusion weighted imaging; Dynamic contrast enhanced; Musculoskeletal system; Cartilage; DIXON; Arthritis

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Core tip: New magnetic resonance imaging (MRI) techniques, successfully applied in other anatomical areas, can help to improve the diagnostic accuracy for arthritis evaluation. Advanced fat suppression techniques like DIXON or functional sequences such as cartilage imaging, diffusion weighted imaging or dynamic contrast enhanced-MRI are showing promising results for arthritis assessment. These techniques provide both morphological and functional information in several clinical scenarios including infection, degenerative or inflammatory arthritis.

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INTRODUCTION

Joint diseases are first evaluated through conventional plain radiography, although this technique is limited in that only late subchondral and bony abnormalities in arthropathies can be detected. Bone scintigraphy has been used to detect the presence of active disease^[1]. Ultrasound (US) with Doppler capabilities plays a complementary role in the evaluation of soft tissue involvement for active synovial inflammation assessment without use of radiation or administration of exogenous contrast agents^[2]. However, US is limited by operator-dependency and lack of visualization of deep joints. Computed tomography (CT) can help to better define bone involvement in specific joints, particularly when the diagnosis is questionable based on other imaging techniques^[3]. A major drawback of CT is its use of ionizing radiation, which limits its use in pediatric population.

The introduction of magnetic resonance imaging (MRI) for joint assessment has overcome several limitations of conventional imaging techniques due to its higher tissue contrast, the ability to obtain multiplanar acquisitions, and the absence of ionizing radiation. Furthermore, MRI sequences permits an early detection of cartilage changes, better depiction of bone and soft tissue edema, and the characterization of synovial involvement^[4]. Also, several disease-specific scales based on MRI changes have been proposed to measure arthritis related changes in clinical practice and have been applied in research trials to increase reproducibility^[5].

Currently, several new functional MRI techniques have been translated from the brain to the musculoskeletal system which provide physiopathological information of normal tissue and disease. The DIXON sequence allows for very homogeneous fat-suppression in large and small joints, leading to improved detection of bone edema, synovial enhancement, and subchondral involvement. The Dixon sequence also is able to quantitatively define the fat and water content of a tissue, which can be useful in treatment monitoring of arthropathies. Diffusion-weighted imaging (DWI) evaluates the movement of the free water within tissues, allowing for an indirect estimation of cellularity and cell membrane integrity which enables discrimination between hypercellular lesions, such as malignant and inflammatory processes, from normal tissues. DWI can evaluate arthritis in a quantitative manner while avoiding the use of contrast agents.

Dynamic-contrast enhanced MRI (DCE-MRI) exploits differences in tissue vascularization. In this manner, this technique has been used to differentiate the etiology of synovial involvement in arthropathies according

to the enhancement pattern and other quantitative derived biomarkers. The use of T2 mapping, which acquires different echo times (TE) within the same sequence, has been shown to aid in the early detection and quantification of cartilage abnormalities based on changes in water content, which indirectly reflects collagen content and collagen fiber orientation in the extracellular matrix. T2 mapping has been primarily used for early detection of osteoarthritis in the knee, as areas of initial cartilage degeneration show longer T2 values.

This review visits the technical basis and quantitative biomarkers provided by all these new advanced MRI techniques in the assessment of arthropathies and succinctly analyze their clinical applications.

ADVANCED MRI SEQUENCES FOR ARTHRITIS EVALUATION

Fat suppression techniques

The detection of bone edema is considered, along with synovial involvement, as the key feature in assessing joint involvement in arthropathies. The presence of bone edema has been demonstrated to correlate with overall patient outcome, preceding the existence of bone erosions and joint deformity^[6,7]. Given its excellent tissue contrast, MRI is considered the single modality able to properly assess the presence, location, and extension of bone edema^[8]. Edema imaging is mainly based on fat-suppressed T2-weighted sequences, as the higher water content of involved bone marrow is better depicted against a background of suppressed fat signal. Several sequences have been classically used for evaluation of bone marrow edema, including short inversion time recovery (STIR), spectral presaturation with inversion recovery (SPIR) and spectral adiabatic inversion recovery (SPAIR)^[9,10]. Table 1 summarizes the main physical properties of these techniques and their clinical applications.

Bone marrow edema is also well detected on T1-weighted imaging, specifically with chemical shift imaging (CSI). This gradient-echo (GE) based technique exploits the different resonance frequencies of fat and water. In CSI, two different TE are acquired, providing an image where fat signal is subtracted from water signal (opposed-phase image) and another where the signal of water and fat are added (in-phase imaging)^[5,6]. CSI has shown potential to differentiate true bone replacement from red bone marrow in different locations, and helps to better identify the presence of bone edema and its extension^[11,12].

Chemical shift and DIXON

Several types of advanced sequences have emerged as a technical optimization of chemical shift based on the DIXON technique. This technique acquires several TE at the same time and combines them to obtain, not only an "in phase" or "opposed phase" imaging, but also "fat only" and "water only" maps^[13,14]. In this manner, time

Table 1 Fat suppression techniques in musculoskeletal system

	In phase-out of phase	Fat saturation (CHESS)	Water excitation	DIXON	STIR	SPIR	SPAIR
Physical basis	Change of TE	Selective RF pulse that suppresses fat	Selective RF pulse that excites water	Different TEs, mathematic post-processing	Selective inversion of short T1 tissues	Spectrally selective RF pulse that suppresses fat	Spectrally adiabatic selective RF pulse that suppresses fat
Advantages	Fast High SNR	High SNR Contrast enhanced studies	Fast 3D acquisition	Four images in one acquisition Quantification Less prone to B0 and B1	Less prone to B0 and B1	Pre- and post-contrast studies	Insensitive to B1
Drawbacks	Sensitivity to B0	Sensitivity to B0 and B1 at large FOV	Sensitivity to B0	Acquisition time	Suppress all short T1 structures	Sensitivity to B0	Sensitivity to B0
Clinical applications	Detection of bone infiltration	Bone edema evaluation in joints MR-arthrography	Cartilage evaluation	All in one technique High SNR Less metal induced artifacts	Large FOV (spine) Multiple interfaces (fingers, toes, metal)	Postcontrast imaging of inflammatory or neoplastic conditions	Large FOV and high SNR needed: thigh or MR-neurography

CHESS: Chemical Shift Selective; STIR: Short inversion time recovery; SPIR: Spectral presaturation with inversion recovery; SPAIR: Spectral adiabatic inversion recovery; TE: Time of echo; RF: Radiofrequency; SNR: Signal noise ratio; FOV: Field of view.

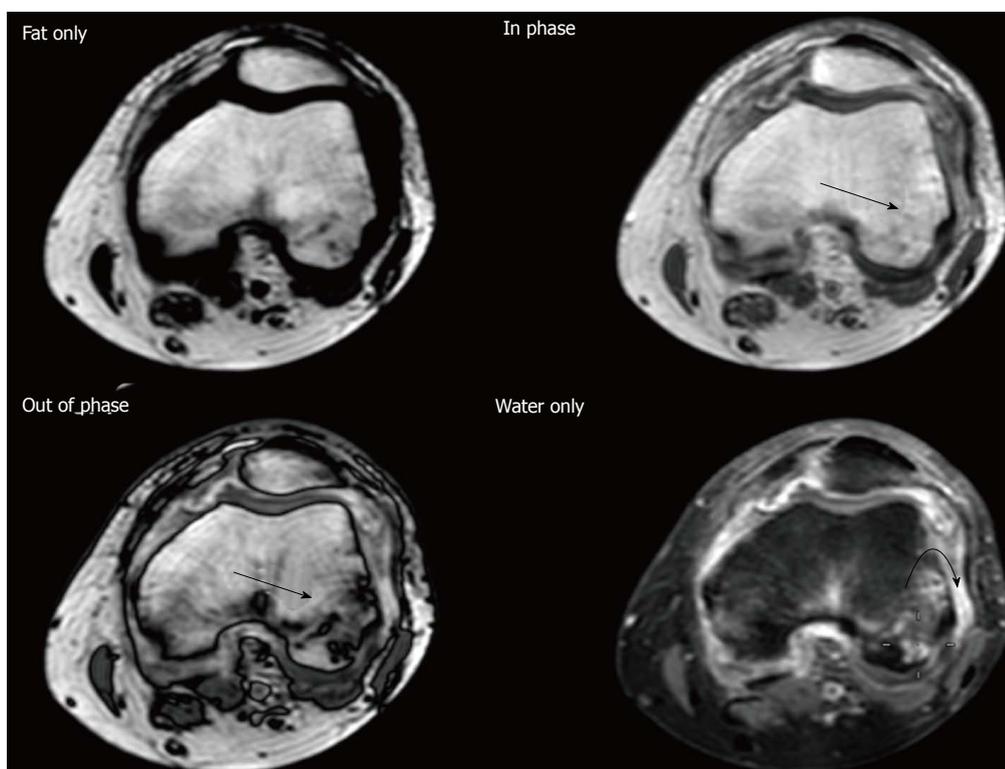


Figure 1 DIXON. Thirty-two years old woman with knee pain and suspected rheumatoid arthritis. Post-contrast DIXON study was performed. Opposed-phase image shows large hypointense areas in both condyles (arrows), which are hardly seen on the in-phase image, consistent with bone marrow edema. Note the presence of bone erosions and synovitis (curved arrow) better depicted on water only imaging.

can be saved by obtaining several stacks of images from only one acquisition (Figure 1).

The DIXON sequence is suitable for routine MRI to evaluate soft tissue and bone disorders and is compatible with a wide variety of pulse sequences, such as Turbo Spin Echo (TSE) and GE, and weightings (T2-weighted, T1-weighted or proton density images). The insensitivity of DIXON imaging to B0 and B1 heterogeneity offers robust fat suppression with higher SNR than other fat-suppressed techniques. Furthermore,

the use of DIXON improves image quality in areas traditionally challenging for obtaining homogeneous fat-suppression, such as in regions of high magnetic susceptibility (*i.e.*, metallic implants) or in small anatomic areas, such as toes and fingers. DIXON sequences can be especially helpful in patients who cannot tolerate uncomfortable positions, particularly the pediatric and elderly populations^[14,15], saving time in the acquisition of other sequences. Finally, DIXON provides quantitative parameters about water and fat

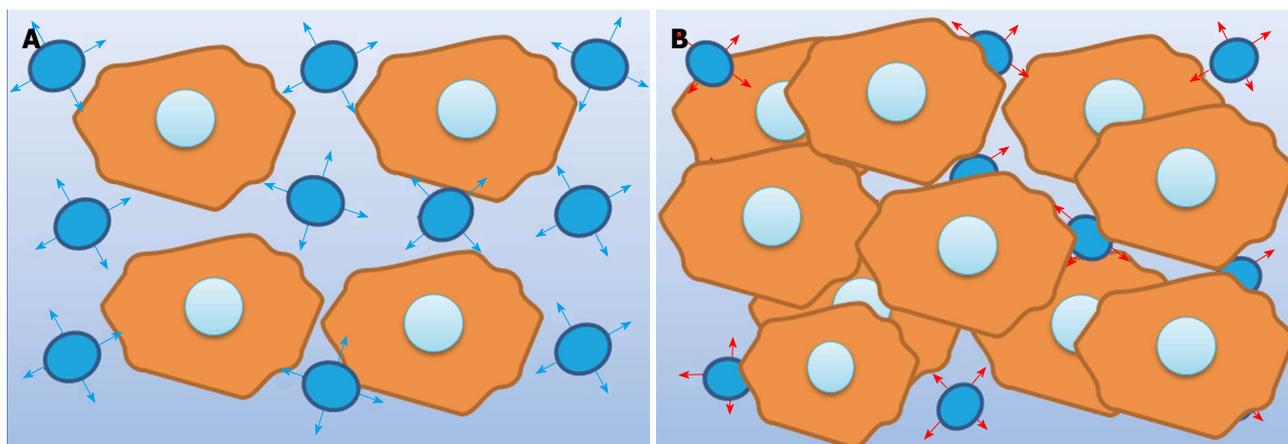


Figure 2 Diffusion-weighted imaging. A: Free water diffusion. The diagram represents the free motion of water molecules in the extracellular space between cells in normal tissue; B: Restricted water diffusion. The diagram represents the restricted motion of water molecules in the extracellular space due to hypercellularity. Another condition that leads to a decrease in the extracellular space is the presence of cytotoxic edema, while the presence of debris and detritus as in the case of abscesses may result also in restricted diffusion.

content of bone marrow and other tissues, including the percentage of signal loss between in phase and opposed phase images (fat fraction), which may provide potential biomarkers for treatment monitoring of arthritis^[12,16]. Water only GE T1-weighted images provide high quality fat-suppression, which can be especially useful in dynamic postcontrast series or high-resolution late post-contrast studies, thereby improving the detection of subtle areas of enhancement^[17].

DWI

DWI evaluates the movement of free water within biological tissues. This property indirectly estimates cellularity and cell membrane integrity and allows for discrimination between hypercellular lesions and normal tissues^[18] (Figure 2). DWI provides quantitative information through the Apparent Diffusion Coefficient (ADC) that represents the exponential decay of a single component of diffusion signal. DWI improves detection of malignant lesions which show reduced water motion secondary to the occupancy of the interstitial space by malignant cells. Furthermore, it has been proposed as an important oncological biomarker due to its ability to discriminate between malignant and benign lesions^[19]. In a similar fashion, infection and inflammation demonstrate reduced water motion and restriction of diffusion. In this manner, DWI and ADC have demonstrated its ability for lesion characterization and treatment monitoring in musculoskeletal applications^[20].

Specific technical adjustments are necessary to perform DWI in musculoskeletal radiology. Most commonly, DWI is performed using a single shot-echo planar imaging (SS EPI) sequence, which is prone to susceptibility and motion artifacts, that are usual in joint evaluation, especially in fingers and toes, due to air-bone-soft tissue interfaces. For bone evaluation, as well as for other anatomical regions, multi-channel or surface coils are usually needed for parallel imaging in order to obtain adequate SNR and reduce artifacts^[21].

DWI provides a qualitative and quantitative assessment of arthritis in a relative short scan time and without need for exogenous contrast^[22]. Normal bone marrow demonstrates low signal intensity on DWI images with low ADC values due to its low cellularity and scarce free water content and dominance of fatty tissue, especially in yellow (fatty) marrow. Characteristically, active arthritis will appear as areas of high signal on highly-weighted diffusion images, also known as high b values images, with concomitant decreased signal on ADC maps. As mentioned previously, one benefit of DWI is that the use of contrast agents is not required. This is particularly important for patients with joint diseases, as it is not uncommon for these patients to have an underlying systemic disease with renal function impairment. In this population, the administration of gadolinium chelates should be taken with caution to decrease the potential risk of develop nephrogenic systemic fibrosis. Also, children with juvenile idiopathic arthritis have inherent drawbacks for intravenous puncture^[23]. In this setting, DWI can be considered as an alternative to contrast-enhanced sequences.

For articular disease assessment, DWI may also be used for soft tissue evaluation, particularly for synovial involvement, joint effusion characterization, and bone marrow edema detection thanks to its ability to assess the water molecules movement.

DCE MRI

Conventional delayed postcontrast T1-weighted sequences only provide morphological information about areas of enhancement. DCE-MRI goes beyond conventional postcontrast MRI by providing pathophysiological information of the inflammatory processes themselves. DCE-MRI is usually based on a 3D gradient echo sequence with high temporal resolution, applying a dynamic scan faster than 4 s per dynamic^[24]. This approach with high temporal resolution has shown several advantages over conventional multi-phase DCE-MRI (temporal resolution

Table 2 Main parameters derived from dynamic contrast enhanced-magnetic resonance imaging studies

Parameter	Biological meaning
Area under the curve	The integral in a plot of concentration of contrast agent in blood plasma against time
Maximum (relative) enhancement	The maximum signal difference between the signal intensity at its maximum and baseline
Time to peak	Time elapsed between the arterial peak and the end of the steepest portion of enhancement
Wash in rate	The maximum slope between the time of onset of contrast inflow and the time of peak enhancement on the time intensity curve
Wash out rate	The clearance rate of contrast agent
K^{trans}	Volume transfer constant between blood plasma and EES
K^{ep}	Rate constant between EES and blood plasma
V_e	Volume of EES per unit of volume of tissue

EES: Extravascular extracellular space.

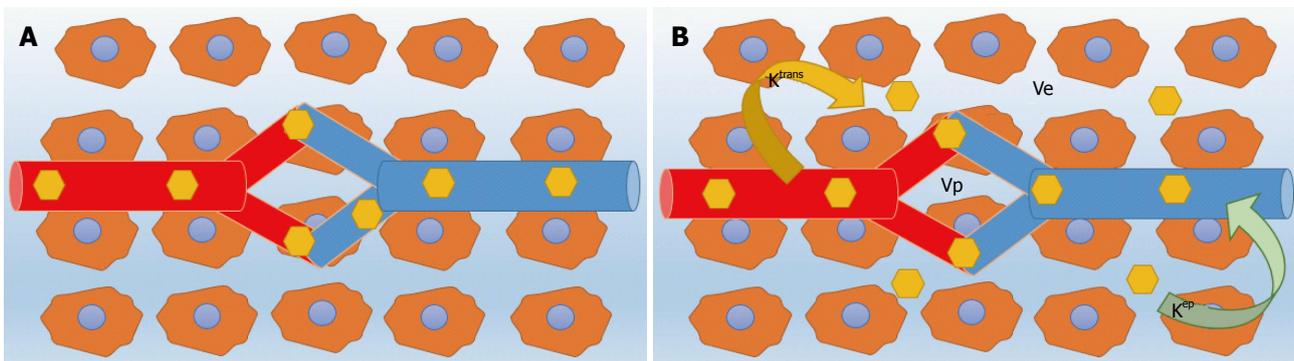


Figure 3 Dynamic-contrast enhanced-magnetic resonance imaging. Dynamic-contrast enhanced-magnetic resonance imaging analysis may be performed using a monocompartmental or a bicompartamental model. A: Diagram represents a monocompartmental model in which only vascular space is considered for distribution of gadolinium chelate; B: Diagram represents a bicompartamental model in which, besides the vascular space, the extracellular extravascular space with leakage and recirculation of gadolinium molecules are also considered. The main parameters derived for those models are detailed in Table 2.

between 12 to 20 s) with improved assessment of the dynamic enhancement process (Figure 3). New 4D acquisitions that combine high temporal and spatial resolution are able to provide simultaneous assessment of both structural and vascular properties^[25]. This technique also permits MR-angiography reconstructions of regional vasculature.

In joint disease, the target structure on DCE-MRI is the synovium. DCE-MRI helps to understand the specific and complex physiopathological process that underlies each specific type of arthritis. The differential diagnosis may be narrowed based on the enhancement characteristics of the synovium, along with bone edema pattern and its distribution. The most helpful features for distinguishing the etiology of the joint process is the steepness and speed of enhancement during the first phases of DCE-MRI. For example, significant differences have been found in relative enhancement rate (RER), not in the first phases, but at delayed acquisition 15 min after Gad injection, with greater RER in rheumatoid arthritis (RA) than in psoriatic arthritis (PA). These results are a reflection of histopathology of synovitis in RA which presents higher cellularity and greater number of vessels compared with PA^[26].

The analysis of DCE-MRI images has been classically performed using regions of interest (ROI). ROI-based analysis provides an average of all data included on a

usually freehand drawn area^[27,28]. Although widely used, this method is prone to sample errors. Other semi-automatic analysis methods have been proposed, using pixel by pixel maps of signal intensity data recorded on DCE-MRI studies^[28,29].

Several types of time-intensity curves (TIC) have been described depending on the morphology and shape of the enhancement curve^[30,31]. Type I TIC is no enhancement, type II curve reflects a slowly and progressively rising enhancement. Type III TIC has a fast wash-in phase followed by a plateau and Type IV curve demonstrates fast wash-in and an early wash-out phase, usually linked to inflammatory activity. Finally, type V is related to a fast wash-in with later progressive enhancement^[27,32].

Parameters derived from monocompartmental or bicompartamental models of analysis of DCE studies are being considered as potential biomarkers for arthritis evaluation^[33]. These biomarkers may predict aggressiveness of the arthritis and potentially aid in treatment monitoring^[34]. Table 2 summarizes the main parameters derived from DCE-MRI studies and its biological meaning.

Cartilage imaging

Imaging of cartilage is one of the primary goals for MRI of the joints. The loose of the normal physiologic

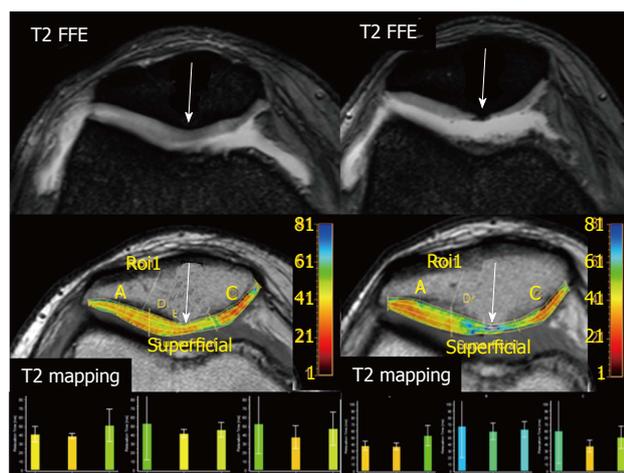


Figure 4 Osteoarthritis progression. A 49-year-old woman with knee pain is studied with two consecutive MRI studies. The first MRI (left images) shows a moderate joint effusion with patchy areas of increased signal intensity on T2 FFE sequence within the patellar cartilage. T2 mapping demonstrates diffuse increase in T2 relaxation times, more conspicuous at the patellar apex (arrows) consistent with early cartilage damage. Follow-up MRI performed 15 mo later (right images), demonstrates severe cartilage thinning, especially at patellar apex, that correlates with a severe increase in T2 relaxation times on the T2 mapping study. This clinical example demonstrates how T2 mapping can help to detect patients with evidence of early OA. MRI: Magnetic resonance imaging; OA: Osteoarthritis.

extracellular matrix precedes the development of bone damage and joint deformity. Articular hyaline cartilage has been classically evaluated with MRI using a morphological approach, which is limited due to the absence of pathophysiological information. In the last two decades, several functional sequences have been developed to allow a better understanding of cartilage structure. Functional MRI provides a qualitative and quantitative leap in early cartilage damage detection and treatment monitoring.

Nowadays, the most commonly applied functional technique for assessment of cartilage damage is T2 mapping. To obtain these images, multiple TE are acquired within the same sequence, computing the T2 relaxation time for each of those acquisitions. A voxel-based parametric map is generated showing the T2 relaxation time of cartilage, which can be assessed visually (qualitative analysis) or quantitative (ROI-based analysis)^[35]. T2 relaxation time depends on the amount of water and the integrity of extracellular matrix, mainly secondary to collagen fiber density. The chemical interaction of collagen fibers with water protons results in a shortening of T2 relaxation time of the normal cartilage (Figure 4). There is a direct correlation between T2 values and water content and an inverse correlation with collagen concentration^[36]. In this manner, areas of injured cartilage show a decrease in extracellular matrix (mainly collagen and proteoglycans) and increased water content. By increasing the TE, T2 mapping can detect these areas of early injury.

CLINICAL SCENARIOS

Infectious arthritis

The most frequent cause of septic arthritis is direct

invasion through a skin defect/ulcer or haematogenous spread. In other cases, the infection is related to previous joint replacement surgery. Clinical and biochemical criteria are usually enough for an appropriate diagnosis, however in many cases, imaging is needed in order to evaluate the extent of the infection, particularly to evaluate for bone involvement. MRI has demonstrated a high accuracy for septic arthritis assessment^[37,38]. As will be discussed in the next section, the introduction of functional MRI sequences may improve the specificity of the diagnosis, especially in evaluating the physiologic characteristics of the synovium, joint fluid, and neighboring bone.

DWI has shown potential for assessing joints and synovial fluid. One of the most useful applications of DWI in joint assessment is the evaluation of joint fluid and periarticular collections, in particular for depiction of infectious synovitis. In inflammatory fluid, hyaluronidases disrupt hyaluronic chains (that confer fluid viscosity) resulting in an increase in ADC values^[39] (Figure 5). On the other hand, in septic arthritis, the presence of inflammatory cells, detritus, and pus produces an increase in viscosity which results in lower ADC values^[40] (Figure 6). Thus, DWI is able to determine the nature of synovial fluid without the need for contrast agent injection and may also obviate the need for arthrocentesis, reducing potential complications such as infection and haemorrhage.

DWI has also demonstrated high accuracy in the differentiation between synovial thickening and reactive joint effusion, with high signal intensity at synovium on high b values due to hypercellularity. In cases of synovial thickening, intermediate ADC values ($1.3\text{--}2.2 \times 10^{-3} \text{ mm}^2/\text{s}$) may be found due to increased vascularization and associated perfusion-related effects in the synovium^[20,40].

In cases of reactive bone involvement, there will be an increase in signal intensity on high b value DWI with concomitant high ADC values compared with normal bone due to the increase in water content of the damaged subchondral bone. When subchondral bone is affected by septic arthritis (osteomyelitis), involved areas will show hyperintensity at high b values with low ADC values due to the presence of pus and inflammatory cells^[41].

DCE-MRI is also able to discriminate between synovial thickening and effusion and allows for the assessment of soft tissue involvement, synovitis (Figure 7), and necrotic areas in severe septic arthritis^[42].

Postcontrast fat suppressed T1-weighted sequences usually help in the detection of bone marrow involvement as areas of increased enhancement. Normal yellow marrow will show no significant change in signal intensity after contrast injection compared to baseline. Involved bone in joints with septic arthritis will show a characteristic TIC (type II curve), with an intense early enhancement and later slight progressive increase of the enhancement slope compared to baseline marrow, without evidence of delayed washout^[43]. Perfusion of epiphysis of involved bone has been shown to be lower

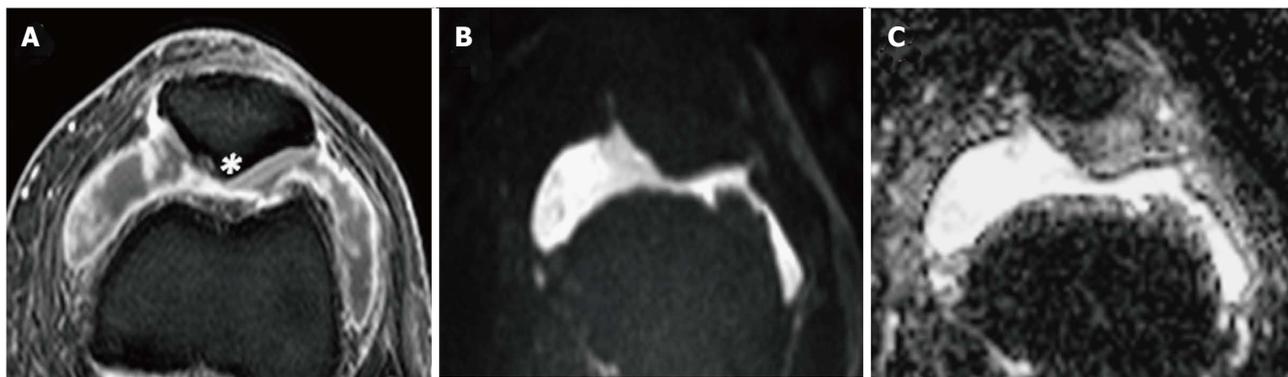


Figure 5 Synovial fluid evaluation with diffusion-weighted imaging. In a 42-year-old woman with RA and knee swelling. A: Axial post contrast fat-suppressed TSE T1-weighted sequence shows articular fluid and synovial enhancement; B, C: DWI with a b value of 900 s/mm² and corresponding ADC map confirm the presence of an effusion without significant restriction of free water motion (ADC: $2,8 \times 10^{-3}$ mm²/s) consistent with transudate due to rheumatoid arthritis, as confirmed by arthrocentesis. In this case, DWI helps to exclude infection. Note the presence of a prominent chondral erosion near to patellar apex (asterisk on A). DWI: Diffusion-weighted imaging; RA: Rheumatoid arthritis; ADC: Apparent diffusion coefficient.

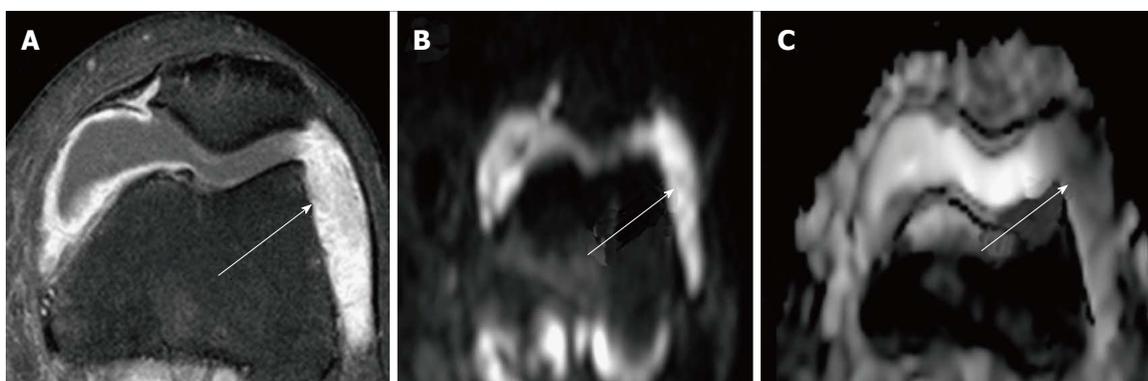


Figure 6 Septic synovitis. Magnetic resonance imaging findings in a 22-year-old man with knee pain and fever. A: Axial post contrast fat-suppressed TSE T1-weighted image shows a large joint effusion with synovial thickening and intense enhancement; B, C: DWI with a b value of 800 s/mm² and corresponding ADC map demonstrate areas of severely restricted diffusion (ADC: $1,8 \times 10^{-3}$ mm²/s) within the articular fluid at the lateral patellar recess consistent with exudate, as proven by arthrocentesis. DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient; TSE: Turbo spin echo.

than expected on the initial phases of DCE-MRI likely due to an increase in hydrostatic pressure or possibly septic thrombosis of epiphyseal vessels. Furthermore, these changes may lead to avascular necrosis^[44].

Inflammatory arthritis

Sacroiliitis: For sacroiliitis (SI) evaluation, conventional fat suppression techniques have high accuracy but a relative lack of specificity in the discrimination between early acute and sub-acute disease. Recently, several reports have focused on the potential of DWI to assess the sacroiliac joints, given its ability to detect subchondral bone edema with similar accuracy to fat suppressed contrast-enhanced T1-weighted images^[45]. This may determine the degree of activity in acute sacroiliitis, although with lesser SNR than fat suppressed T2-weighted sequences^[46]. In active sacroiliitis, areas of high signal intensity will be detected on high b value images in the subchondral bone but with higher ADC values than normal bone marrow, reflecting the presence of an inflammatory process. In chronic sacroiliitis, due to fatty changes, the involved joint will show lower signal intensity on high b value images and

lower ADC values than normal bone marrow (Figure 8)^[47].

DWI has also been shown to increase the conspicuity of bone subchondral edema, likely related to a proper suppression of background signal, and thus may increase the specificity of these changes in patients with early SI. Higher ADC values ($0.5-1.5 \times 10^{-3}$ mm²/s) have been found in affected subchondral bone compared with control groups ($0.2-0.6 \times 10^{-3}$ mm²/s)^[48].

Post contrast fat suppression T1-weighted images as well as DCE-MRI have demonstrated its usefulness for SI detection with higher accuracy of the latter for detection of active disease even in the earliest phases^[49].

Rheumatoid arthritis: Rheumatoid arthritis (RA) pathogenesis starts with an autoimmune inflammatory reaction against antigens located at the synovium that usually results in eventual joint destruction. As in SI, MRI has demonstrated to be superior to conventional imaging for detection of RA even in early phases^[2].

Detection and characterization of synovitis and subchondral bone edema are the primary focus of MRI,

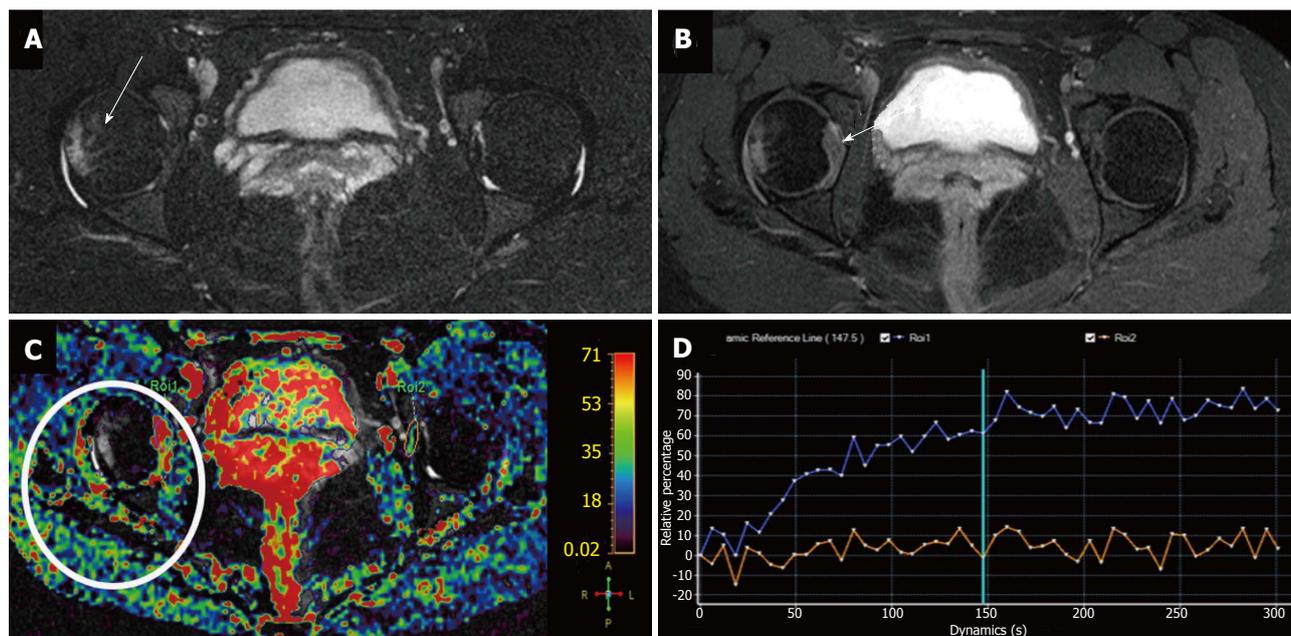


Figure 7 Evaluation of inflammatory arthritis with dynamic-contrast enhanced-magnetic resonance imaging in a 42-year-old woman with rheumatoid arthritis and right hip pain. A: Axial STIR shows mild articular effusion in the right hip with subtle signs of subchondral bone edema (arrow); B: Axial post-gadolinium SPIR GE T1-weighted image demonstrates moderate synovial thickening and enhancement especially at the medial articular surface (arrow); C: Relative enhancement map; D: Dynamic-contrast enhanced-magnetic resonance imaging demonstrate a type I TIC (blue curve) in the right hip, with progressive enhancement, compared to absence of significant enhancement in the contralateral hip (orange curve). This finding helps to confirm the inflammatory involvement of right hip. STIR: Short inversion time recovery.

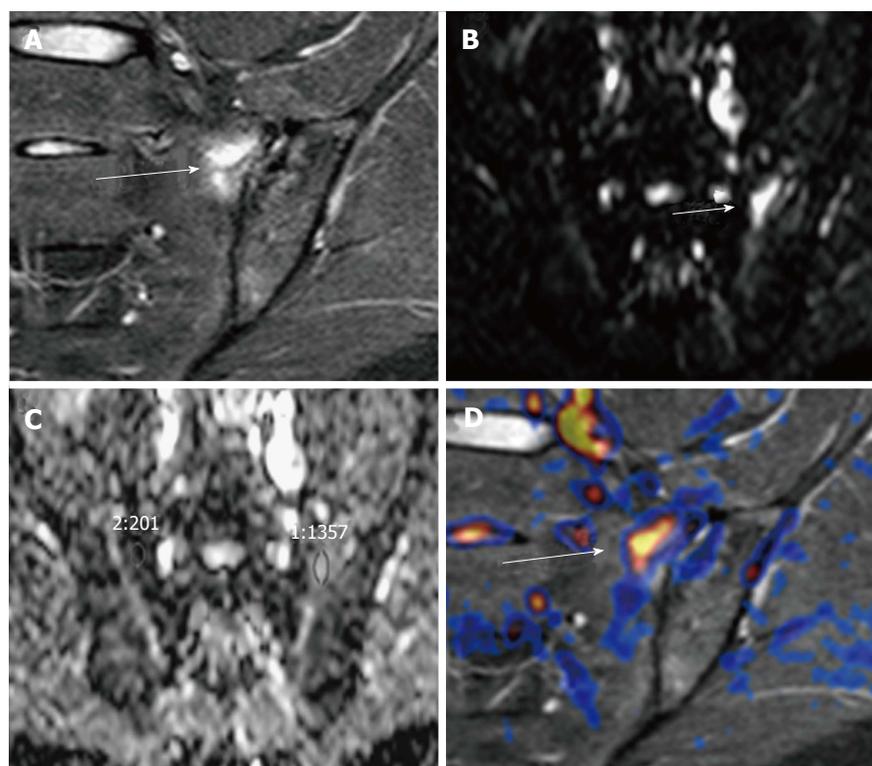


Figure 8 Acute sacroiliitis in a 32-year-old woman with left hip pain. A-C: Coronal STIR shows a focus of subchondral bone edema in the left hemisacrum (arrow, A), which appears hyperintense on (B) high *b* value DWI, with (C) significantly higher ADC values than contralateral bone marrow ($1.3 \times 10^{-3} \text{ mm}^2/\text{s}$ vs $0.2 \times 10^{-3} \text{ mm}^2/\text{s}$); D: Fused DWI and STIR images allow a better depiction of bone edema. STIR: Short inversion time recovery; DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient.

as these features have been demonstrated to be the strongest predictors of early RA and bone erosions,

respectively^[50]. These characteristics have been included in a MRI scoring system for RA evaluation (RAMRIS),

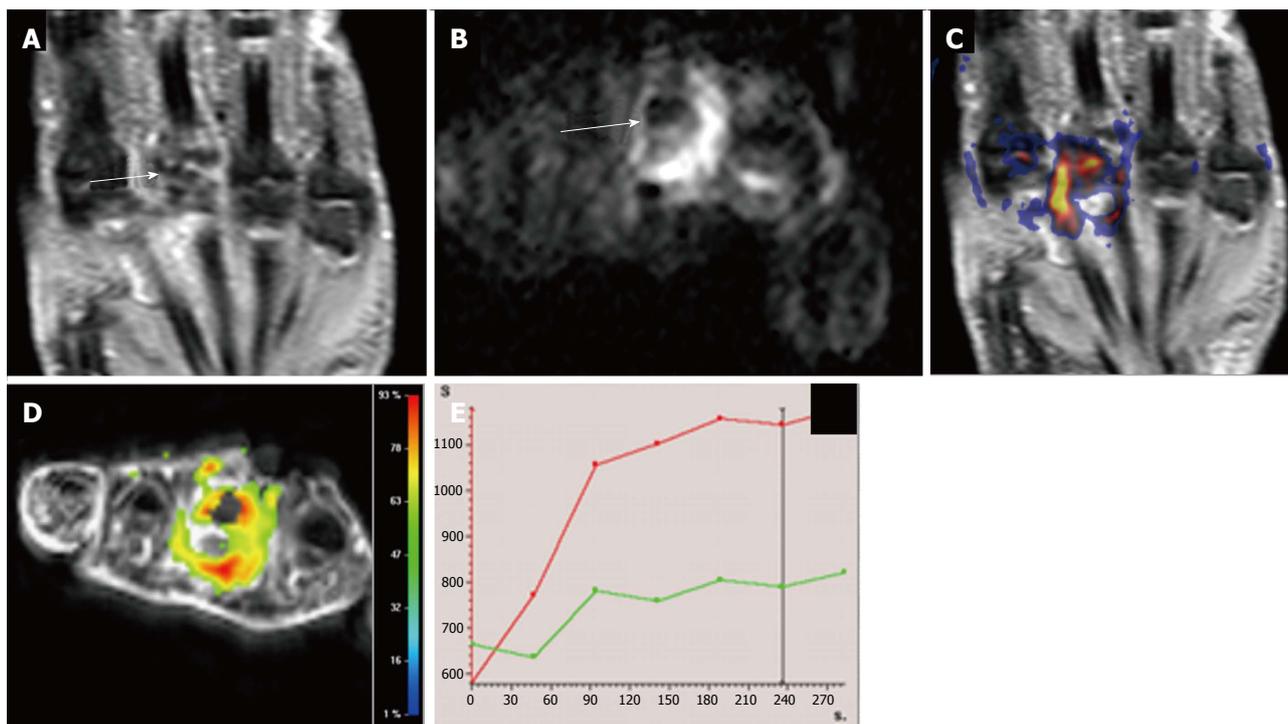


Figure 9 Multiparametric evaluation of rheumatoid arthritis in a 40-year-old woman with hand involvement. A: Coronal STIR shows severe articular surface erosions with subchondral edema and synovial hypertrophy at the 3rd metatarsal-phalangeal joint (arrow); B: Axial DWI b800 demonstrates markedly restricted diffusion within this joint (arrow, B) with good correlation on (C) STIR and DWI b 800 fused image; D, E: (D) DCE-MRI relative enhancement map shows increased enhancement and (E) TIC of the involved joint (red curve) shows an initial fast enhancement which becomes more progressive and slow in late phases in comparison to the adjacent normal joint (green curve). STIR: Short inversion time recovery; DWI: Diffusion-weighted imaging; MRI: Magnetic resonance imaging; DCE: Dynamic contrast enhancement.

as indicator of disease activity^[51]. Fat suppression techniques have improved the ability of MRI for bone edema detection as discussed previously.

Functional sequences like DWI and DCE-MRI have also contributed to the increase in overall accuracy of MRI for RA assessment, providing several quantitative parameters which may be used as biomarkers of RA activity^[2]. DWI has demonstrated a high accuracy for synovitis detection in the wrist and hand, especially in the metacarpophalangeal and proximal phalangeal joints, in patients with RA^[52]. Synovial infiltration by inflammatory cells may affect the mobility of water molecules (Figure 9). Furthermore, the inherent background suppression of surrounding tissues increases the sensitivity and specificity of DWI over other MRI techniques for synovitis and bone edema detection, which have been linked to rapid radiographic progression in patients with early signs of RA^[51,52]. One downside of DWI is the susceptibility to inhomogeneities in the magnetic field and low SNR, limiting its application in assessment of the hands and feet.

The interest of applying DCE-MRI studies for the evaluation of RA, particularly in the assessment of synovitis, is rising nowadays, as it has demonstrated a high correlation with clinical, biochemical, and histological markers of disease activity^[33]. The steepness of the TIC in cases of active disease, usually demonstrating a fast initial enhancement phase and later plateau or washout, better reflects the physiopathological process

behind synovitis than the single use of pre and post-gad T1 sequences. Semi-quantitative parameters such as maximum enhancement (ME) and rate of early enhancement (REE) may be used as potential biomarkers and allow the detection of changes in synovial vasculature before changes in synovial volume or bone edema occur^[53].

Besides clinical and biochemical criteria, DCE-MRI has demonstrated the ability to discriminate between RA and psoriatic arthritis (PA), as previously discussed. A significant difference is in the relative enhancement rate (RER), at delayed acquisition 15 min after gadolinium injection has been reported between both entities. These results are a reflection of histopathology of synovitis in RA which has a higher cellularity and a greater number of recruited vessels compared with PA^[26].

Juvenile idiopathic arthritis: Juvenile idiopathic arthritis has also been successfully evaluated with classical morphological MRI sequences, and more recently with functional imaging with promising results for the assessment of knee, wrist, and hip involvement^[54,55]. DWI has several advantages in the depiction of bone edema and synovitis in young patients, including the lack of ionizing radiation, the ability to assess active and subclinical synovitis in patients with a difficult clinical examination, the identification of high-risk patients, and ultimately, in treatment monitoring^[20].

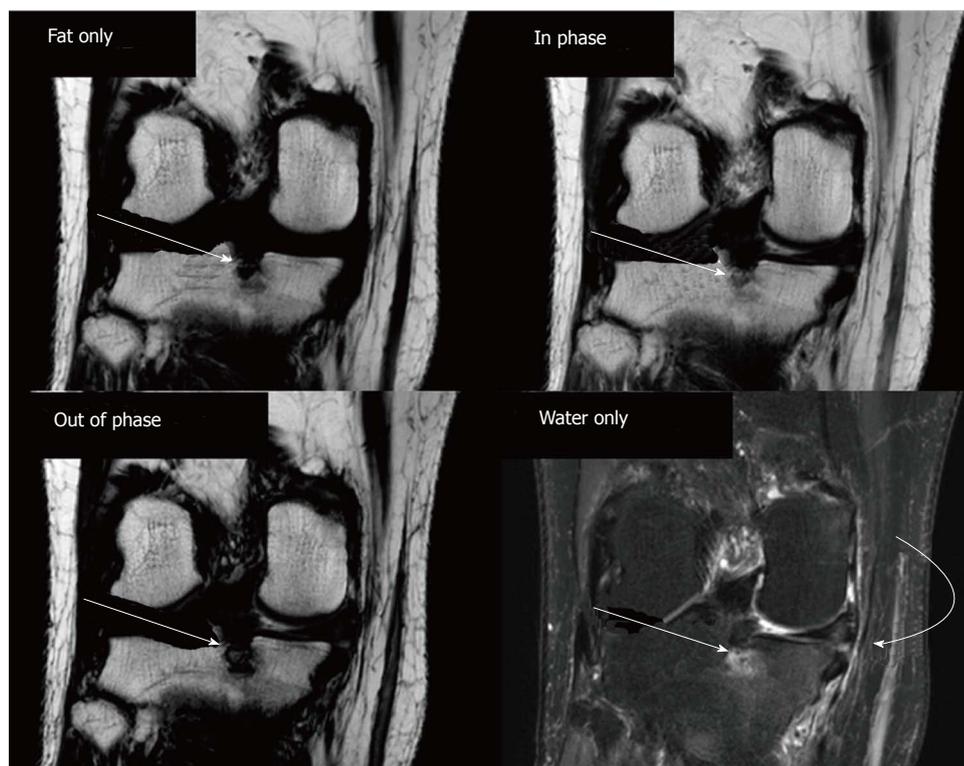


Figure 10 DIXON for evaluation of osteoarthritis in a 56-year-old woman with chronic knee pain. A subchondral geode is identified at the medial aspect of the medial tibial plateau (arrow), which is more conspicuous in the opposed-phase image than in the in-phase image suggesting edematous changes, as confirmed in the water-only acquisition. The water only image also shows soft tissue edema at the body of the medial meniscus and medial collateral ligament (curved arrow).

Finally, DCE-MRI has been proposed as a potential biomarker in children with juvenile idiopathic arthritis and wrist involvement demonstrating an association between clinical active disease and derived-parameters such as maximum relative enhancement^[56].

Osteoarthritis

The active erosive changes that occur in the first phases of osteoarthritis (OA) may be studied by functional MRI sequences. If treatment is introduced in this phase, before reparative changes occur, the course of the disease may be altered enough to avoid joint deformities.

Based on DCE-MRI, differences between RA and OA can be found that reflects the different physiopathology of RA (inflammatory) and OA (degenerative). OA shows higher semi-quantitative (REE) and quantitative (K^{trans} , K^{ep}) values than control subjects, but lower ones than those in RA, likely due to an inferior angiogenic potential and decreased permeability of synovium in OA^[57].

Joint imaging requires multiple planes and several fat-suppression sequences, factors that prolong the total scan time. Some studies have demonstrated that CSI and DIXON techniques, through in-phase and out of phase sequences as well as through the use of water only images, can accurately assess subchondral bone thickness while reducing the scan time (Figure 10)^[58].

Early detection of cartilage damage may allow the treatment of patients with potentially better outcomes than in advanced OA stages^[59]. As previously discussed, T2 mapping techniques are able to detect areas of

elevated T2 values within normal-appearing hyaline cartilage on morphological sequences^[60,61]. In OA, cartilage damage is usually present at high pressure points, unlike in RA and other inflammatory arthritis whereas can be seen at any area of cartilage joint surface^[62].

Therapy monitoring

Functional MRI techniques for joint evaluation can be also used in treatment monitoring. As drugs used for modulation of articular disease progression in SI and other inflammatory arthritis have non-negligible adverse side effects, these advanced MRI sequences may accurately determine the effectiveness of treatment. Normalization of ADC values and signal intensity on DWI is related to proper treatment response, while the presence of high ADC values after treatment may reflect persistence of inflammatory signs^[63]. For example, for SI, DWI has demonstrated the potential to be a tool for therapy monitoring of active sacroiliitis^[47,63,64]. In inflammatory arthritis, the response to steroid and non-steroid anti-inflammatory drugs can be assessed by reduction of angiogenesis in DCE- derived parameters^[65]. In a similar manner, in septic arthritis, DCE-MRI can aid in the assessment of response to antibiotherapy (Figure 11). Parameters derived from pharmacokinetic models, such as K^{trans} and K^{ep} , are also elevated in patients with RA, reflecting the increase in perfusion, extravascular space, and permeability in synovitis. Their reduction after successful treatment provides a mechanism for noninvasive

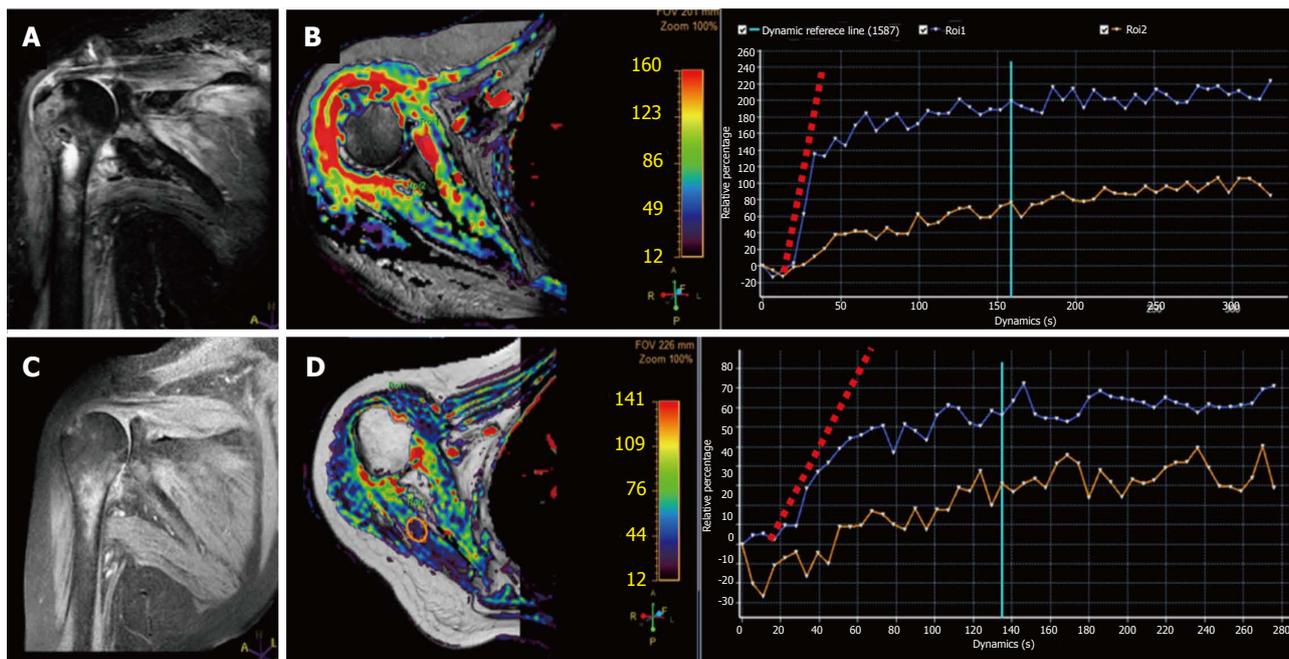


Figure 11 Magnetic resonance follow-up of septic arthritis in a 58-year-old woman with shoulder pain, fever, and swelling. A: Coronal STIR shows severe edema within the proximal humerus as well as in the surrounding soft tissues with minimal intraarticular fluid; B: DCE-MRI relative enhancement map demonstrates extensive enhancement in the synovium and the humeral head; C, D: Follow-up MRI study 3 wk after intravenous antibiotic therapy demonstrates adequate response to treatment with reduction of edema on STIR and enhancement on DCE-MRI. Note also the change in the initial slope of the blue TIC (synovial enhancement) between pre and post-treatment studies. The orange TIC shows healthy muscle contrast enhancement as an internal reference. STIR: Short inversion time recovery; DWI: Diffusion-weighted imaging; MRI: Magnetic resonance imaging; DCE: Dynamic contrast enhancement.

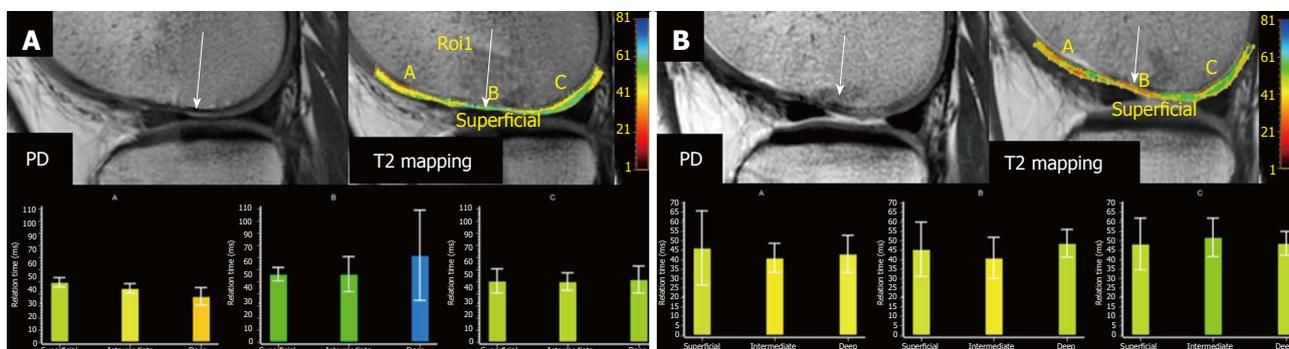


Figure 12 Treatment monitoring with magnetic resonance imaging in a 26-year-old gymnast with knee pain. Initial MRI (A) shows mild cartilage thinning at the medial femoral condyle with subchondral damage PD image. A moderate increase in T2 relaxation values (arrow) confirms the loss of collagen fibers in this area. Patient underwent MTX therapy and a follow-up MRI performed 3 mo later (B) demonstrates moderate chondral irregularity with focal areas of increased signal intensity on PD. T2 mapping demonstrates normalization of T2 relaxation time values compared with the pre-treatment study due to the generation of new fibrous cartilage. MRI: Magnetic resonance imaging; MTX: Microfracturing therapy; PD: Proton-density images.

treatment monitoring^[31]. These parameters also allow for the discrimination between patients with active disease from inactive disease and healthy persons^[66].

In a similar manner, for OA treatment monitoring, new specific drugs and cartilage repairing techniques have been developed trying to slow, or even revert, the progression of OA. Thus, accurate imaging biomarkers that can provide an earlier diagnosis of OA and can detect immediate signs of progression during treatment monitoring are crucial. The effectiveness of these treatments is closely related to their early introduction at the first stages of OA. Surgical techniques in pa-

tient with chondromalacia such as microfracturing therapy (MTX) and matrix autologous chondrocyte transplantation (MACT) are now used in clinical practice, and functional MR sequences may be able to assess the success or failure of the surgical intervention^[67]. T2 values of the repaired tissue after MTX is initially lower than after MACT due to the presence of repairing fibrous cartilage rather than hyaline cartilage (Figure 12). However, during long-term follow-up, T2 values of the repaired cartilage in patients treated with MTX tend to normalize in comparison to the rest of cartilage. If this normalization does not occur, a therapy failure may

be considered^[68].

CONCLUSION

The introduction of MRI for joint evaluation has improved the assessment of arthropathies. However, in many cases, conventional MRI studies are insufficient for a specific diagnosis and limited in their assessment of treatment success. A wide range of advanced MRI techniques are now available in musculoskeletal radiology and can be applied for evaluating arthritis. Technical improvements in fat suppression sequences such as DIXON enable a faster and better detection of bone involvement. DWI and DCE-MRI provide pathophysiological information regarding the cellularity and vascularization of bone and soft tissue in joint diseases, which can aid in determining the specific type of arthritis, the extent of disease, and the success or failure of treatment. T2 mapping allows the evaluation of early cartilage damage before conventional sequences, leading to earlier, and thus potentially more successful, treatment. Integration of these functional techniques within conventional protocols should be considered not only for diagnostic purposes but also for treatment monitoring of arthropathies.

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Mesenchymal stem cells for cartilage regeneration in osteoarthritis

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Abstract

Osteoarthritis (OA) is a slowly progressive disease where cartilage of the synovial joint degenerates. It is most common in the elderly where patients experience pain and reduce physical activity. In combination with lack of conventional treatment, patients are often left with no other choices than arthroplasty. Over the last years, multipotent stromal cells have been used in efforts to treat OA. Mesenchymal stem/progenitor cells (MSCs) are stromal cells that can differentiate into bone, fat, and cartilage cells. They reside within bone marrow and fat. MSCs can also be found in synovial joints where they affect the progression of OA. They can be isolated and proliferated in an incubator before being applied in clinical trials. When it comes to treatment, emphasis has hitherto been on autologous MSCs, but allogenic cells from healthy donors are emerging as another source of the cells. The first adaptations of MSCs revolved in the use of cell-rich matrix, delivered as invasive surgical procedure, which resulted in production of hyaline cartilage and fibrocartilage. However, the demand for less invasive delivery of cells has prompted the use of direct intra-articular injections, wherein a large amount of suspended cells are implanted in the cartilage defect.

Key words: Intra-articular injection; Mesenchymal stem cells; Osteoarthritis; Regeneration; Cartilage

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Core tip: There are several published reviews of the role of multipotent stromal cells in osteoarthritis (OA) of the knee. However, there is also need for additional current therapeutic options and clinical trials of multipotent stromal cells for OA. We review additional therapeutic potentials of mesenchymal stem cells in knee OA using either autogenous or allogenic cells. Direct intra-articular injections of cells in suspension become a delivery method, being both relatively simple and cost effective compared to major surgical procedures. The amount of

cells injected is a critical factor; higher numbers of cells resulting in greater pain reduction and increased cartilage volume.

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INTRODUCTION

Increases in life expectancies and an ageing population results in rise of chronic and degenerative diseases which are becoming a major public health concern. Osteoarthritis (OA) is characterized by degeneration of articular cartilage, leading to articular cartilage damage, subchondral cysts, joint space narrowing, subchondral sclerosis, osteophyte formation at the joint margin, and synovitis^[1]. Known risk factors include advancing age, genetics, obesity, mechanical stress and joint trauma^[2]. Predominantly occurring in the elderly, OA can afflict any joints even nonweight-bearing ones. Major weight-bearing joints or joints under repetitive stress, including hands, hips and knees are in particular risk of developing OA^[3]. Conservative treatment options do not stop the onset of OA and are mainly focused on pain control. They include physiotherapy, rehabilitation, pain relief with acetaminophen and non-steroidal anti-inflammatory agents, as well as intra-articular injection of hyaluronic acid (IA-HA). Although these therapeutic strategies may be helpful in reducing symptoms, they are no longer considered effective. Due to lack of compelling medical treatments, advance-stage OA patients often undergo total joint arthroplasty. Surgical procedures come with risks of failure and infection as well as the cost of hospital care, physiotherapy, and rehabilitation. The lack of conventional treatment, combined with risks and high costs of joint replacement surgery has driven researchers towards application of multipotent stromal cells for the repair of full thickness articular cartilage.

Mesenchymal stem/progenitor cells (MSCs) are multipotent stromal cells first identified and described in 1966 by Alexander Fridenstein^[4]. MSCs from bone marrow (BM) have been demonstrated to exhibit differentiation potentials for mesodermal cell lineage, including osteo-, adipo-, chondro- and myogenic potentials^[5]. MSCs are partly responsible for the maintenance and healing of connective tissues and Karp *et al*^[6] indicated that MSCs could migrate from their reservoirs following tissue injury or inflammation.

MSCs are adult stem cells present in various parts of our body, for instance BM, peripheral blood, umbilical cord blood, fatty tissues, skeletal and cardiac muscles, Wharton's Jelly of umbilical cord, facet joints, interspinous ligaments, and ligamentum flavum^[7-10].

They are primarily isolated from the BM, with major harvesting sites being the iliac crest, tibia and femur. MSCs are then separated from the rest of the marrow cells and expanded to obtain sufficient amounts. Adipose tissues are also rich in MSCs, even more so than BM with up to 1000 times more MSCs per gram of fatty tissues contrasted with that of BM^[11]. Therefore, a sufficient amount of cells can be obtained from adipose tissues without the need of culture expansion, resulting in minimum manipulation of cells. MSCs grown under standard culture conditions feature a fibroblast like phenotype, exhibit plastic adherent property and are capable of giving rise to a cell colony derived from a single cells called colony-forming fibroblast unit^[12], nonetheless only a fraction of the population remains clonogenic. The plasticity of MSCs has made them a promising candidate for various tissue engineering applications to treat several diseases including immune-mediated disorders, genetic abnormalities, and OA^[13].

The publications reviewed here were collected manually from NCBI PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) from 1966 until December 2016. The following keywords or combination of keywords were used in the search engine to achieve the articles presented in this review: MSCs, OA, intra-articular injection, tissue engineering, and regeneration. Initial selection was done by screening titles and abstracts. No special screening process was applied, even though restrictions were utilized to select exclusively human investigation and the English language. Preference was given to clinical studies. Articles featuring pioneering methods or vast improvements of existing methods according to the author opinions were selected for this review. Figure 1 illustrates the flowchart and the assortment step.

MSCs AND OA

Synovial joints consist of number of different tissues and MSCs have been isolated from most of them although their functions within the joints are not yet fully understood. It has been suggested that they act as a source of cells which are able to be stimulated for the repair and reconstruction or regeneration of the joints. Moreover, they might also be involved in the suppression of T-cells to reduce inflammation within the joint^[14]. Although chondrocytes are the predominant cell type within cartilage, MSCs have also been found to have no capability for cartilage regeneration after articular cartilage damage. Since MSCs are progenitors of young and mature chondrocytes, chondrogenic progenitor cells may help restore the superficial zone with lubricating glycoprotein to lessen friction in the articular cartilage (Figure 2)^[15].

Murphy *et al*^[16] revealed that MSCs isolated from end-stage OA patients showed impaired differentiation capacity as well as reduced proliferation activity *in vitro*. They compared BM-derived MSCs (BMSCs) from patients who underwent total knee arthroplasty

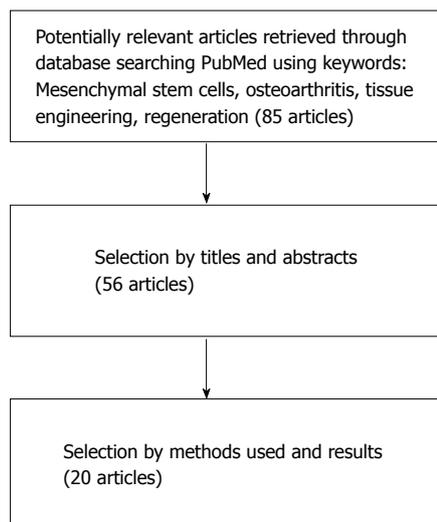


Figure 1 Flow chart representing the search and selection of articles for review.

(TKA) with cells isolated from healthy individuals. They reported that a significantly lower amount of MSCs could be isolated from OA patients and that they had reduced proliferation activity. Interestingly, they also observed the MSCs having altered differentiation profiles, favouring osteogenic differentiation, whilst having reduced adipogenic and chondrogenic potentials. Another study found that patients' age and stage of OA also affected the differentiation capability and expression of stemness genes of localized adipose-derived MSCs^[17]. More shockingly, recent study reported that synovial fluid from OA patients inhibited the *in vitro* chondrogenic differentiation in MSC cultures of healthy donors^[18]. Albeit, these functional deficiencies can be ameliorated by culture media supplementation with growth factors^[19].

CELL BASED THERAPIES FOR CARTILAGE REPAIR

Cell based tissue engineering for OA have been used with varying results for over two decades. Autologous chondrocyte implantation (ACI) is a cell based technology wherein the cultured chondrocytes are applied on the injured area for regenerating and repairing cartilage^[20]. This method has evinced promising outcomes in subjects with a variety of articular cartilage lesions that had responded poorly to prior treatments. However, the results have been conflicting^[21] and the self-renewal rate and activity of chondrocytes is low, leading to slow an inadequate healing. Additionally, arthroscopy is required to obtain healthy cartilage from unaffected non-weight bearing joints and implanted during an open knee surgery, resulting in high costs, morbidity at donor sites and increased stress for patients. Reductions in pain, improvements in the joint function and the formation of functional hyaline cartilage have all been reported. The

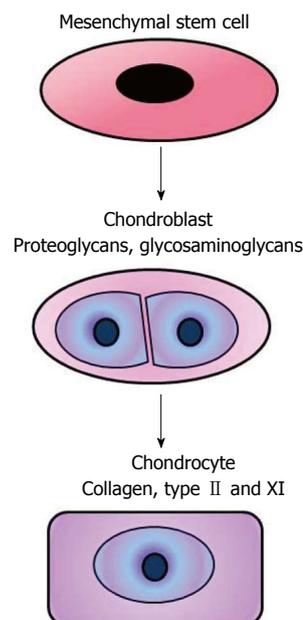


Figure 2 The way in which mesenchymal stem cells contribute to cartilage repair still remains unknown. Paracrine signalling and chondrogenic differentiation most likely play a crucial role.

destruction of articular cartilage is irreversible in OA and does not relieve symptoms. Patients are often left with no other choice than total joint replacement. Consequently, autologous chondrocyte implantation may not be a favourable surgical procedure for subjects with OA. In addition, this method faces challenges with cartilage tissues having a limited capacity for repair. Accordingly, MSCs are emerging as a potential substitute or alternate cellular materials for more durable treatment of cartilage defects.

MICROFRACTURE AND MSCs

Microfracture is a well-established and studied surgery technique that stimulates migration of cells from the BM to cartilage lesions. Small holes are drilled at the target site into the subchondral BM which then bleeds into the lesion and forms a clot of marrow cells, including BMSCs^[22]. This technique has given good results on small lesions but comes with limitations. BMSCs are only a portion of total cells within the BM and a relatively few BMSCs are recruited through microfracture being inadequate treatment for bigger cartilage lesions. Researchers have focused on isolating and expanding cells before applying them to the target area and a number of studies illustrated successful BMSC treatment for repairing focal chondral defects. Knowledge on MSC extraction, chondrogenic capacity, and tissue engineering has encouraged scientists and surgeons to test clinical potentials of MSCs to stop and reverse onset of OA, as well using their plastic adherent ability to resurface large cartilage lesions and facilitate osteochondral integration within the affected joints (Figure 3).

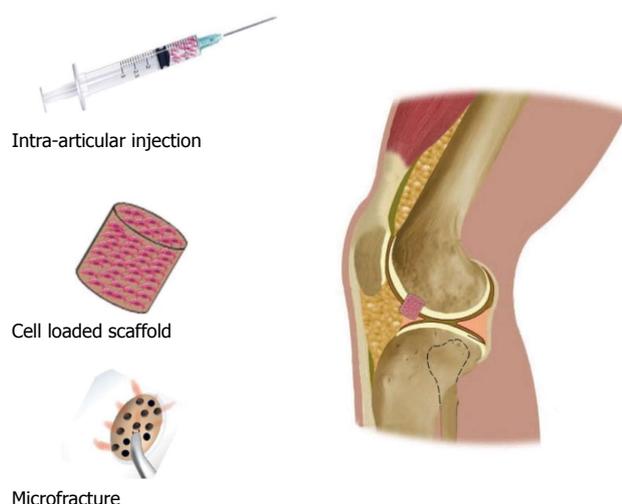


Figure 3 There are 3 major methods in which mesenchymal stem cells can be applied: Intra-articular injection of mesenchymal stem cell suspension, implantation of cell-mixed composite scaffold, and microfracture through articular cartilage and subchondral bone.

Buda *et al.*^[23] established a one-step surgical procedure which employs BMSCs to heal osteochondral lesions of the knee. The procedure was completed in a single setting where BM aspiration and concentration were accomplished in the same operating room as knee arthroscopy. The BM aspirate concentrate was fixed in hyaluronic acid blended membranes before being transplanted to the site where it was applied with autogenous platelet-rich-fibrin glue, providing growth factors to further stimulate the healing process. All of the patients treated with this technique showed significant improvements for parameters measuring the severity of OA and pain scores. Moreover, magnetic resonance imaging (MRI) showed that the cartilage lesion was fully covered in at least 70% of the subjects. This method was both feasible and effective for treating most of the patients enrolled and the whole process could be completed within a day. Furthermore, it did not require any cell expansion or manipulation, reducing costs and risks involved. Nevertheless, as only a fraction of BM cells are MSCs, one may speculate that the quantity of MSCs recruited this way was somewhat unsatisfactory. Another major contributing factor might have been growth factors embedded in the platelet-rich-fibrin glue produced from the peripheral blood of the subjects. Gobbi *et al.*^[24,25] reported a similar “one-step cartilage repair” technique in 2011 and 2014. The advantage of the one-step approach is that it only requires one surgery and it involves no long-term cell expansion, resulting in fewer visits to the clinic. However, it is nearly impossible to estimate the number of MSCs recruited in this process making standardized treatment with reproducible results challenging.

INTRA-ARTICULAR INJECTION OF MSCs

In 2008, Centeno *et al.*^[26,27] reported two male patients

with knee OA. MSCs were harvested from the posterior superior iliac spine and simultaneously venous blood was harvested to prepare platelet lysate (PL) containing growth factors to facilitate the repair. The first subject received an injection of one milliliter of phosphate-buffered saline (PBS) consisting of 2.2×10^7 MSCs. The second subject received 4.6×10^7 MSCs suspended in one milliliter PBS. Both cases then received one milliliter of 10% PL in PBS one and 2 wk after the initial injections. Additionally, after one week, the subjects obtained intra-articular injection of dexamethasone as low-dose dexamethasone treatment has been demonstrated to stimulate chondrogenic differentiation^[12]. Modified visual analogue scale (VAS) scores have been utilized to estimate pain followed by MRI to evaluate cartilage volume. Both subjects showed improvements in VAS scores and cartilage volume following 3 and 6 mo follow-up with up to 28.6% cartilage volume increase. While a decrease was also observed in the latter patient, it was not considered significant since it was below the measurement error. These studies revealed that increased cartilage volume and reduction in pain could be achieved with minimum invasive measures and is a promising treatment for OA. However, a major weakness in these cases was the short follow up time consisting of 6 mo for the first and 3 mo for the second patient. Besides, long-term follow-up results are unavailable.

In recent years, Wong *et al.*^[28] examined the outcomes of BMSC injection following a microfracture and medial opening-wedge high tibial osteotomy (HTO). The study was a randomised controlled trial that included 56 patients with unicompartmental osteoarthritic knees. The participants were classified into two groups, all received HTO combined with microfracture, and 3 wk later the intervention group received an intra-articular injection of 1.5×10^7 autologous BMSCs suspended in hyaluronic acid, while the control group obtained exclusively hyaluronic acid. The observed time spanned two years, during which both groups showed improvements in the International Knee Documentation Committee scores as well as Tegner and Lysholm scores. Interestingly, the intervention group showed significantly better improvements in all parameters. Moreover, MRI performed 1 year following injections, found cartilage thickness to be significantly greater in the intervention group. In this study, MSCs were recruited for cartilage repair by two means, such as microfracture in both groups and intra-articular injections in the intervention group. In conclusion, the postoperative injection of cultured expanded MSCs, significantly improved the treatment outcome and rate of cartilage regeneration. Additionally, the MSCs could be collected during operation and proliferated in culture to achieve sufficient numbers before the patients return to the hospital. Although microfracture and HTO are an effective means to treat OA, they are still major surgical procedures with high cost and risk.

Table 1 Summary of studies using mesenchymal stem cells for cartilage regeneration in osteoarthritis

Ref.	Type of study	Type of cells	Significance
Wakitani <i>et al</i> ^[33]	Case and control study	Autologous BMSCs from Iliac crest	Autologous BMSCs cell implants are effective for treating OA cartilage defects in humans, producing hyaline like cartilage
Centeno <i>et al</i> ^[26]	Case study	Autologous BMSCs from Iliac crest	Autologous BMSCs can be introduced by intra-articular injections into an osteoarthritic knee promotes cartilage regeneration and reduction pain
Buda <i>et al</i> ^[23]	Case series	Autologous BMSCs from Iliac crest	One-step repair technique utilising bone-marrow concentrate is a simple and time-efficient way to treat large chondral defects
Koh <i>et al</i> ^[34]	Case and control study	Autologous AMSCs from infrapatellar fat pad	Intra-articular injections of AMSCs are a safe treatment option, reducing pain and improving the function of knee OA patients
Wong <i>et al</i> ^[28]	Randomized control trial	Autologous BMSCs from Iliac crest	Postoperative intra-articular injections of autologous BMSCs improves the MOCART outcomes of patients with varus knees undergoing HTO and microfracture
Vangsness <i>et al</i> ^[30]	Randomized, double-blind, controlled study	Allogenic BMSCs from 18-30 years old donors	Postoperative intra-articular injections of allogenic BMSCs contribute to meniscus regeneration and reduction in pain following medial meniscectomy
Jo <i>et al</i> ^[29]	Cohort study	Autologous AMSCs from abdominal subcutaneous fats	Cartilage regeneration and pain reduction is significantly improved when high amounts of AMSCs are injected into OA knees compared with low amounts
Sekiya <i>et al</i> ^[35]	Therapeutic study	Autologous synovial MSCs	Localized synovial MSCs can be used to treat cartilage defects resulting in hyaline like cartilage and improved pain scores

AMSCs: Adipose-derived MSCs; BMSCs: Bone marrow-derived MSCs; HTO: High tibial osteotomy; MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue; MSCs: Mesenchymal stem cells; OA: Osteoarthritis.

DETERMINATION OF THE OPTIMAL DOSE

In 2014, Jo *et al*^[29] investigated the dose effects of MSCs in OA treatment. Their phases I/II clinical trial consisted of 18 patients suffering from knee OA who received injections of adipose-derived MSCs. In phase I, patients were divided into 3 groups receiving either low dose (1.0×10^7), mid dose (5.0×10^7) or high dose (1.0×10^8) injections of MSCs. Whereas in phase II, the high dose treatment was given to 9 patients. The MSCs were harvested from abdominal subcutaneous fats *via* liposuction before being suspended in 3 mL of saline and injected into the knee joints. During the 6 mo follow up period, the high dose group showed a significant reductions in Western Ontario and McMaster Universities Arthritis Index scores, VAS pain scores and improvements were also observed in the low and mid dose groups. Although, pain improvements were observed in the low dose group, the size of the cartilage defect increased, whereas in the mid and high dose groups it showed significant reduction in size. Arthroscopy and histological staining further revealed the presence of hyaline-like cartilage covering the site in the high dose group. No adverse effects were observed during the follow-up time and the researchers concluded that the high dose treatment reduced pain, was safe and improved the knees function by forming hyaline-like cartilage.

ALLOGENIC MSCs FOR TREATMENT

The first randomised, double blinded control study was reported in 2014 when Vangsness *et al*^[30] treated 55 patients with allogenic MSCs. Furthermore, it was the first study investigating the safety, effectiveness and

clinical outcome of intra-articular injections of non-matched human leukocyte antigen (HLA) allogenic BMSCs. Patients were blindly divided into 3 groups, and all groups underwent partial medial meniscectomy. Afterwards, group A received 5.0×10^7 cells and group B 1.5×10^8 cells in 5 mL injections of HA, whereas the control group received only HA. Patients were evaluated before and 2 years post-treatment using MRI to measure cartilage volume and VAS scores for measuring level of pain. The MRI revealed a significant increase in cartilage volume, with group A showing the best outcome. Pain reduction was observed for groups A and B, whilst no pain reduction was recorded in the control group. Even though cartilage growth was not observed in all patients, the study confirmed the effectiveness and safety of using non-matched HLA allogenic BMSCs. Several reports have since demonstrated the successful treatment of cartilage regeneration using MSCs in OA (Table 1). Recent evidences have highlighted the importance of MSCs from development to postnatal joint homeostasis and OA^[31]. Possible mechanisms of MSCs in the treatment of OA may be attributed to the ability of MSCs to initiate the repair process by promoting cartilage regeneration^[32]. Further research efforts will be needed to better understand the exact role of MSCs in the treatment of OA.

CONCLUSION

In summary, these studies show that MSCs can be employed successfully to treat mild to moderate OA through various ways. They provide alternative treatment options and treatment can start early during progression of OA. The traditional major surgeries used to treat late stages are expensive and come with risks. The less invasive techniques outlined in this minireview

have revealed good outcomes, but the field merits further investigation. Superior outcome was evident with greater quantity of MSCs injected. Allogenic cells from healthy young donors can also be utilized. These findings have further empowered researchers to investigate the potentials of MSCs for tissue engineering and a number of clinical trials are now underway. Most of the emphasis on minimally invasive therapeutic alternatives including intraarticular injections of MSCs, aim to cut out cost and risks of major surgeries. Additional investigations are warranted to validate the safety and efficiency of different application before a standardized treatment regimen can be established.

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Basic Study

Electron probe microanalysis of experimentally stimulated osteoarthritis in dogs

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Abstract**AIM**

To develop methods of articular cartilage preparation for X-ray-electron probe microanalysis and to study its elements content in experimental osteoarthritis.

METHODS

Twenty dogs aged 2-8 years were divided in research (aged 2 years, induction of osteoarthritis - IOA) and intact group. Intact group included three subgroups (aged 2, 5 and 8 years). Samples of cartilage after araldite saturation and pouring were partially cut into semithin sections stained with methylene blue and with methylene blue-basic fuchsin. Their smooth surfaces were investigated by X-ray-electron probe microanalysis. Spatial distribution of sulfur, calcium and phosphorus and their concentrations (weight %) were investigated.

RESULTS

X-ray electron probe microanalysis revealed non-uniform

sulfur distribution in cartilage of intact animals: Its content increases from superficial zone to deep one, this regularity was preserved in animals with IOA. Differences of IOA with spontaneous chondropathy were revealed. Spontaneous aging was characterized by calcium and phosphorus storage in deep and calcified zones and compensatory increase of sulfated glycosaminoglycans in intermediate and deep cartilage zones as evidenced by the metachromatic reaction and microanalysis data. Unlike spontaneous chondropathy connected with aging in experimentally stimulated osteoarthritis more intensive storage of calcium but minor phosphorus in intermediate zone were marked. In IOA the calcified cartilage thinning and osteoclastic resorption are apparent with few changes of elements composition; the only difference from control is minority phosphorus content.

CONCLUSION

The obtained results demonstrate specific tricks of X-ray electron probe microanalysis and its possibility in the research of mechanisms of articular cartilage alterations in osteoarthritis.

Key words: Osteoarthritis; Articular cartilage; Dog; X-ray electron probe microanalysis

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Core tip: In this basic study we present the development of methods of articular cartilage preparation for X-ray-electron probe microanalysis and elements content in articular cartilage in animal experimentally induced (IOA) osteoarthritis and during spontaneous animal aging (SA). SA was characterized by calcium and phosphorus storage in deep and calcified articular cartilage zones and compensatory increase of sulfated glycosaminoglycans in intermediate and deep zones. In IOA more intensive storage of calcium but few phosphorus in intermediate zone were marked. As for Sulphur content, all zones of uncalcified cartilage in two-year-old animals with IOA were comparable with cartilage of five-year-old intact animals.

Stupina T, Shchudlo M, Stepanov M. Electron probe microanalysis of experimentally stimulated osteoarthritis in dogs. *World J Orthop* 2017; 8(9): 681-687 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i9/681.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i9.681>

INTRODUCTION

Osteoarthritis (OA) has great social impact in terms of disability, pain, illness and treatment costs. Pathogenesis of OA involves the structures of the whole joint especially subchondral bone and synovium but is characterized predominantly by articular cartilage destruction^[1]. Cartilaginous tissues possess relatively few amounts cells

(chondrocytes) that account 1%-5% of volume^[2] and large amounts of extracellular matrix that constitutes the bulk of tissue and protects chondrocytes from mechanical overloading.

Cartilage destruction in osteoarthritis is multifactorial cascade process in which participate both cells and extracellular matrix, especially sulfated glycosaminoglycans. These last are included in proteoglycans and play the leading role in support of tissue homeostasis, architectonics and mechanical stability, cellular mitogenic activity, receptive functions and intercellular relations^[3].

Mineralization of cartilage has been associated with OA progression and cartilage destruction^[4] but some authors consider it as primarily an effect of aging^[5].

A lot of biochemical and microscopical methods are used in modern researches of cartilage content and structure but X-ray-microprobe analysis was performed very rare though it permit to evaluate glycosaminoglycans and mineral content by corresponding chemical elements.

To develop the optimal methods of articular hyaline cartilage sample preparation for X-ray-electron probe microanalysis and to compare its elements content in intact animals and in animals with experimentally induced osteoarthritis.

MATERIALS AND METHODS

Twenty healthy adult mongrel dogs of either sex, aged 2-8 years, weighing 18-25 kg, were used in this study. All animals have received human care in compliance with the protocol approved by the Institutional Ethical Committee. The animals were acclimatized to laboratory conditions for one month prior experimentation. Dogs were housed in individual cages (floor area 4.5 m²) and were provided water three times daily and food two times daily with a measured volume. Animals were divided in research (aged 2 years) and intact group (control). Intact group included three subgroups (aged 2, 5 and 8 years). In research group modelling of primary gonarthrosis was performed by reduction of limb blood supply and knee immobilization^[6]. So, dogs of research group were operated. Anesthesia was first induced with intramuscular injections of atropine, dimedrol and xylazine and then maintained with intravenous injection sodium pentobarbital (30 mg/kg *i.v.*). Briefly, each femoral artery was freed from surrounding tissues and after proximal and distal ligation was resected. Each knee joint were immobilized with external fixation apparatus. After 28 d of immobilization dogs of research group were euthanized. Dogs of intact group were also euthanized by barbiturate overdose (intravenous injection, 150 mg/kg pentobarbital sodium) for tissue collection.

Samples of cartilage were harvested from lateral femoral condyles - presented in Figure 1A. Samples consisted of slices 2-3 mm thick, 5-6 mm long and 2-3 mm wide were cut with a scalpel tangentially within

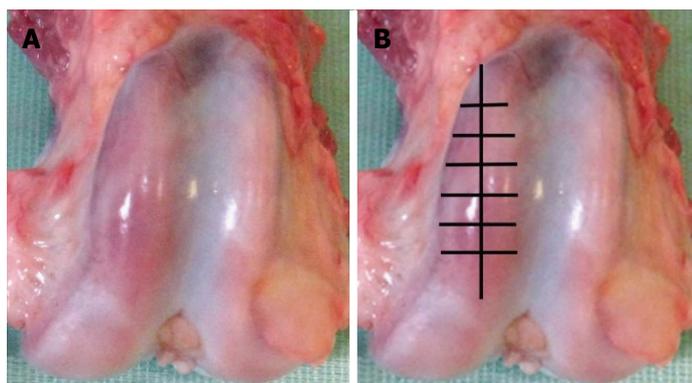


Figure 1 Condyles of canine thigh bone after experimental modelling of osteoarthritis (A), scheme of articular cartilage harvesting (B).

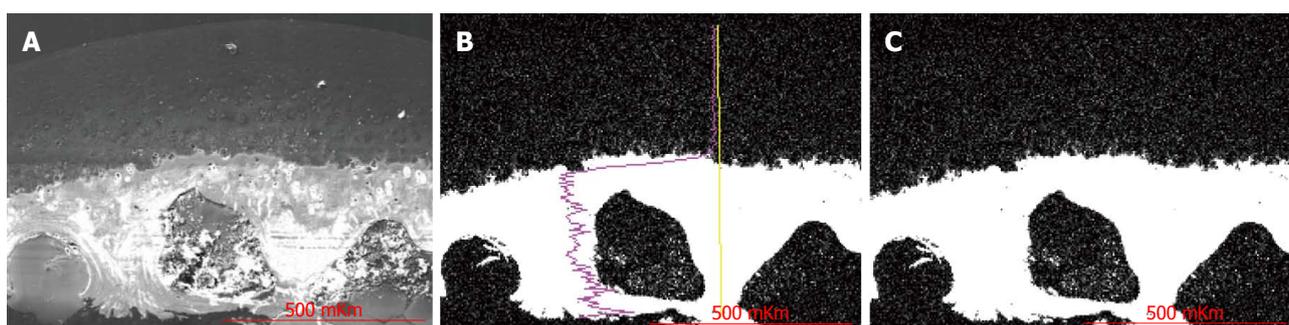


Figure 2 X-ray electron probe microanalysis of articular cartilage in intact dog. A: SEM micrograph of articular cartilage and subchondral zone; B: Scanning line regimen, graph shows calcium distribution on line; C: Scanning area regimen shows calcium distribution on the sample surface. Instrumental magnification $\times 110$.

articular cartilage - presented in Figure 1B. Samples were fixed in glutaraldehyde-paraformaldehyde mixture excluding postfixation in tetraoxide osmium because X-ray peaks of heavy metals may mask and overlap on rays of analyzed elements^[7,8]. Taking into consideration very high water content in cartilage^[2] the specimens were dehydrated with smooth transition from ethanol to acetone according to known methods^[9] but with increasing of exposition in 70%-96% ethanol to within the hour. Stages of araldite saturation and pouring were performed according to recently described method^[10]. Increased density of cartilage matrix in araldite in comparison with native material decrease volume of X-ray excitation and provide the increase of microanalysis sensitivity.

Further investigation included two stages. At the first stage epoxy blocks were partially cut into semithin (1 μm) sections with a glass knife using ultramicrotome "Nova" (LKB, Sweden). Slices were stained with methylene blue (metachromatic reaction for sulfated glycosaminoglycans) and with methylene blue-basic fuchsin (for detection of matrix basophilia). Histology slides were examined using the "Opton-3" photomicroscope (Germany).

At the second stage smooth surfaces of epoxy blocks resulting from semithin slices cutting were investigated by X-ray-electron probe microanalysis. This technique prevents artifacts and saves the sample preparation time excluding the stage of grinding and polishing.

Three blocks was selected randomly from each animal. They were attached to polished clean aluminium

discs with current-conducting adhesive. Surfaces of epoxy blocks were exposed to silver deposition using Eico IB-6 ion coater and JEOL JEE-4X vacuum evaporator. The investigation of element composition was performed using scanning electron microscope JSM-840 (JEOL, Japan) equipped with energy dispersive X-ray analyser (INCA 200, Oxford Instruments).

Results were obtained as smart maps, showing spatial distribution of elements and quantitative data in weight per cents. Spatial distribution of sulfur, calcium and phosphorus and their concentrations (ωS , ωCa , ωP - weight %) were investigated. For standard results equipment was calibrated by comparison templet made of wollastonite ($\text{CaO} : \text{SiO}_2$). Two regimens were used for collecting X-ray spectra: Scanning line and scanning area - presented in Figure 2. In the second regimen strict longitudinal alignment of parallel scanning rows without overlapping fields provided the most representative total sample.

Statistical analysis

For quantitative data analysis the unpaired Student *t* test and Mann-Whitney *U* test were used (software package Attestat Program, version 9.3.1, developed by I.P. Gaidyshev, Certificate of Rospatent official registration No. 2002611109). If the *P*-value was less than 0.05, the data was considered statistically significant.

RESULTS

In 2 years-aged intact group metachromatic reaction in

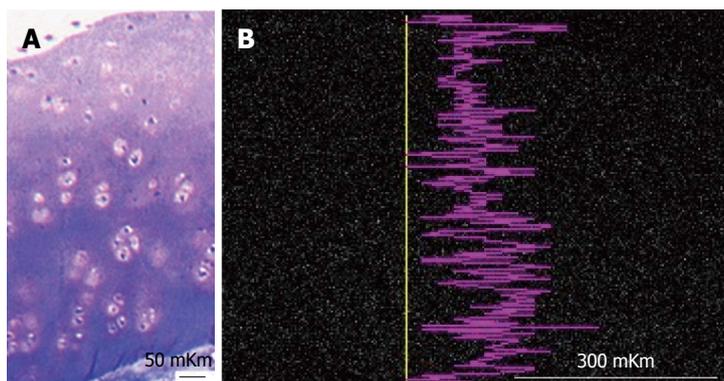


Figure 3 Articular cartilage of intact dog. A: Semithin section, methylene blue stain. Ob. -6.3 x; oc. -12.5 x; B: Smart map shows sulphur distribution on scanned line. Instrumental magnification 170.

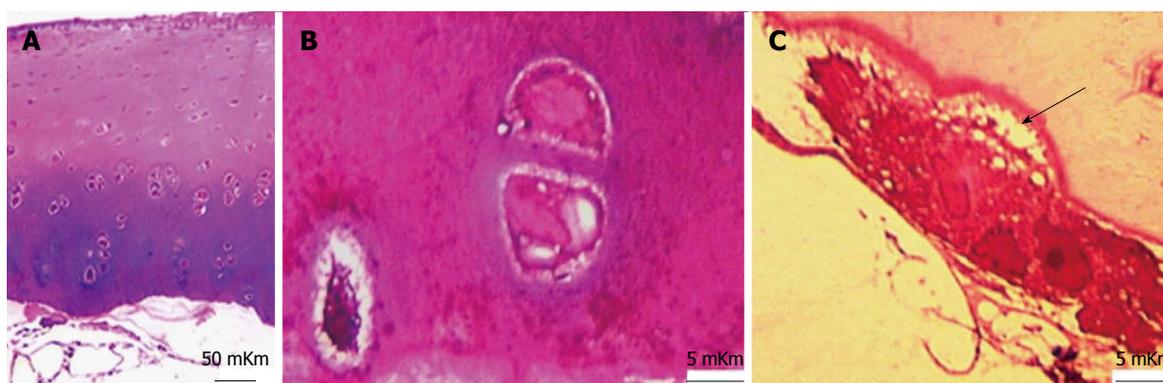


Figure 4 Articular cartilage in dog with experimentally induced osteoarthritis. Methylene blue - basic fuchsin staining. A: General appearance. Ob. - 6.3 x, oc. - 12.5 x; B: Focal basophilia of intercellular matrix in deep zone. Ob. - 100 Ol, oc. - 12.5 x; C: Osteoclast, resorbing the ground substance of calcified cartilage. Howship lacuna (arrow). Ob. - 100 Ol, oc. - 12.5 x.

interterritorial matrix of superficial zone was moderate but in territorial matrix of intermediate and deep zones it was highly intensive - presented in Figure 3A. X-ray electron probe microanalysis revealed nonuniformity of Sulphur zonal distribution - presented in Figure 3B.

In IOA (induced osteoarthritis) group metachromatic reaction was localized, its intensity was lowered and accompanied with fibrillation of matrix in superficial zone. Intensively basophilic matrix was revealed in intermediate and deep zones and presented in Figure 4A and B. The calcified cartilage zone was thinned or absolutely absent in some areas (Figures 4A and 5). At the borderline between calcified cartilage and subchondral bone the osteoclastic resorption was marked - presented in Figure 4C.

In 5 years-aged intact group histochemical reaction for sulfated glycosaminoglycans was weak, metachromasy was focal (Figure 6A), matrix of superficial zone was basophilic, many of cells had signs of destruction.

In 8 years-aged intact group metachromatic reaction was also focal, locuses of intensive metachromasy were revealed in intermediate and deep zones (Figure 6B), cartilaginous cells had increased sizes, light homogeneous nuclei and basophilic cytoplasm. Territorial matrix of deep zone was basophilic.

In IOA group ω S were decreased in all of cartilage zones besides calcified, but its distribution with maximal

meanings in intermediate and deep zones was the same as in two-year-old intact group. In five-year-old intact group in comparison with two-year-old intact group ω S was decreased in superficial, intermediate and deep zones, but increased in calcified cartilage. In eight-year-old intact group in comparison with two-year-old intact group ω S was increased in intermediate, deep and calcified cartilage zones, but not in superficial zone - presented in Table 1.

In IOA group in comparison with two-year-old intact group ω Ca was increased in all zones of cartilage besides the calcified. In five-year-old intact group ω Ca was increased only in superficial zone and in calcified cartilage. In eight-year-old intact group more expressed increase in deep and calcified zones were marked (Table 1).

Changes of ω P were differently directed. In IOA it was increased in intermediate and deep zones but decreased in calcified cartilage. In 5 years-aged and especially in 8 years-aged intact groups ω P was increased in all zones including calcified cartilage - presented in Figure 7 and Table 1.

DISCUSSION

So, X-ray electron probe microanalysis revealed non-uniform serum distribution in cartilage of intact animals: its content increases from superficial to deep zone,

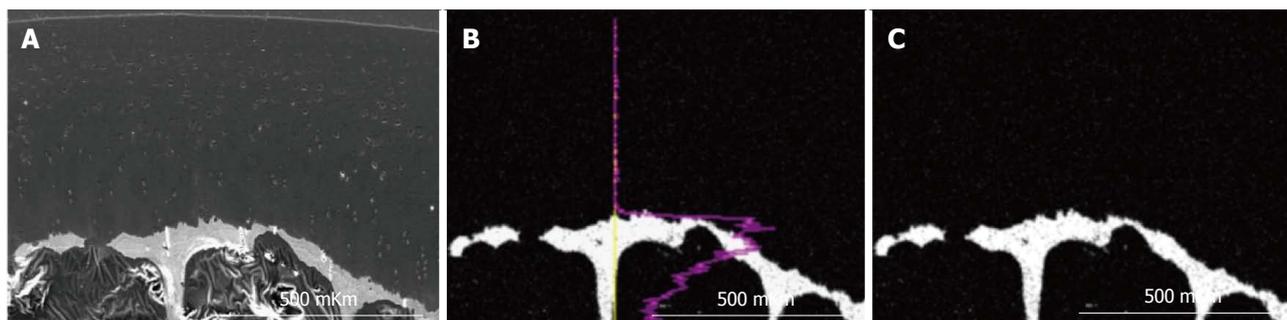


Figure 5 X-ray electron probe microanalysis of articular cartilage in dog with experimentally induced osteoarthritis. A: SEM micrograph of articular cartilage and subchondral zone; B: Scanning line regimen, graph shows calcium distribution on line; C: Scanning area regimen shows calcium distribution on the sample surface. Instrumental magnification 100.

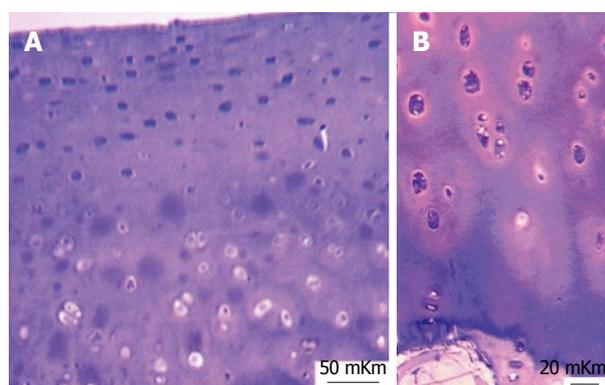


Figure 6 Age-related changes of articular cartilage in intact group. Semithin section. Methylene blue - basic fuchsin staining. A: Focal metachromasy of articular cartilage in five year old dog. Ob. -6,3 x; oc. - 12,5 x; B: Intensive metachromasy in intermediate and deep zones of articular cartilage in eight year old dog. Ob. -16 x; oc. - 12,5 x.

this regularity was preserved in animals with induced experimental osteoarthritis. The obtained data are in agreement with literature: The aggrecan content in superficial zone is lower than in others^[11]. It is known that metabolism of sulfated glycosaminoglycans changes in the early stages of articular cartilage damage^[12].

Recently we obtained histological characteristics of articular cartilage in experimentally induced osteoarthritis^[13,14] corresponding to grade 1-3 according to OARSI classification^[15]. It was revealed^[14] that in this experimental model chondrocytes of intermediate zone were the most vulnerable: More than 50% cells had signs of necrosis or apoptosis. It is known that apoptotic bodies contain alkaline phosphatase and precipitate calcium promoting cartilage calcification^[16].

According to other authors hypertrophic chondrocytes of osteoarthrotic cartilage produce large amounts of collagen X, matrix proteinase 12 and alkaline phosphatase influencing calcification^[17]. Ohira and Ishikawa^[18] (1986) found precipitates of hydroxiapatite crystals around degenerated chondrocytes.

In current research substantial difference of experimentally induced osteoarthritis from spontaneous chondropathy were revealed. Spontaneous aging characterizes by calcium and phosphorus storage in deep

and calcified zones and compensatory increase of sulfated glycosaminoglycans in intermediate and deep cartilage zones as evidenced by the metachromatic reaction and microanalysis data. Unlike spontaneous chondropathy connected with aging in experimentally reduced osteoarthritis more intensive storage of calcium but minor phosphorus in intermediate zone were marked. The revealed contradistinction is in agreement with research of human aging, which leads to suggest that phosphorus exuded from bones stores in arteries and cartilage tissue^[19].

In experimentally induced osteoarthritis the calcified cartilage thinning and osteoclastic resorption are apparent with few changes of elements composition; the only difference from control is minority phosphorus content.

Preparation of biologic samples for X-ray electron probe microanalysis perform according the same principles as preparation for electron microscopy but possess its own specific tricks; peculiar properties of research object also must be taken into consideration. The obtained results demonstrate definitely the possibility of X-ray electron probe microanalysis in the research of mechanisms of articular cartilage alteration in osteoarthritis, these changes is documented and assessed quantitatively.

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COMMENTS

Background

Multiple biochemical and microscopic methods are used in modern researches of cartilage content and structure in normal and diseased human and animal beings but X-ray-microprobe analysis was performed very rare though it permit to evaluate glycosaminoglycans and mineral content by corresponding chemical elements. The optimal methods of articular hyaline cartilage sample preparation for X-ray-electron probe microanalysis and comparison of its elements content in intact animals of different ages and in animals with experimentally induced osteoarthritis were not investigated.

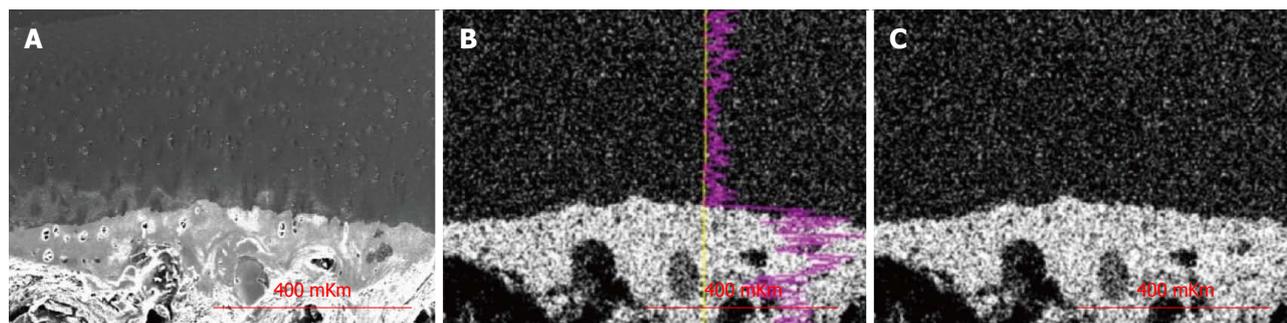


Figure 7 X-ray electron probe microanalysis of articular cartilage in intact five years old dog. A: SEM micrograph of articular cartilage and subchondral zone; B: Scanning line regimen, graph shows phosphorus distribution on line; C: Scanning area regimen shows phosphorus distribution on the sample surface. Instrumental magnification 120.

Table 1 Content of chemical elements in canine articular cartilage

Cartilage zones/groups	Superficial zone	Intermediate zone	Deep zone	Zone of calcified cartilage
ω S (mean \pm SD, weight%)				
IOA in 2 yr	0.18 \pm 0.04 ^a	0.23 \pm 0.02 ^a	0.28 \pm 0.03 ^a	0.13 \pm 0.02
Intact				
2 yr (control)	0.35 \pm 0.01	0.42 \pm 0.04	0.52 \pm 0.02	0.14 \pm 0.02
5 yr	0.20 \pm 0.02 ^a	0.28 \pm 0.04 ^a	0.34 \pm 0.02 ^a	0.28 \pm 0.04 ^a
8 yr	0.33 \pm 0.03	0.52 \pm 0.01 ^a	0.63 \pm 0.04 ^a	0.41 \pm 0.07 ^a
ω Ca (mean \pm SD, weight%)				
IOA in 2 yr	0.04 \pm 0.02	0.08 \pm 0.02 ^a	0.15 \pm 0.02 ^a	9.72 \pm 0.03
Intact				
2 yr (control)	< 0.01	0.04 \pm 0.01	0.09 \pm 0.01	13.93 \pm 0.02
5 yr	0.04 \pm 0.01	0.05 \pm 0.03	0.10 \pm 0.02	16.16 \pm 1.04 ^a
8 yr	0.03 \pm 0.02	0.05 \pm 0.03	0.22 \pm 0.02 ^a	21.16 \pm 3.04 ^a
ω P (mean \pm SD, weight%)				
IOA in 2 yr	< 0.02	0.03 \pm 0.01	0.08 \pm 0.01	4.74 \pm 0.02 ^a
Intact				
2 yr (control)	< 0.01	< 0.01	< 0.01	6.89 \pm 0.01
5 yr	< 0.02	0.07 \pm 0.01 ^a	0.09 \pm 0.02 ^a	7.44 \pm 1.47 ^a
8 yr	0.04 \pm 0.02 ^a	0.09 \pm 0.02 ^a	0.11 \pm 0.02 ^a	9.44 \pm 1.29 ^a

^aP < 0.05, vs control.

Research frontiers

Previous research have already proved that in this experimental model of primary osteoarthritis chondrocytes of intermediate zone were the most vulnerable and that apoptotic bodies promote cartilage calcification.

Innovations and breakthroughs

This is the first study evaluating substantial difference of experimental gonarthrosis induced by reduction of limb blood supply and knee immobilization from spontaneous age-related chondropathy. The optimized methods of articular hyaline cartilage sample preparation for X-ray-electron probe microanalysis are described.

Applications

In experimentally induced osteoarthritis the uncalcified cartilage was characterized with minority Sulphur content, calcium and phosphorus storage in comparison with intact animals of corresponding age. The calcified cartilage thinning and osteoclastic resorption in induction of osteoarthritis are apparent with few changes of elements composition; the only difference from control is minority phosphorus content.

Terminology

Experimentally stimulated osteoarthritis in used biological model histologically corresponds to grade 1-3 according to OARS classification.

Peer-review

Stupina *et al* developed methods of articular cartilage preparation for X-ray-electron probe microanalysis and to study its elements content in experimental osteoarthritis. It is well designed and written manuscript. It is a potential important study to the fields of osteoarthritis research, diagnosis and therapy.

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Basic Study

Benefits of Ilizarov automated bone distraction for nerves and articular cartilage in experimental leg lengthening

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Abstract**AIM**

To determine peculiarities of tissue responses to manual and automated Ilizarov bone distraction in nerves and articular cartilage.

METHODS

Twenty-nine dogs were divided in two experimental groups: Group M - leg lengthening with manual distraction (1 mm/d in 4 steps), Group A - automated distraction (1 mm/d in 60 steps) and intact group. Animals were euthanized at the end of distraction, at 30th day of fixation in apparatus and 30 d after the fixator removal. M-responses in gastrocnemius and tibialis anterior muscles were recorded, numerical histology of peroneal

and tibialis nerves and knee cartilage semi-thin sections, scanning electron microscopy and X-ray electron probe microanalysis were performed.

RESULTS

Better restoration of M-response amplitudes in leg muscles was noted in A-group. Fibrosis of epineurium with adipocytes loss in peroneal nerve, subperineurial edema and fibrosis of endoneurium in some fascicles of both nerves were noted only in M-group, shares of nerve fibers with atrophic and degenerative changes were bigger in M-group than in A-group. At the end of experiment morphometric parameters of nerve fibers in peroneal nerve were comparable with intact nerve only in A-group. Quantitative parameters of articular cartilage (thickness, volumetric densities of chondrocytes, percentages of isogenic clusters and empty cellular lacunas, contents of sulfur and calcium) were badly changed in M-group and less changed in A-group.

CONCLUSION

Automated Ilizarov distraction is more safe method of orthopedic leg lengthening than manual distraction in points of nervous fibers survival and articular cartilage arthrotic changes.

Key words: Limb lengthening; Articular cartilage; Nerve; Histomorphometry; Dog

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Core tip: Limb lengthening developed by Ilizarov is now well accepted method for correction of orthopedic problems but in some cases it is complicated with nerve and joint malfunctions or disturbances. In this animal study we present the comparative analysis of quantitative indices of nerves and articular cartilage structural reorganization during lengthening with manual and automatic Ilizarov bone distraction. Results of the study have indicated the benefits of automatic distraction.

Shchudlo N, Varsegova T, Stupina T, Shchudlo M, Saifutdinov M, Yemanov A. Benefits of Ilizarov automated bone distraction for nerves and articular cartilage in experimental leg lengthening. *World J Orthop* 2017; 8(9): 688-696 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i9/688.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i9.688>

INTRODUCTION

The technology of gradual limb lengthening developed by Ilizarov is now well accepted method for correction of limb length discrepancy, short stature or treatment of bone defects, resulting from trauma, congenital abnormality or oncologic resection. Distraction osteogenesis is an effective method for new bone tissue creation but in some cases is complicated with nonunion, neurovascular

disturbances, muscle contractures and joint stiffness. Using manual circular distractor and specially developed automatic device, Ilizarov^[1] investigated various rates and rhythms of distraction and have concluded that "rate of 1.0 mm/d led to the best results". He also reported that "the greater the distraction frequency, the better the outcome" comparing the automatic distraction (1 mm/d in 60 steps) with manual (1 mm/d in 4 steps). This conclusion has been confirmed in clinical practice^[2] but automatic distraction is not widely implemented method because of its technical difficulties and costs.

There are few research groups dealing with automatic distraction. Nakamura *et al.*^[3] have found less damage in knee cartilage in automatically distracted group (1 mm/d in 120 steps) compared with manual group (1 mm/d in two steps). In goats undergoing leg lengthening with automated distractor producing one, four or 720 increments per day it was found that "the intensity and dispersion of degenerative changes in muscles were in reverse proportion to the frequency of distraction"^[4]. Distraction mode 1 mm/d in 1440 steps in comparison with 1 mm/d in 3 steps resulted in better range of motion and somatosensory evoked potentials, though muscle histology was the same^[5]. Aarnes *et al.*^[6] reported that high frequency of distraction improved tissue adaptation during leg lengthening in humans. In recent research there was no difference in time to union or in the incidence of complications in comparison with manual low-frequent distraction^[7].

Taking into account discrepancies in results it is important to revise experimental leg lengthening series from the points of quantitative histological and physiological methods. Such data is absent in global literature. The safety of automatic Ilizarov distraction for muscles, nerves and cartilage^[8-11] was substantiated in Russian articles, but peculiarities of structural response to manual and automatic Ilizarov bone distraction in nerves and articular cartilage were not revealed.

The aim of our research - comparative analysis of structural changes in leg nerves and knee cartilage during experimental leg lengthening with manual (1 mm/d in four steps) and automatic (1 mm/d in 60 steps) distraction.

MATERIALS AND METHODS

Experiments were carried out in accordance with Principles of Laboratory Animal Care (NIH Publication No. 85-23, revised 1985). Twenty-nine mongrel adult dogs (weight 20-25 kg, 18-20 cm leg length) were used. Five animals formed the intact group and 24 were operated.

Surgery and experimental design

Anesthesia with intramuscular injections of atropine, dimedrol and xylazine was maintained with sodium pentobarbital (30 mg/kg *i.v.*) intravenously. Mid-diaphyseal osteoclasts and osteosynthesis by Ilizarov were performed. In M-group ($n = 12$) the lengthening

protocol involved a 5-d latent period, and then manual movement of graded traction nodes at the rate of 1 mm/d in 4 steps was performed for 28 d. In A-group ($n = 12$) protocol was the same as in M-group, but distraction rate was 1 mm/d in 60 steps. The animals were euthanized at three time-points: D28 - the end of distraction (15% increase the initial leg length in both groups), F30 - 30 d of fixation in apparatus (bone regenerate consolidation in all animals of A-Group, but in M-Group consolidation was evident only in three animals), WA30 - 30 d without apparatus (full weight bearing of the operated limb in M-Group, but in A-Group it was noted immediately after the apparatus removal).

Neurophysiologic evaluation

Intramuscular EMG was performed after anesthesia also at D 28, F 30 and WA 30. M-responses in gastrocnemius and tibialis anterior muscles were recorded using a digital EMG-system DISA-1500 (DANTEC, Denmark). Bio potential leads were monopolar with modified needle electrodes. The active recording electrode was inserted percutaneously in muscle belly and the reference electrode - in its tendon. M-responses were recorded after supramaximal electrical stimulation of sciatic nerve through para neural needle electrodes using rectangular wave pulses of 1-ms duration. Muscle action potential amplitudes were measured from the top of the negative peak to the top of maximal positive peak.

Morphological evaluation

Histologic analysis was performed in 19 animals (all intact and seven from each experimental group). Animals were euthanized. Nerves and cartilage samples were fixed in mixture of 20 g/L solutions of glutaraldehyde and paraformaldehyde in phosphate buffer (pH 7.4) adding 1 g/L picric acid and then were partially embedded in paraffin. Paraffin sections were cut on "Reichert" microtome (Austria) and mounted in glasses with poly-L-lysine for reaction with ki-67 according protocols of producing company using the visualization system RE7140-K (Novocastra, Great Britain). Another parts were post-fixed in 1 g/100 mL tetraoxide osmium solution with 1.5 g/100 mL potassium ferricyanide and embedded in araldite. Transverse semi-thin sections (thickness 0.5-1.0 μm) were made with glass knives using the Nova ultratome LKB (Sweden), mounted on glass slides and then stained with toluidine blue and methylene blue-basic fuchsin. For numerical analysis the semi-thin epoxy sections of enlarged area (4-8 mm^2 instead of standard 1 mm^2) were used. Such technology provided the cellular details visualization in the light microscope and the sample representativeness^[12]. Two calibrated experts conducted numerical analysis. True-color images were digitized using the stereomicroscope "AxioScope.A1" with camera "AxioCam" (Carl Zeiss MicroImaging GmbH, Germany). Histomorphometry was performed with "VT-Master-Morphology" program

(VideoTest, Russia, St. Petersburg). In 3 total sections (magnification 32 \times) nerves areas and summary areas of nerve fascicles with perineurium were determined. In 25 nonoverlapping fields of the endoneurial compartment (magnification 1250 \times), collected in a systematic random order, the numerical densities of endoneurial vessels were evaluated. About 400 samples of myelinated fibres for each nerve site were made, and morphometric parameters-diameters of myelinated nerve fibers, their axons and myelin sheath thickness-were measured. Per cent of degenerated myelinated nerve fibers in the samples were calculated.

Cartilage depth and volumetric chondrocytes density in 30 digital images were estimated, per cents of isogene groups and empty lacunas in random selection of 100 chondrocytes were calculated. Surfaces of epoxy blocks were exposed to silver deposition using Eico IB-6 ion coater and JEOL JEE-4X vacuum evaporator. The investigation of element composition was performed using scanning electron microscope JSM-840 (JEOL, Japan) equipped with energy dispersive X-ray analyzer (INCA 200, Oxford Instruments). Using accelerated voltage 20 kV concentrations of sulfur (ωS , weight %) and calcium (ωCa , weight %) were assessed. Results were obtained as smart maps, showing spatial distribution of elements and quantitative data in weight per cents. For SEM-micrographs cartilage samples were dehydrated in alcohols of ascending concentrations, permeated with camphene according to original method^[13], air dried and coated with silver.

Statistical analysis

Statistical treatment of numerical data was performed in software package Attestat Program (version 9.3.1, developed by I. P. Gaidyshev, Certificate of Rospatent official registration No. 2002611109), the paired and unpaired Student *t* tests, Mann-Whitney *U* test and Fisher exact test were used at 0.05 significance level.

RESULTS

EMG changes

M-responses amplitudes were badly changed in all animals especially in m. tibialis anterior of M-group. At D28 and F30 the intramuscular EMG revealed fibrillations and sporadic positive sharp waves in both groups. At WA30 they disappeared. Table 1 shows that in m. gastrocnemius M-response amplitudes at D28 tended to be lower in A-group than in M-group, but at F30 and WA 30 the parameters of A-group became better than of M-group. In m. tibialis anterior they were better in A-group at all *t*-points.

Changes of nerves sheaths

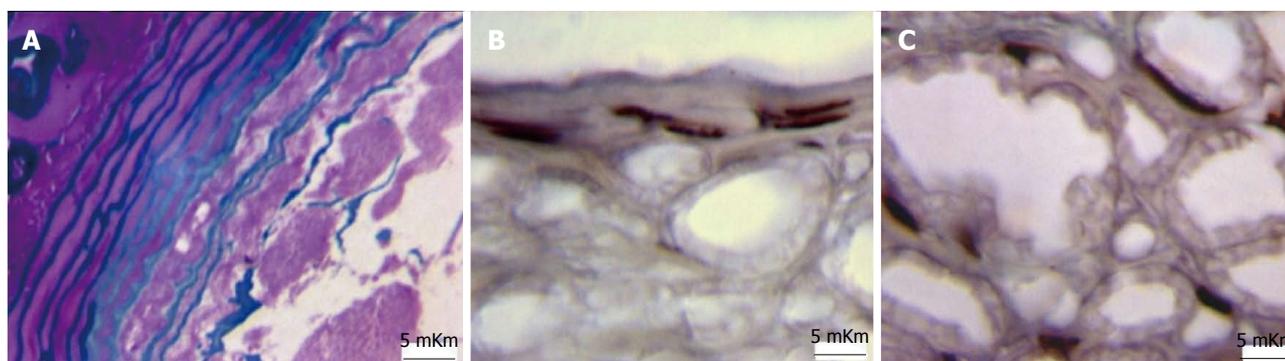
Pathologic conditions of epineurium, subperineurial space and endoneurium were more prominent in M-group. Table 2 shows that at F30 the thickening of Tn was noted in A-group and the thinning of Pn - in M-group. The first

Table 1 M-response amplitudes in leg muscles

<i>t</i> -points of EMG-testing	M. gastrocnemius		M. tibialis anterior	
	mean \pm SE (mV)	Difference <i>vs</i> initial (%)	mean \pm SE (mV)	Difference <i>vs</i> initial (%)
Initial (before experiment)	32.0 \pm 2.9	-	22.6 \pm 1.3	-
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	13.4 \pm 3.1	-58.1	8.8 \pm 1.9	-61.1
30 d of fixation	10.6 \pm 4.6	-66.9	8.3 \pm 1.3	-63.3
30 d without apparatus	16.3 \pm 5.8	-49.1	8.9 \pm 0.1	-60.6
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	12.0 \pm 1.7	-62.5	12.7 \pm 1.6 ^a	-43.8
30 d of fixation	11.9 \pm 1.2 ^a	-62.8	10.5 \pm 0.5 ^a	-53.5
30 d without apparatus	18.3 \pm 4.6 ^a	-42.8	14.0 \pm 2.0 ^a	-38.1

^a*P* < 0.05 *vs* group M.**Table 2** Areas of nerves histologic transverse sections (A_n)

Nerves/group and <i>t</i> -points	Tibial nerve		Peroneal nerve	
	(mean \pm SD) (10 ⁴ mKm ²)	Difference <i>vs</i> contra-lateral (%)	(mean \pm SD) (10 ⁴ mKm ²)	Difference <i>vs</i> contra-lateral (%)
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	353.7 \pm 34.8	3	41.6 \pm 9.4	-2
30 d of fixation	291.6 \pm 26.2	-4	63.6 \pm 1.1	-11 ^a
30 d without apparatus	248.7 \pm 29.2	3	53.3 \pm 8.8	-3
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	287.3 \pm 60.0	-2	56.2 \pm 3.4	-1
30 d of fixation	306.8 \pm 76.7	15 ^{a,c}	75.8 \pm 16.3	-1 ^c
30 d without apparatus	224.8 \pm 31.1	10 ^c	46.5 \pm 1.1	1

^a*P* < 0.05 *vs* contralateral; ^c*P* < 0.05 *vs* group M.**Figure 1** Peroneal nerve, F30, M-group. A: Perineurium, fragment of transverse semithin section, methylene blue - basic fuchsin stain; B: Proliferating cells in perineurium; C: Proliferating cells in endoneurium; fragments of paraffin-embedded sections stained using antibodies to Ki-67. Magnification 1250 \times .

was determined by thickening and hypervascularity of epineurium, the second - by fibrotic changes of epineurium with marked loss of adipocytes. Laminated cellular structure of perineurium in lengthened nerves was maintained in both groups - presented in Figure 1A. In M-group the signs of subperineurial edema were noted - also visible in Figure 1A. Numerosity of perineurial cells nuclei was increased, fibrillar interlayers were thickened. In perineurial cells nuclei the high expression of ki-67 was noted - presented in Figure 1B.

Table 3 shows that at D28 the summary fascicular areas in transverse histologic sections of lengthened

nerves were decreased compared to corresponding contralateral ones. Fascicular thinning was more prominent in Pn than in Tn. Extent of it in corresponding nerves in M and A-groups was approximately equal. At WA30 nerves restored their fascicular areas in A-group, in M-group nerve fascicles were thickened because of endoneurial fibrosis.

The level of ki-67 expression in endoneurial cells was increased especially at F30 - presented in Figure 1C. Table 4 shows that in M-group the numerical density of endoneurial microvessels in lengthened Tn was increased only at F30, Pn nerve - at all *t*-points

Table 3 Summary fascicular areas (A_f) in transverse histologic sections of nerves

Nerves/group and t-points	Tibial nerve		Peroneal nerve	
	(mean \pm SD) (10^4 m Km^2)	Difference vs contra-lateral (%)	(mean \pm SD) (10^4 m Km^2)	Difference vs contra-lateral (%)
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	68.7 \pm 6.9	-8	18.8 \pm 8.1	-15
30 d of fixation	73.5 \pm 5.8	-7	40.1 \pm 2.3	-1
30 d without apparatus	54.2 \pm 4.8	9 ^a	27.8 \pm 9.5	14 ^a
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	83.7 \pm 13.5	-9 ^a	25.7 \pm 2.5	-16 ^a
30 d of fixation	86.8 \pm 13.5	-4	29.6 \pm 7.0	1
30 d without apparatus	82.0 \pm 6.4	5	25.9 \pm 0.6	0 ^c

^aP < 0.05 vs contralateral; ^cP < 0.05 vs group M.

Table 4 Numerical densities of microvessels (N_{Amv}) in endoneurium

Nerves/group and t-points	Tibial nerve		Peroneal nerve	
	mean \pm SE (mm ⁻²)	Difference vs intact (%)	mean \pm SE (mm ⁻²)	Difference vs intact (%)
Intact	182 \pm 22	-	141 \pm 8	-
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	180 \pm 11	-1.1	192 \pm 47 ^a	36.17
30 d of fixation	203 \pm 3 ^a	11.54	157 \pm 36	11.35
30 d without apparatus	187 \pm 10	2.75	197 \pm 52 ^a	39.72
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	135 \pm 21 ^a	-25.8 ^c	164 \pm 8 ^a	16.31 ^c
30 d of fixation	181 \pm 30	-0.5 ^c	171 \pm 29 ^a	21.28 ^c
30 d without apparatus	219 \pm 22 ^a	20.3 ^c	164 \pm 28 ^a	16.31 ^c

^aP < 0.05 vs intact; ^cP < 0.05 vs group M.

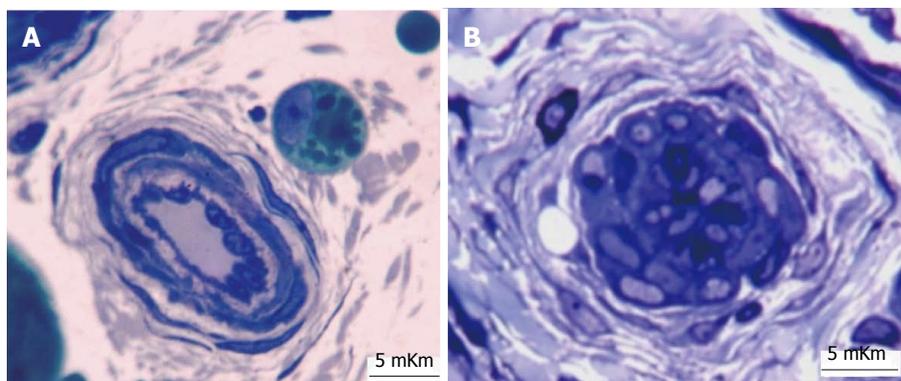


Figure 2 Fragments of canine Pn semithin sections. WA30, M-group. Toluidine blue stain. A: Normal condition of artery in epineurium; B: Epineurial artery with closed lumen. Magnification 1250 \times .

especially at D28 and WA30. In A-group the numerical density of endoneurial microvessels in Tn were decreased at D28 compared with intact nerve, at F30 it was approximately equal to parameter of intact nerve and at WA 30 endoneurium of Tn was highly vascularized. The numerical densities of endoneurial vessels in Pn in A-group were increased at all t-points.

Nerve fibers changes

Majority of nerve fibers in lengthened nerves survived but shares of nerve fibers with atrophic and degenerative changes were bigger in M-group.

In two cases (one for each group) massive nerve fibers degeneration (more than 40% of nerve fibers with signs of demyelination, axonal or Wallerian degeneration) was revealed in Pn on the background of epineurial vessels obliteration or closing - presented in Figure 2. In all the rest animals of M-group the shares of degenerated myelin fibers overcame the corresponding indexes of intact nerves and of nerves in A-group at all t-points of experiment - presented in Tables 5 and 6. The shares of degenerated myelinated nerve fibers in Tn of A-group at F30 and WA30 were even smaller than in intact nerves.

Table 5 Average morphometric parameters of tibial myelinated nerve fibers (mean \pm SE)

Parameters/group and t-points	Share of degenerated nerve fibers (%)	Nerve fibers diameters (mKm)	Axonal diameters (mKm)	Myelin sheath thickness (mKm)
Intact control	1.6 \pm 0.2	6.75 \pm 0.01	4.63 \pm 0.13	1.06 \pm 0.02
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	5.0 \pm 0.7 ^a	6.91 \pm 0.17	4.57 \pm 0.19	1.16 ^a \pm 0.01
30 d of fixation	4.0 \pm 0.9 ^a	6.77 \pm 0.47	4.44 \pm 0.28 ^a	1.17 \pm 0.10
30 d without apparatus	4.4 \pm 2.4	6.61 \pm 3.19	4.37 \pm 2.10 ^a	1.12 \pm 0.64
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	2.4 \pm 0.7 ^b	6.29 \pm 0.13	4.63 \pm 0.10	0.83 \pm 0.02 ^a
30 d of fixation	0.5 \pm 0.2 ^{bc}	6.88 \pm 0.11	4.99 \pm 0.10 ^a	0.95 \pm 0.12
30 d without apparatus	0.9 \pm 0.1 ^{bc}	7.26 \pm 0.13 ^a	5.05 \pm 0.09 ^a	1.11 \pm 0.05

^a*P* < 0.05 vs intact; ^b*P* < 0.05 vs group M.

Table 6 Average morphometric parameters of peroneal myelinated nerve fibers (mean \pm SE)

Parameters/group and t-points	Share of degenerated nerve fibers (%)	Nerve fibers diameters (mKm)	Axonal diameters (mKm)	Myelin sheath thickness (mKm)
Intact control	1.9 \pm 0.3	6.46 \pm 0.07	4.39 \pm 0.08	1.04 \pm 0.04
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	6.0 \pm 1.4 ^a	5.37 a \pm 0.41	3.69 \pm 0.29 ^a	0.84 \pm 0.09 ^a
30 d of fixation	4.3 \pm 1.3 ^a	6.09 \pm 0.63	4.44 \pm 0.57	0.98 \pm 0.06
30 d without apparatus	4.2 \pm 0.4 ^a	5.90 \pm 0.43	4.10 \pm 0.10 ^a	0.90 \pm 0.17 ^a
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	4.0 \pm 0.8 ^{ac}	5.56 \pm 0.26 ^a	3.70 \pm 0.53 ^a	0.92 \pm 0.13
30 d of fixation	3.3 \pm 0.1 ^{ac}	5.62 \pm 0.07 ^a	3.91 \pm 0.09 ^a	0.85 a \pm 0.07
30 d without apparatus	2.4 \pm 0.6 ^c	6.17 \pm 0.45	4.14 \pm 0.16	1.01 \pm 0.06

^a*P* < 0.05 vs intact; ^b*P* < 0.05 vs group M.

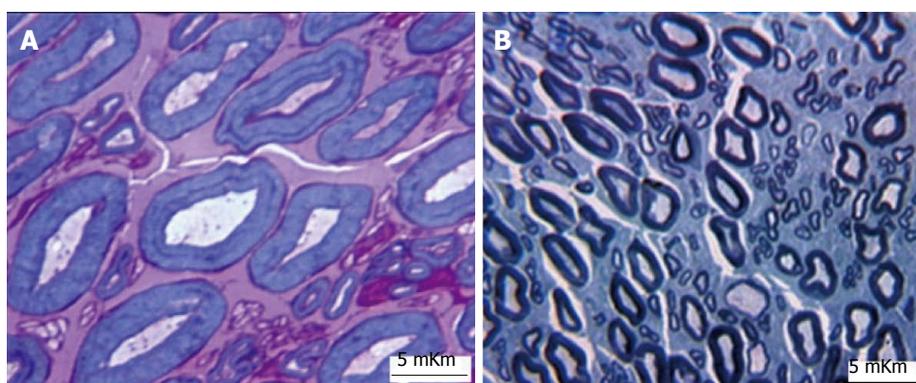


Figure 3 Fragments of canine Tn semithin sections, WA30. A: Some large myelinated nerve fibers has visibly thinned axons and thickened myelin sheaths, M-group, methylene blue - basic fuchsin stain, magnification 1250 \times ; B: Two large nerve fibers (in the lower part of the image) are hypomyelinated; A-group, toluidine blue stain, magnification 500 \times .

In comparison with intact nerves the average axonal diameter of Tn myelinated nerve fibers in M-group was decreased, the average myelin thickness increased. These changes are consistent with findings of myelinated fibers with signs of axonal atrophy and hypermyelination - presented in Figure 3A. In A-group the average axonal diameter in Tn at D28 was comparable with intact nerve, but the average myelin thickness was decreased. At subsequent t-points the average axonal diameter was bigger than in intact Tn nerve, the average myelin thickness was restored, although some nerve fibers were hypomyelinated at

the end of experiment - presented in Figure 3B. In Pn the average axonal diameter was decreased in both groups at D28 and F30, but at the end of experiment this parameter didn't significantly differed from intact nerve (Table 6). Restoration of all morphometric indices was evident only in Group A. In Group M the average diameter of nerve fibres and the average myelin thickness remained decreased.

Articular cartilage changes

Alteration of morphometric parameters and mineral contents developed in both groups - more prominently

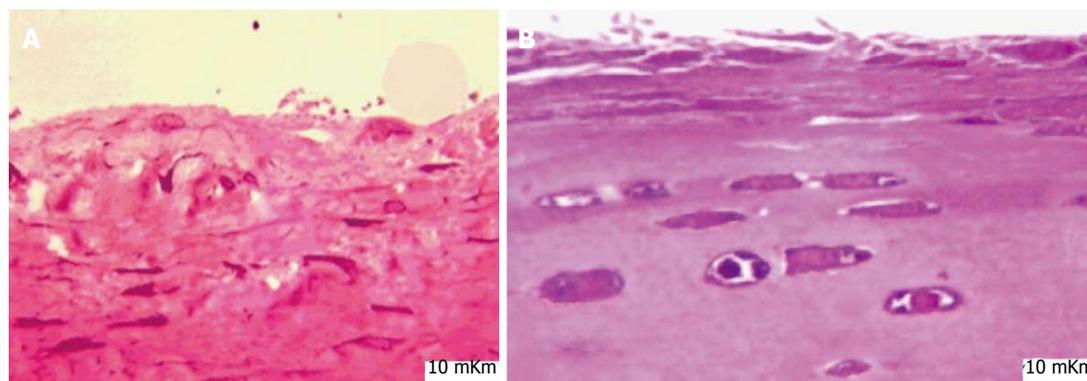


Figure 4 Superficial zone of articular cartilage at D28 in semithin sections. A: M-group; B: A-group. Methylene blue - basic fuchsin stain. Magnification 500 ×.

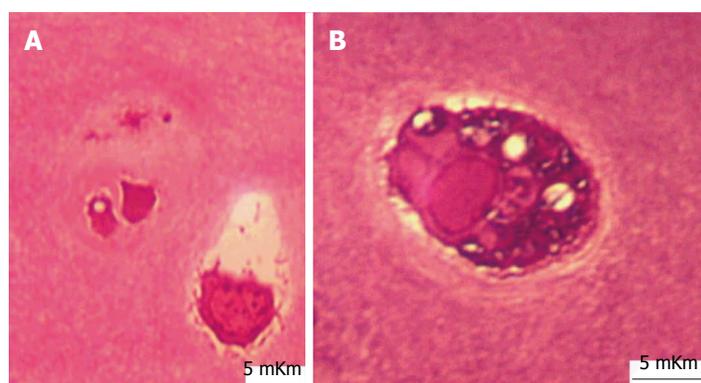


Figure 5 Chondrocytes of intermediate cartilage zone at F30. A: In the left lacuna there are two degenerated chondrocytes, in the right lacuna - chondrocyte shrinkage, chromatin condensed on periphery of caryolemma, M-group; B: Chondrocyte with well-developed functionally active vacuolated cytoplasm occupies the whole lacuna. A-group. Semithin sections. Methylene blue - basic fuchsin stain. Magnification 1250 ×.

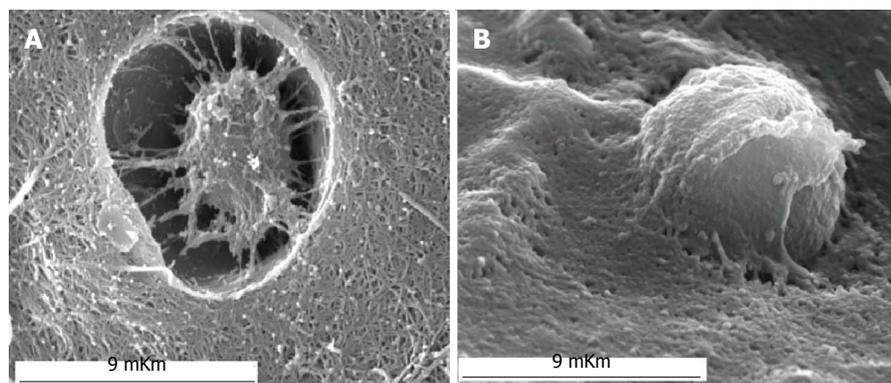


Figure 6 Chondrocytes in SEM at F30. A: Cellular shrinkage. M-group; B: Rounded cell. A-group. Magnification 5500.

in M-group. At D28 injuries of superficial cartilage zone were revealed - presented in Figure 4. More intensive separation of collagen network with usuras formation was noted in M-group. At F30 some chondrocytes of intermediate zone were with signs of apoptosis or necrotic death ranged mainly in M-group - presented in Figure 5A. In A-group many of chondrocytes were functionally active. They occupied the whole lacuna, had homogenic nuclei and well developed vacuolated cytoplasm - example of such cell presented in Figure 5B. Chondrocytes shrinkage and rounding of functionally

active chondrocytes were also revealed by SEM - presented in Figure 6. At WA30 restoration of cellular cartilage architectonics was noted only in A-group. Cartilage thickness changes were divergent in studied groups - presented in Table 7. In M-group parameter increased at D28 and decreased at F30 and WA30 - compared with intact control. In A-group the thickness of cartilage decreased at D28 and at F30, but recovered at WA30. In both groups chondrocytes with signs of destruction were revealed mainly in superficial and deep cartilage zones. Maximal indices of empty lacunas and

Table 7 Average morphometric parameters of articular cartilage (mean \pm SD)

Parameters/group and t-points	Cartilage thickness (mKm)	Chondrocytes volumetric density (%)	Isogenic groups	Empty lacunas
			(% of chondrocyte sample)	
Intact control	475.5 \pm 1.31	9.03 \pm 1.51	14.5	13.6
M-group - manual distraction (1 mm/d in 4 steps)				
28 d of distraction	710.3 \pm 7.16 ^a	4.13 \pm 0.28 ^a	24.7	29.97
30 d of fixation	421.1 \pm 4.81 ^a	5.1 \pm 0.27 ^a	20.18	20.85
30 d without apparatus	416.9 \pm 4.37 ^a	5.6 \pm 0.19 ^a	16.1	21.12
A-group - automatic distraction (1 mm/d in 60 steps)				
28 d of distraction	356.45 \pm 1.55 ^{b,c}	8.34 \pm 0.48 ^{b,c}	25.6	24.3
30 d of fixation	392.7 \pm 2.12 ^{b,c}	6.8 \pm 0.45 ^{b,c}	28.8	16.3
30 d without apparatus	464.6 \pm 6.51 ^c	7.96 \pm 0.37 ^{b,c}	29.9	15.4

^a*P* < 0.05 vs intact; ^b*P* < 0.05 vs group M.

Table 8 Content of sulfur and calcium in articular cartilage (mean \pm SD, weight %)

Parameters/group and t-points	ω S	ω Ca
Intact control	1.26 \pm 0.02	0.15 \pm 0.02
M-group - manual distraction (1 mm/d in 4 steps)		
28 d of distraction	0.71 \pm 0.01 ^a	0.19 \pm 0.02 ^a
30 d of fixation	0.96 \pm 0.02 ^a	0.39 \pm 0.03 ^a
30 d without apparatus	0.94 \pm 0.02 ^a	0.27 \pm 0.02 ^a
A-group - automatic distraction (1 mm/d in 60 steps)		
28 d of distraction	0.79 \pm 0.01 ^a	0.16 \pm 0.01 ^c
30 d of fixation	1.09 \pm 0.02 ^{b,c}	0.18 \pm 0.02 ^c
30 d without apparatus	1.15 \pm 0.02 ^c	0.20 \pm 0.02 ^{b,c}

^a*P* < 0.05 vs intact; ^b*P* < 0.05 vs group M.

utmost decrease of chondrocytes volumetric densities were noted in M-group. Compensatory increase of isogenic clusters index was more prominent in A-group. In all experimental animals ω Ca increase and ω S decrease were marked - more prominently in M-group presented in Table 8.

DISCUSSION

So, better restoration of M-response amplitudes in leg muscles in group with automatic distraction was consistent with less structural alterations of nerves and articular cartilage. Adaptive growing processes in nerve sheaths were marked with ki-67-positive cells in both groups but probably the smaller incremental length (0, 017 mm in group with automatic distraction instead of 0, 25 mm in group with manual distraction) was associated with fewer disturbances in nerves sheaths. Subperineurial edema and fibrosis were evident only in group with manual distraction and restoration of nerve fascicles summary area was achieved only in group with automatic distraction. Per cents of degenerated nerve fibers were smaller in group with automatic distraction than in group with manual distraction at all time points of experiment. Being expressed in per cents this difference seems to be rather small, but in absolute figures it means that in group with automatic distraction thousands neurons don't lose their connections with periphery and survive.

Thousands neurons with degenerated axial cylinders in M-Group enter into regenerative status and create new outgrowths but such active changes may lead to death many of them. As for morphometric parameters of survived myelinated nerve fibers population, in peroneal nerve all of them were restored at the end of experiment only in group with automatic distraction. Automatic distraction prevented axonal atrophy and absolute myelin thickening in tibial nerve. Such changes were evident in group with manual distraction and even in conditions without distraction - after experimental shin bone fracture^[14]. Increased axonal diameters in tibial nerves in group with automatic distraction were associated with better nerve fibers survival because shares of degenerated nerve fibers were smaller even in comparison with intact nerves. Limitation of our study - we have not study endoneurial circulation and axonal transport with special methods. But restoration of fascicular areas, smaller per cents of degenerated nerve fibers and bigger axonal diameters in group with automatic distraction bear indirect evidence that more discrete (high frequent) mode of automatic distraction resulted in fewer disturbances of endoneurial fluid and axoplasmic flow.

Articular cartilage alterations also depended on distraction frequency. All quantitative parameters (cartilage thickness, volumetric densities of chondrocytes, percentages of isogenic clusters and empty cellular lacunas, contents of sulfur and calcium) were less

changed in group with automatic distraction.

And thus, automated distraction developed by Ilizarov (1 mm/d in 60 steps) is more advantageous because few alterations of nerves and cartilage structure than in manual mode (1 mm/d in 4 steps) provide better initial functional recovery and better functional prognosis.

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COMMENTS

Background

Comparative study of the effects of manual low-frequent and automated high-frequent distraction on the results of orthopedic limb lengthening at clinics is problematic. The safety of automatic Ilizarov distraction for nerve, cartilage and muscles changes in experimental animal leg lengthening was substantiated in Russian articles but careful multiparametric comparative analysis has not been done.

Research frontiers

It was stated that for a definite rate of distraction the higher frequent distraction improve bone formation and consolidation. Previous experimental researches have proved that automatic distraction is safer for nerves ultrastructures and cartilage relief than manual.

Innovations and breakthroughs

Special technology of tissue semi thin sections of enlarged shear provided representative histomorphometric data. This is the first study evaluating substantial difference of peroneal and tibial nerves adaptability to conditions of orthopedic leg lengthening. Complex research of articular cartilage histomorphometry, scanning electron microscopy and X-ray electron probe microanalysis revealed fewer alterations in group with automatic distraction.

Applications

Better nerve fibers survival and less arthrotic cartilage changes in conditions of automatic distraction are critically important for good functional prognosis of orthopedic leg lengthening. Development of axonal atrophy and degenerative myelin sheath thickening in tibial nerve fibers evident in group with manual distraction was effectively prevented in group with automatic distraction.

Terminology

Ilizarov method is one of the most clinically implemented distraction osteogenesis procedures. Ilizarov discovered that gradual tension stress maintain the regeneration and growth of living tissues. He was the first who developed the automated high frequent distraction. Different tissue responses on distraction with various frequencies may be revealed in standard experimental models, when groups differ in only one experimental condition - the frequency of distraction. Subtle differences in tissue structures may be of critical importance for functional prognosis.

Peer-review

The topic is interesting and the study may have a point.

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Retrospective Study

Lumbar ganglion cyst: Nosology, surgical management and proposal of a new classification based on 34 personal cases and literature review

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Abstract**AIM**

To analyze different terms used in literature to identify lumbar extradural cysts and propose a common scientific terminology; to elaborate a new morphological classification of this pathology, useful for clinical and surgical purposes; and to describe the best surgical approach to remove these cysts, in order to avoid iatrogenic instability or treat the pre-existing one.

METHODS

We retrospectively reviewed 34 patients with symptomatic lumbar ganglion cysts treated with spinal canal decompression with or without spinal fixation. Microsurgical approach was the main procedure and spinal instrumentation was required only in case of evident pre-operative segmental instability.

RESULTS

The complete cystectomy with histological examination was performed in all cases. All patients presented an improvement of clinical conditions, evaluated by Visual Analogic Scale and Japanese Orthopaedic Association scoring.

CONCLUSION

Spinal ganglion cysts are generally found in the lumbar spine. The treatment of choice is the microsurgical cystectomy, which generally does not require stabilization.

The need for fusion must be carefully evaluated: Pre-operative spondylolisthesis or a wide joint resection, during the operation, are the main indications for spinal instrumentation. We propose the terms "ganglion cyst" to finally identify this spinal pathology and for the first time its morphological classification, clinically useful for all specialists.

Key words: Synovial cyst; Lumbar spine; Instability; Surgery; Ganglion

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Core tip: This paper is an original study that analyzes for the first time the many words and acronyms used in literature to describe lumbar extradural cysts, suggesting the term "ganglion cyst" in clinical practice. It also propose a morphological classification of these cysts, which could be useful for clinicians and surgeons. Finally, a description of microsurgical approaches to resect the cyst and avoid spinal instability is reported: As a guide to a common therapeutical strategy, we report a flow-chart, evaluating clinical conditions, mechanical stability and the most suitable treatment.

Domenicucci M, Ramieri A, Marruzzo D, Missori P, Miscusi M, Tarantino R, Delfini R. Lumbar ganglion cyst: Nosology, surgical management and proposal of a new classification based on 34 personal cases and literature review. *World J Orthop* 2017; 8(9): 697-704 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i9/697.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i9.697>

INTRODUCTION

Ganglion cysts, more common in the hands and wrists^[1,2], have been described for more than 2 millennia^[3]. The Greek term "ganglion" indicates a knot of the tissues.

Ganglion cysts of the minor and major joints, especially at the level of the wrist and back of the hand, have been known since ancient times and were described by Hippocrates^[3] more than two millennia ago. These cysts have an high incidence: Burke *et al*^[1], reviewing the period 1990-2000, found between 44 and 55 new cases per 100000 inhabitants each year.

In the past century, similar cysts were also described as originated from lumbar zygapophyseal joints and occupying the spinal canal, most frequently in the lumbar spine and occasionally, in the cervical and thoracic spine^[4-6]. To define these spinal neoformations, many terms have been adopted in the literature, according to the site of development or to the supposed origin: Ganglion^[6], juxtafacet^[7], flavum^[8], cyfmos^[9] and synovial^[7,8,10-14].

The etiology of the cyst, not fully clear, could be strongly related to inflammatory phenomena secondary to facet hypermobility, which would produce modifications of the articular synovial membrane

leading to cyst formation^[13]. Microsurgical cystectomy is today the treatment of choice^[15], with or without arthrodesis: Generally, microsurgical approach does not produce vertebral instability and arthrodesis is required only in case of a clear pre-operative instability, such as spondylolisthesis.

Evaluating all etiological factors and all treatment options, we propose an original morphological classification of lumbar ganglion cysts, based on their relation with the other anatomical structures. Lastly, in order to clarify the confusing terminology that describes these particular cysts, we suggest "spinal ganglion cyst" (SGC) as definitive term to be applied in clinical practice.

MATERIALS AND METHODS

Thirty-four cases of symptomatic lumbar SGCs surgically treated from 1995 to 2011 were enrolled in this study. They include 18 previously published arthrodesis, with 3 hemorrhagic SGCs. All patients underwent preoperative magnetic resonance imaging (MRI) and computed tomography (CT) scan. To assess lumbar segmental instability, dynamic X-ray were also obtained in all patients but 4 cases, in which pain did not allow standing position.

Pain was evaluated by the Visual Analogic Scale (VAS score). Neurological examination was performed to assess signs of roots compression with any sensory and/or motor deficits.

All patients were operated through a microsurgical approach^[15], to maintain articular congruence and not jeopardize vertebral stability. Cystectomy was achieved through laminotomy or hemilaminectomy. In presence of demonstrated pre-operative or iatrogenic intraoperative segmental instability (wide resection of the articular process), instrumented arthrodesis was also performed.

Histological examination of the cyst was performed in all cases to confirm the diagnosis.

Average follow-up was 28.5 mo (range 12-60). All patients underwent MRI, plain X-rays and were evaluated by VAS and modified Japanese Orthopaedic Association score (JOA score) for neurological improvement in the lower limbs.

The Wilcoxon signed rank test was used for statistical analysis, considering *P* value equal to or less than 0.05 as significant.

Based on our experience and literature review, we were able to construct a new and original classification of the ganglion cysts. By some drawings, performed by the first author (Maurizio D), we reported for the first time the main locations of these cysts, summarizing and comparing our radiological and surgical data with those from the pertinent literature.

RESULTS

The data regarding our 34 cases are summarized in Table 1. Average age was 63 (range 50-76 years): 13 (38%)

Table 1 Data regarding our 34 cases

Case	Age and sex	Location (side)	Instability		Treatment		Other data
			Verified	Supposed	Type 1	Type 2	
1	68 M	L5-S1 (left internal)		a	y		
2	75 M	L4-L5 (right medium)		a, b, c	y		Re
3	50 F	L4-L5 (right medium-internal)		a, b	y		
4	63 F	L5-S1 (right medium)		b, c	y		
5	76 F	L4-L5 (left medium-internal)		a	y		
6	75 M	L5-S1 ¹ (right medium-lateral)		a, b, d	y		
7	75 F	L4-L5 (right medium-lateral)	y	b, c		y	
8	62 M	L4-L5 (right medium-internal)	y	a, b		y	
9	60 M	L4-L5 (right lateral)		a, b, c	y		
10	73 F	L5-S1 (right lateral)		a, b, d	y		
11	55 M	L2-L3 (left medium-lateral)		a	y		
12	55 M	L4-L5 (left medium)	y	a, b		y	
13	74 F	L3-L4 ¹ (right medium-lateral)		b, c	y		
14	56 F	L3-L4 (left medium-lateral)	y	a		y	
15	67 F	L4-L5 (left medium-lateral)		b	y		
16	56 F	L4-L5 (right medium-lateral)		b, c	y		
17	66 F	L4-L5 (left medium-internal)		b	y		IF
18	68 M	L4-L5 ¹ (left medium-lateral)		a	y		
19	73 F	L5-S1 ¹ (left medium)		a, b	y		
20	53 F	L5-S1 (left medium-lateral)		a, b, c, d		y	
21	60 F	L4-L5 (right internal)		a, b, c, d		y	
22	52 M	L4-L5 (right medium-internal)	y	a		y	
23	64 F	L5-S1 (left internal)	y	a, b		y	
24	53 M	L5-S1 (left medium)	y	a, b		y	
25	73 F	L4-L5 (left medium-lateral)		a, b, c		y	IF
26	54 F	L3-L4 (right medium-internal)	y	a, b		y	
27	61 M	L4-L5 (left medium)		a, b, c		y	
28	65 M	L5-S1 (left medium)		a, d	y		
29	71 M	L5-S1 (right medium-internal)		a	y		
30	52 F	L4-L5 (left medium-lateral)		a, b	y		
31	63 F	L4-L5 (right medium)		a, b	y		
32	72 F	L4-L5 (right lateral)		a, b, d	y		
33	56 F	L4-L5 (right lateral)		a	y		
34	62 F	L4-L5 (left medium-lateral)		a	y		

¹Hemorrhagic cyst; L: Left; R: Right; y: Yes; Type 1: Decompression; Type 2: Decompression with stabilization; Verified: Mobile olisthesis; a: Black disc; b: Interarticular liquid; c: Hyperintensity of the ligament on STIR MR images; d: Stable olisthesis; Re: Reoperated for postoperative instability with fusion; IF: Intraoperative fistula.

patients were males and 21 (62%) females. All patients had radicular pain, generally associated with lumbago. In 7 cases (21%), neurological deficits were also present. No cauda equina syndrome was detected. Duration of symptoms prior to surgical treatment varied from 1 to 3 years in 10 cases, whereas in the others average duration was 142 d (range 10-300 d). An acute onset, with a brief preoperative symptomatology, occurred in 4 hemorrhagic cysts.

Preoperative dynamic X-rays showed a mobile olisthesis in 8 cases (23%) and a stable one in 6 (18%). In all cases, preoperative CT and MRI showed signs of microinstability consisting of a reduced disc space and black disc (28 cases, 82%), increased interfacet synovial fluid (24 cases, 70%) and/or signal hyperintensity of the interspinous ligament on STIR sequences (10 cases, 29%).

All 14 pre-operative spondylolisthesis were submitted to arthrodesis. Instrumented fusion was achieved at the level of the cyst in 10 cases (Figure 1), while, in the remaining 4, it was extended to the level

above (Figure 2).

During surgery, we observed 2 dural laceration that were successfully repaired. Histology confirmed the nature of the lesions as ganglion or synovial cysts.

Based on neuroradiological investigations and operative findings, the lumbar SGCs were classified according to the scheme illustrated in Figures 3 and 4. Using this classification, 3 cysts were internal, 7 medium, 8 medium-internal, 12 medium-lateral and 4 lateral.

In the immediate post-operative period, all patients presented remission of pain, gradual recovery from radicular deficits or improvement of claudication. At 12-mo follow-up, one patient developed an olisthesis at the level of cystectomy with low back pain. Instability was correlated with an excessive demolition of the articular process. Therefore, stabilization and fusion achieved remission of pain and good long-term outcome. No recurrences or new contralateral or adjacent SGCs were observed.

At long-term follow-up, VAS reduced from $7.4 \pm$

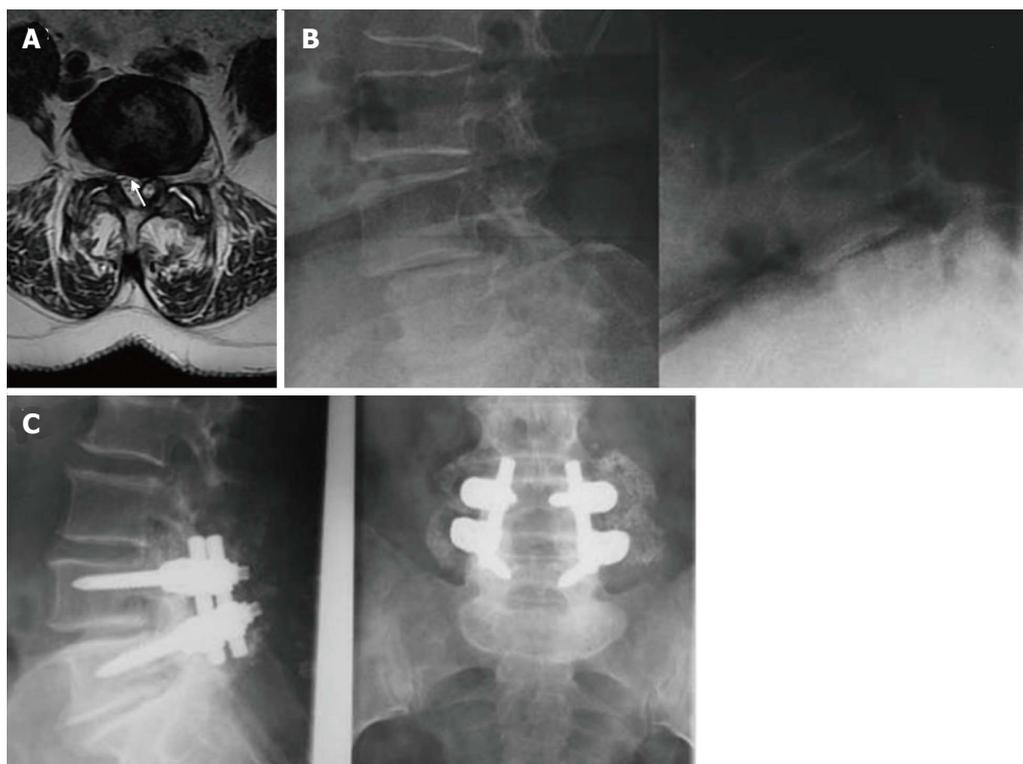


Figure 1 Case 2, Table 1. Preoperative axial T2-weighted MR image (A) showing a dehydrated and hypointense disk with a hyperintense cystic formation at right L4-L5 level (arrow). The cyst appeared to be of the internal or flavum type (see text for the classification). Sagittal dynamic images (B) 12 mo after the first surgical treatment showed an unstable olisthesis at L4-L5 level. Standard X-rays performed 1 year after surgical stabilization (C) showed the instrumentation to be well-positioned with an optimal profile and fusion at L4-L5.

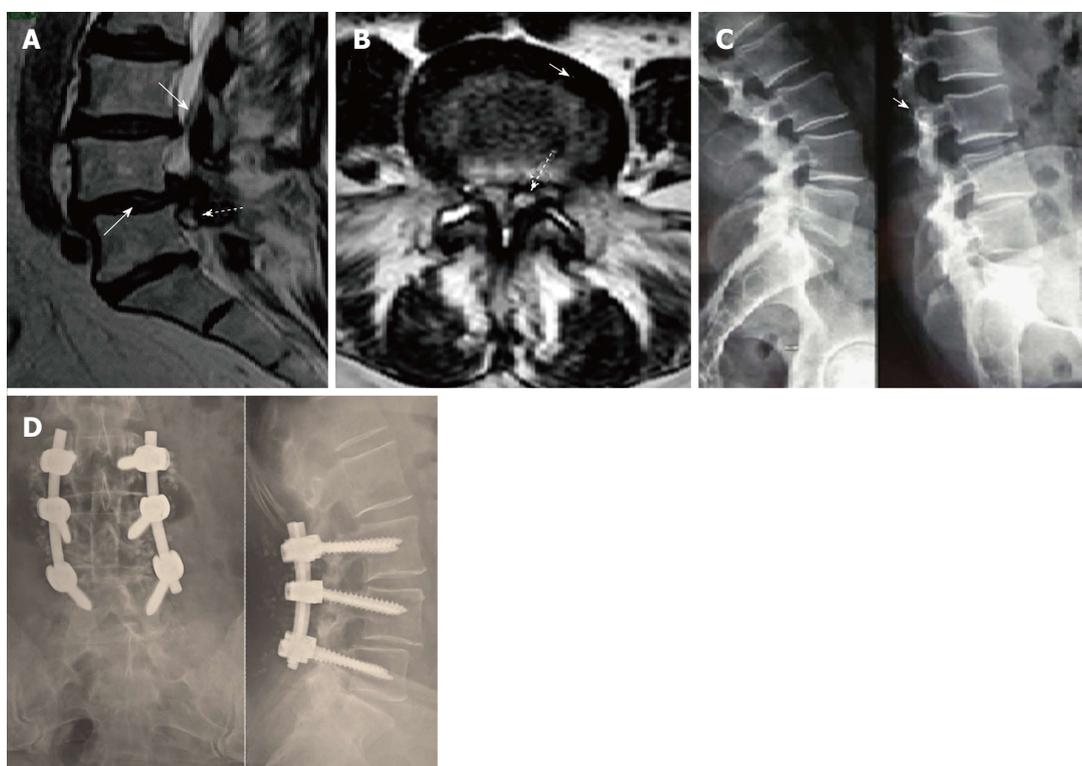


Figure 2 Case 12, Table 1. Preoperative sagittal T2-weighted MR image (A) showing a spinal ganglion cyst (dotted arrow) accompanied by olisthesis at L4/L5 with a dehydrated intervertebral disk (arrow), partially herniated into the spinal canal. On axial images (B) the cyst (dotted arrow) appeared to be of the medium or articular type (see text for classification). The interfacetal space contained an anomalous abundance of "sinovia" (commonly called synovial fluid), as the contralateral one did. Dynamic X-rays (C) showed an unstable olisthesis at L4/L5 and L3/L4. Postoperative outcome of the L3/L5 stabilization is documented by standard X-ray films (D) which confirmed good stability and fusion of the lumbar spine.

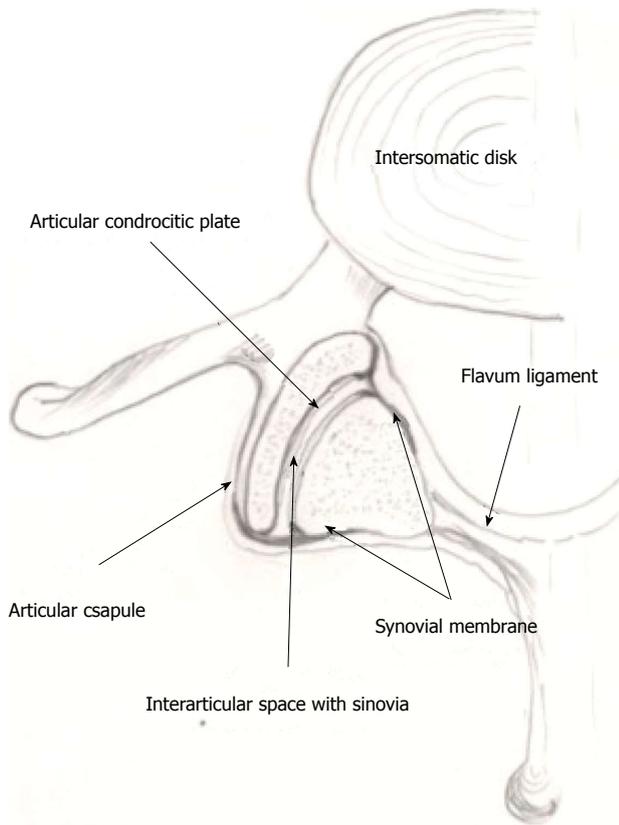


Figure 3 Schematic drawing of a lumbar facet joint showing the extension and distribution of the synovial membrane localized on the internal face of the articular capsule, extending to the external margins of the joint, up to the chondrocytic plates.

1.5 (6-10) to 1.3 ± 0.9 (0-2) ($P = 0.037$). JOA score improved from 7.6 ± 1.3 (7-9) to 2.5 ± 0.3 (0-3) ($P = 0.041$).

DISCUSSION

During the second half of the last century, articular cysts of the spine, prevalently lumbar, were likened to those of the wrist, hand, knee and hip and called, in the Greek language, *γαγγλιον* (ganglion). Hippocrate (460-377 a.C.), translated by Foesio *et al*^[3] in 1596, in the chapter "De Articulis" describes some cutaneous periarticular cysts as "...quae ganglia dominant, quaecunque fluida sunt, et mucosam carnem continent..." (... these so-called ganglion, that contains a fluid or a mucous substance...). In 1930, Elmslie^[16], during a knee surgery, observed a communication between the cyst and the synovial membrane, and used for the first time the term "synovial cyst". In 1968, Kao *et al*^[6] described the first two cases of lumbar intraspinal extradural cyst, calling it "ganglion". In 1973, Syper *et al*^[10] referred the possible origin from the synovial cells of the lumbar zygapophyseal joints. In 1974, Kao *et al*^[7], trying to establish terminology and nosology, published a review on spinal ganglion and synovial cysts, grouping them under a single definition: "Juxtafacet synovial cysts". This term was subsequently adopted by several

authors^[13,17-22], while others proposed other terms such as "flavum cyst"^[8] or "cyfmos"^[9], according respectively to the site of pathology or biomechanics of the mobile spine. They are all essentially correct, in relation to the tissue of origin^[6,10], site^[7-9] or etiology, but, in our hands, create some confusion. In order to identify this specific pathology in terms of pathogenesis, symptomatology and treatment, we reconsidered the ancient term of "ganglion": Spinal ganglion cyst (SGC) may be the term of choice if the cyst originates from the articular process: The distinction between ganglion and synovial cyst is in fact purely histological. Psaila and Mansel^[23] defined that a ganglion cyst "...mainly consists of sheets of collagen fibers arranged in multidirectional strata" and "the ganglion tissue may be produced by the multifunctional mesenchymal cells". The main histological feature of the ganglion is the loss of continuity with the capsule of the facet joints, that makes it free inside and/or outside the spinal canal. On the contrary, the real and conserved synovial cyst is always in continuity with the capsule and recurrently presents synovial villi.

SGCs originate from the joint capsule, more precisely from the mesenchymal tissue^[23] that constitutes the synovial membrane. This tissue covers the internal face of the capsule and also the external portion of the joint: This extension can explain the intra-articular or extra-articular development of SGCs. On the basis of these considerations, we propose an original classification that distinguishes the cysts between anterior or endocanal and posterior or extra-canal. The anterior variety can be subdivided into lateral or foraminal, medium or articular and internal or flavum.

To the best of the authors' knowledge, a comprehensive classification of SGCs has never been reported. Papers from the literature distinguished between synovial, posterior longitudinal ligament or flavum ligament cysts based on their location, origin or histopathological features. Our paper suggests for the first time the distinction between endo-canal and extra-canal SGC: The last one is posterior, generally asymptomatic and do not require treatment^[24]. On the contrary, endo-canal SGC is frequently symptomatic and neurological impairment is closely related to its position within the spinal canal, explaining different disorders ranging from single radiculopathy to cauda equina syndrome.

Factor responsible for proliferation of the synovial cells seems to be repeated articular micro-trauma that induces chronic inflammation, increase of synovial fluid and development of the cyst. Different grades of instability up toolisthesis can favor the weakening of the capsule and ultimately the cystic formation.

We observed lumbar degenerative olisthesis and SGC in more than 40% of our cases. These associated pathologies are frequently reported in the literature, in varying percentages from 30%^[13] to 50%^[25] of cases. Recently, Boviatis *et al*^[18], reviewing 499 SGCs, have found disc degeneration, osteoarthritis and spondylolisthesis. Many authors^[9,13,18,24-27] underlined that SGCs originate in the most mobile spinal segments,

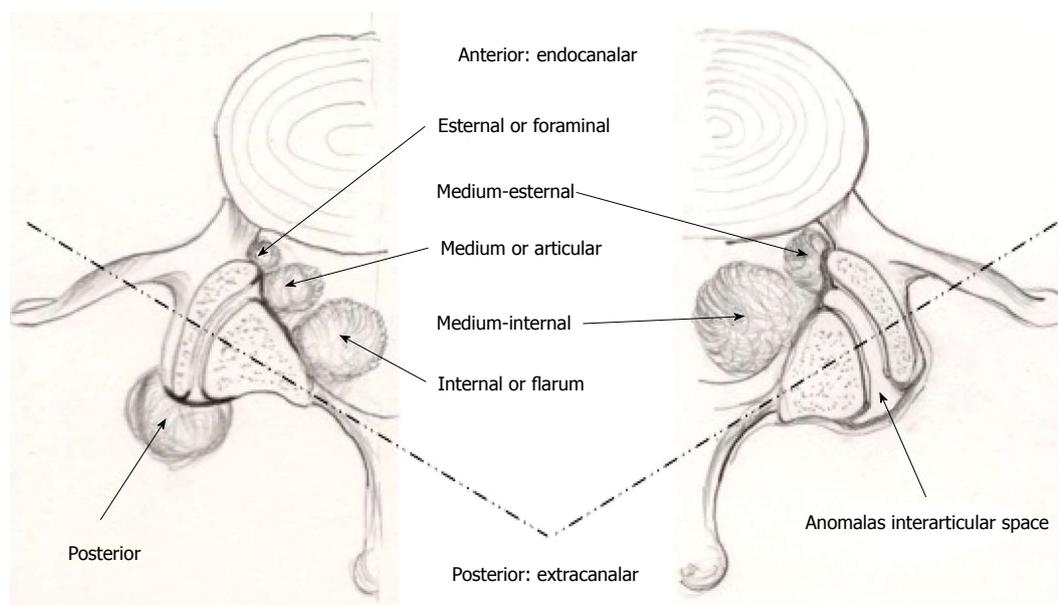


Figure 4 Localizations of lumbar spinal ganglion cysts (see text for the classification). The drawing on the right shows the joint with signs of instability (widened and misaligned interarticular space and increased amount of sinovia).

which are more susceptible to micro or macroinstability.

Cysts formation has been also presented in literature as consequence of an adjacent segment syndrome, due to the hypermobility of a segment just above or below other fixed vertebral segments; also in this case the mechanical stress would be the trigger necessary for mesenchymali tissue degeneration^[28].

In our series and in the literature^[9,13,18,24-26,29,30], SGCs were more frequent at L4-L5, which is notoriously the most mobile spinal level.

Clinical onset of SGCs is generally described as rapid and intense^[14,18,19,21,31], characterized by radicular type disturbances, severe impairment of deambulation due to painful symptoms or, less frequently, motor deficits. Occasionally, onset may be extremely acute and intractable due to intracystic hemorrhage. In agreement with other authors^[32-34], bleeding in such cysts is caused by neo-formed vessels following the repeated inflammations.

Radiological investigations mainly consist of MRI, which can visualize the SGC and relative degenerative phenomena, such as an increased quantity of "sinovia", more commonly described as interfacetal fluid, or inflammatory processes involving the interspinous ligament, which appears "shiny" mainly on T2 and STIR sequences^[35]. In our series these phenomena were present in all cases, either singly or, more often, in combination.

Conventional radiography can play an important role. Standard load-bearing and flexion-extension X-rays may identify hypermobility or instability otherwise unrecognized: However, the severe painful symptoms sometimes make it impossible to perform this type of pre-operative investigation.

Once a diagnosis of SGC has been made, treatment depends on clinical conditions and neurological sym-

ptoms. In the literature^[21], outcomes of different conservative treatments are reported. Surgery is indicated in case of severe pain resistant to medical therapy or when neurological deficits are present.

Operative approach has to totally remove the neoformation, taking into account the degree of instability of the spinal level involved by the cyst. Only when one part of the capsule appears tenaciously adherent to the dura mater it is advisable to perform a subtotal excision, to avoid risks of a CSF fistula. Microsurgical cystectomy seems to be able to maintain vertebral stability: Only one case developed vertebral slippage at follow-up. Fusion can be planned on the basis of preoperative investigations in presence of clear instability, as spondylolisthesis, or can be decided during surgery, evaluating the degree of joint demolition in order to achieve nerve roots decompression and radical cystectomy.

We limited posterior instrumented fusion to about a third of our cases, all suffering from spondylolisthesis: In the literature, fusion varies from over 50% of patients^[29] to a percentage similar or lower than ours^[9,12,13,17,25], whereas in other series surgery was performed without fusion^[15,22,30,36,37]. This variability in surgical strategy illustrates how the indication for fusion do not follow common guidelines. As a guide to a common therapeutical strategy, we have laid out a flow-chart (Figure 5), evaluating clinical conditions, mechanical stability and the most suitable treatment.

The long-term outcomes in patients surgically treated are usually good, with complete remission from pre-operative disturbances, in our series as in others^[9,11,12,13, 17,20,22,25,29,30,36,37]. Only one of our patients presented a symptomatic olisthesis about 1 year after treatment. This iatrogenic deformity, due to an excessive bone demolition, required posterior fusion to achieve resolution of symptoms. In the literature^[11,13,19,20,25,30] a

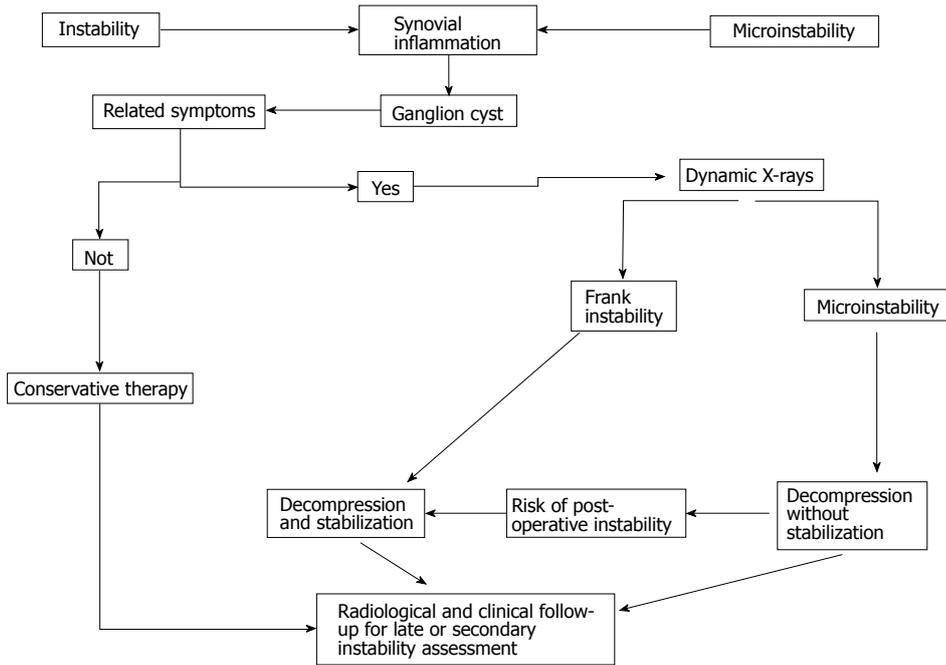


Figure 5 Flow-chart depicting options for the most appropriate approach to the lumbar spinal ganglion cysts.

similar complication was described with the same low incidence in the majority of the larger case series. A recurrence of an operated cyst is exceptional and only one case is described^[13]. The appearance of a new SGC, contralateral, higher or lower, is more frequent and occurred in 15 cases^[13,17,19,20,22,29,38]. No recurrences were observed in our case series.

In conclusion, spinal ganglion cysts are generally found in the lumbar spine. Over the past decades, a wide variety of terms used to describe them has generated confusion: For this reason, the authors decided to return to the ancient definition of "ganglion cyst". Their origin into the spine seems to be attributable to inflammatory phenomena, involving the synovial membrane and caused by repeated joint microtraumas, promoted by facet hypermobility or clear instability. The treatment of choice is microsurgical cystectomy, which generally does not require fusion. The need for fusion must be carefully evaluated: Pre-operative spondylolisthesis or a wide bone joint demolition are the main indications for fusion procedures. The proposal morphologic classification of SGCs is the first that clarifies different localizations of these cysts and may be clinically useful for radiologists and surgeons, together with the definition of ganglion, to speak the same scientific language.

COMMENTS

Background

Ganglion cysts of the minor and major joints, especially at the level of the wrist and back of the hand, have been known since ancient times. These cysts have a high incidence. In the past century, similar cysts were also described as originated from lumbar zygapophyseal joints and occupying the spinal canal, most frequently in the lumbar spine and occasionally, in the cervical and thoracic spine. To define these spinal neoformations, many terms have been adopted in the literature, according to the site of development or to the

supposed origin: Ganglion, juxtafacet, flavum, cyfmos and synovial.

Research frontiers

The etiology of the cyst was related to inflammatory phenomena secondary to facet hypermobility, which would produce modifications of the articular synovial membrane leading to cyst formation. Microsurgical cystectomy is today the treatment of choice. Generally, microsurgical approach does not produce vertebral instability and arthrodesis is required only in case of a clear pre-operative instability.

Innovations and breakthroughs

Evaluating all etiological factors and all treatment options, the authors propose an original morphological classification of lumbar ganglion cysts, based on their relation with the other anatomical structures. Lastly, in order to clarify the confusing terminology that describes these particular cysts, the authors suggest "spinal ganglion cyst" (SGC) as definitive term to be applied in clinical practice.

Applications

The proposal morphologic classification of SGCs is the first that clarifies different localizations of these cysts and may be clinically useful for radiologists and surgeons, together with the definition of ganglion, to speak the same scientific language.

Peer-review

The authors present a case series and a proposed standardized language for lumbar ganglion cysts. The paper is generally well-written and easy to read.

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Retrospective Study

Acetabular components with or without screws in total hip arthroplasty

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Author contributions: Pepe M designed the research, planned the methods to generate hypothesis, conducted literature search and wrote the paper; Kocadal O designed the research and managed of the patients; Erener T designed the research, organized and reported data, contributed to the analysis; Ceritoglu K conducted literature search and explained the results; Aksahin E and Aktekin CN supervised the report.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Ankara Training and Research Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the retrospective anonymous clinical data were used that were obtained after each patient agreed to treatment by written consent. These consent forms are available in hospital archives patient's files. For full disclosure, the details are published on the home page of our hospital (<http://www.ankarahastanesi.gov.tr/>).

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at dr_muradpepe@hotmail.com. Participants gave informed consent for data sharing.

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Abstract**AIM**

To compare the operation time, blood loss, and early outcomes of acetabular components with and without the screw.

METHODS

Thirty patients who underwent cementless acetabular component with or without screw and whose follow-up exceeded one year period in total hip arthroplasty were evaluated. A posterior approach was used in all surgical procedures by one experienced surgeon. Demographic data, operation time, intra- and postoperative blood loss volume, follow-up clinical score, cup migration, and osteolysis were recorded. The Kolmogorov-Smirnov test was performed for testing the normality of study data. Mann-Whitney *U* test was used to analyze the inter-group differences. A *P*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Acetabular components were used in 16 (53.3%) patients with screw and 14 (46.7%) without screw. After one year of follow-up, an osteolytic lesion of 3 mm was found in only one patient in the screw group. No cup migration

was encountered. Intra-group mean Harris hip score significantly increased, but there was no significant inter-group difference. While the mean operation time of the screw group was 121.8 min (range; 95-140), it was 102.7 min (range; 80-120) in the no-screw group, and this difference was statistically significant ($P = 0.002$). The mean intraoperative/postoperative, and total blood loss were 556.6 mL (range: 350-800)/423.3 mL (range: 250-600), and 983.3 mL (range: 600-1350), respectively in the screw group; and 527 mL (range: 400-700)/456 mL (range: 230-600), and 983 mL (range: 630-1250), respectively in the no-screw group. The blood loss difference between the two groups was not significant. In the screw group, the operation time was 19.1 min longer than the no-screw group, and this difference was statistically significant.

CONCLUSION

Acetabular components with or without screw have similar results, but the use of screw increases the operation time significantly, while not changing the blood loss volume.

Key words: Hip arthroplasty; Acetabular fixation; With screw; Without screw; Operation time

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Core tip: This is a retrospective study comparing the perioperative data and early outcomes of the screw and no-screw acetabular components in total hip arthroplasty. There is no study comparing the screw and no-screw components for perioperative data in the literature. Both components were characterized with similar clinical outcomes in the early term. But additional screws significantly increase the mean operative time.

Pepe M, Kocadal O, Erener T, Ceritoglu K, Aksahin E, Aktekin CN. Acetabular components with or without screws in total hip arthroplasty. *World J Orthop* 2017; 8(9): 705-709 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i9/705.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i9.705>

INTRODUCTION

Uncemented porous coated acetabular components have been preferred over cemented ones in primary total hip arthroplasty (THA) in the last 25 years^[1]. Cementless acetabular cups can be implanted with or without screw^[2]. While some studies have reported that the additional screw improves stability, others have mentioned that the press-fit implanted no-screw components have produced similar results with the screw fixation systems^[3-6]. In addition, avoidance of screw reduces the risk of osteolysis of acetabular bone, neurovascular complications, and operational costs^[7-9]. Screws could be responsible for an increased wear due to

two phenomena. One is by contact with the insert, and the other one by corrosion between the screw and the cup. Screws can ensure stability in osteoporotic bones, acetabular defects, and when reliable implantation is not possible during surgery^[10]. Studies comparing acetabular components with and without screws are of limited number, and the majority of them have focused on component migration, osteolysis, and clinical outcome^[4,5,11]. According to our literature survey, no study has yet compared screw and no-screw fixation with respect to blood loss and operation time. In our study, we aimed to compare these two groups in terms of bleeding, surgery time, early clinical outcome, and cup migration.

MATERIALS AND METHODS

Patients who underwent THA with cementless porous coated acetabular component with or without screw for primary hip osteoarthritis and who had at least 12 mo of follow-up were included in this study. Patients with previous hip surgery, revision cases, cemented components, Crowe type 3 and 4 patients, less than 1 year follow-up, tumor or constrained prosthesis, and any bleeding diathesis were excluded from the study. The amount of intraoperative bleeding was determined by a resident by adding the total gauze weight to the difference between the irrigation and vacuum volumes^[12,13]. The postoperative blood loss was calculated by the volume of drainage. No pharmacological agent was used to affect the bleeding; monopolar cauterization was applied for hemostasis during surgery. The time from the beginning of the surgical incision to the closure of the subcutaneous tissue was recorded as the operation time. Harris hip scores (HHP) were recorded by a resident at preoperative period and at postoperative 1st, 3rd, 6th, and 12th months. On the first day after surgery, articular suction drain was removed and walking and strengthening exercises without full loading were started. Patients began to walk with full weight bearing at 6th week after surgery. Radiolucent lines, osteolytic lesions more than 3 mm in diameter^[14] and bone loss were recorded on radiographs of the patients at 3 acetabular regions described by Delee and Charnley^[15]. This study was approved by the ethical committee of our hospital.

Surgical technique

All patients underwent unilateral THA. Preoperatively, pelvis and standing posteroanterior hip radiographs were obtained. Posterior approach was performed in all surgical procedures by one experienced surgeon. A cementless proximal 1/3 porous plasma spray coated Bi-Metric femoral component was used in all patients. A cementless Exceed ABT taper fit acetabular cup with C2A ceramic liner and head was used in patients under 65 years old. A cementless Exceed ABT Ringloc X acetabular cup and E1 10° polyethylene liner and M2A CoCrMo head was used in patients over 65 years old (Biomet, Warsaw,

Table 1 Preoperative and intraoperative data of groups n (%)

	Screw group	No-screw group
No. of patients	16 (53.3)	14 (46.7)
Age (yr)	56.5 (36-82)	54.0 (35-68)
Sex		
Male	4 (25)	6 (42.9)
Female	12 (75)	8 (57.1)
Diagnosis		
Osteoarthritis/posttraumatic	12	9
Inflammatory	2	3
Osteonecrosis	2	2
Head size		
28	1	0
32	15	14

IN). Acetabular socket preparation was similar in both groups and the region was reamed concentrically. When the maximum medial depth was reached, the acetabular cup was implanted. After the surgeon implanted the component, he attempted to move the cup bar antero-posteriorly and supero-inferiorly for the stability control, and two additional screws were used if the stabilization was suspicious. Otherwise it was implanted without screws.

Statistical analysis

SPSS Mac OS X 20.0 (SPSS, Chicago, IL) program was used for statistical analysis. The Kolmogorov–Smirnov test was used to test the normality of study data. Mann-Whitney *U* test was used for the analysis of operation time, bleeding volumes, and clinical scores between the groups. The Wilcoxon test was used to analyze the changes in intra-group clinical scores before and after the operation. A *P*-value below 0.05 was considered statistically significant.

RESULTS

Ten (33.3%) patients were male and 20 (66.7%) were female. Acetabular cups were used with screw in 16 (53.3%) patients and without screw in 14 (46.7%) patients. Table 1 shows the demographic data of the patients. While the mean operation time was 121.8 min (range; 95-140), in the screw group, it was 102.7 min (range; 80-120) in the no-screw group, and this difference was statistically significant (*P* = 0.002) (Figure 1). The mean intraoperative bleeding volume was 556.6 mL (range; 350-800)/527 mL (range; 400-700), the postoperative drainage volume was 423.3 mL (range; 250-600)/456 mL (range; 230-600), and the mean total bleeding volume was 983.3 mL (range; 600-1350)/983 mL (range; 630-1250) in the screw/no-screw group, respectively. The bleeding amount was not statistically significant between the groups (*P* > 0.05). Harris hip scores significantly increased within the groups, but no significant difference was found between the groups (Figure 2). Hip dislocation occurred in two patients. One of them occurred in the screw group 15 d after surgery and was relocated by sedation in the operating

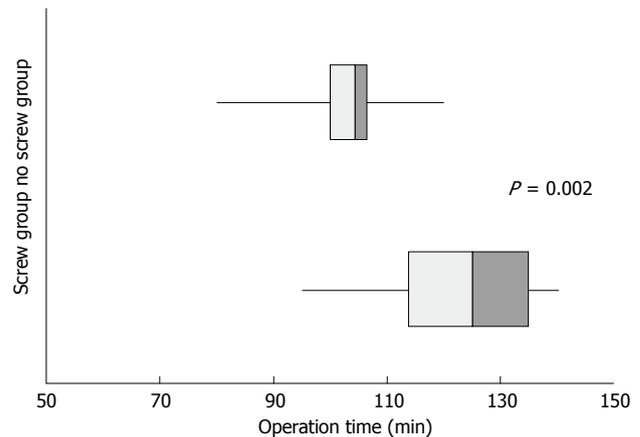


Figure 1 A bar diagram showing operation time and groups. Comparison of operation time between screw and no-screw groups with *P* values illustrated to show differences.

room; the other one was noticed in no-screw group at the early postoperative period and relocated on patient bed. No-screw group had a trochanteric fracture during femoral stem implantation. Plate fixation was performed and callus tissue formed at 6th month. None of the patients had acetabular component migration and revision surgery. One patient in screw group (6.2%) had osteolytic lesions around the screw (Table 1).

DISCUSSION

Transacetabular screw is used by surgeons to improve stability in total hip arthroplasty^[10,16]. It has been shown to improve initial stability in cadaveric studies^[10,17]. However, it is known that additional screws increase neurovascular complications^[8], although there is no consensus whether they increase osteolytic lesions^[11,18,19]. Some authors have attributed the increase in osteolytic lesions to a reaction to the debris escaping from the screw holes to the acetabular bone^[6,20]. In contrast, Schmalzried *et al*^[19] reported in their retrospective study that pelvic osteolysis is associated with significantly greater head size and longer follow-up than screw use. In our study, only one case of osteolysis was identified, which was in the screw group. We attributed the low number of osteolysis cases to a short follow-up period.

Cup migration can be evaluated not only by conventional radiography but also by radiostereometry^[20]. Studies comparing middle- and long-term cup migration have yielded no significant differences between the screw and no-screw groups^[11,20]. In our study, cup migration did not occur in either group at one-year follow up.

Thanner *et al*^[4] reported a comparative study and found a mean HHP of 99 in the screw group and 98 in the no-screw group at the end of 2 years. In our study, at the end of one year, the mean HHP was 81.6 in the screw group and 84 in the no-screw group. Similar to the literature findings, our study did not reveal any significant differences between the two groups in terms of clinical outcomes and cup migration. Short-term follow-up and limited case series were the weak points

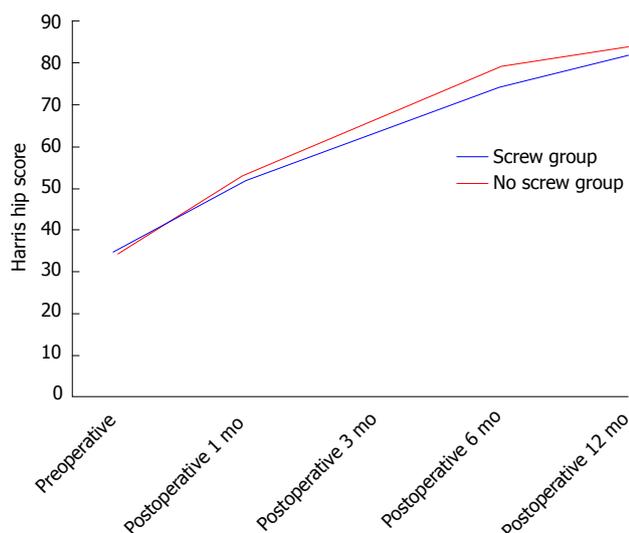


Figure 2 A line chart showing changes Harris hip score over time.

of our study.

The strength of our study is that it compared perioperative data. A review of the literature indicated that no study has yet compared the screw and no-screw groups with regard to volume of blood loss and operation time. Studies have reported that blood loss in THA ranges between 600 and 1800 mL^[21,22]. The mean blood loss in our study was 983.3 mL in the screw group and 983 mL in the no-screw group, with the difference being statistically non-significant. The mean volume of intraoperative bleeding was greater by 29.6 mL in the screw group. We attributed this difference to a bleeding from screw holes, but it was not statistically significant. An analysis of the postoperative drain volumes revealed that the mean volume was greater by 32.7 mL in the no-screw group, which contributed to a slight difference of 0.3 mL between the two groups in the total amount of bleeding.

Duchman *et al*^[23] reported that an operative time greater than 120 min was associated with increased short-term morbidity and risk of complications in THA. We found a mean operative time of 121.8 min in the screw group but no complication such as wound infection was encountered. We compared the screw and no-screw groups for the operation time and found that the mean time was 19.1 min greater in the screw group, and this difference was statistically significant. We attribute this difference to preparation of holes, sterile unpacking, and screwing.

Similar to the literature data, our study showed no difference between clinical outcome and cup migration between the screw and no-screw groups in the short term, whereas not using a screw provided a significant advantage in terms of operation time.

COMMENTS

Background

Cementless acetabular components in total hip arthroplasty can be implanted

with or without screws. It is known that using screws increases neurovascular complications. However, its effects on osteolysis, component stability, and migration are still being debated. No study has compared the perioperative data of screw and no-screw components in the literature. In this study, the authors compared the acetabular components with and without screws in terms of bleeding, operation time, early clinical outcomes, and cup migration.

Research frontiers

The results of this study contribute to clarifying the effect of the screws used in the fixation of the acetabular component in total hip arthroplasty on the operation time, surgical bleeding, and early clinical outcomes.

Innovations and breakthroughs

Using screw did not affect clinical outcome and cup migration at the early postoperative period. Screw and no-screw groups showed similar results in respect to surgical bleeding. However, the use of the screw significantly increased the operation time.

Applications

This study showed that the implantation of the acetabular component without screw would have a significant advantage in the operation time.

Terminology

Osteolysis: Bone matrix resorption by osteoclast cells.

Peer-review

The sample size and the follow up is short of course but interesting.

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Retrospective Study

Single-stage anterior debridement and reconstruction with tantalum mesh cage for complicated infectious spondylitis

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Author contributions: All the authors contributed to the manuscript

Institutional review board statement: This retrospective study was undertaken using data from medical records. This study was approved by the ethical committee of the E-DA hospital (EMRP: 105-064).

Informed consent statement: Our retrospective study contained data from medical records only. The study was registered based on the data protection agency of our institute.

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Abstract**AIM**

To evaluate the clinical and radiographic results of patients with complicated infectious spondylitis treated with single-stage anterior debridement and reconstruction using tantalum mesh cage (TaMC) followed by immediate instrumentation.

METHODS

Single-stage radical debridement and subsequent reconstruction with TaMC instead of autograft or allograft were performed to treat 20 patients with spinal deformity or instability due to complicated infectious spondylitis. Clinical outcomes were assessed by careful physical examination and regular serological tests to determine the infection control. In addition, the visual analog score (VAS), neurologic status, length of vertebral body reconstruction, and the correction of sagittal Cobb angle on radiography were recorded and compared before and after surgery. The conditions of the patients were evaluated based on the modified Brodsky's criteria.

RESULTS

The average VAS score significantly decreased after the surgery (from 7.4 ± 0.8 to 3.3 ± 0.8 , $P < 0.001$). The average Cobb angle correction was 14.9 degrees. The neurologic status was significantly improved after the surgery ($P = 0.003$). One patient experienced refractory infection and underwent additional debridement. Eighteen patients achieved good outcome based on the modified Brodsky's criteria and significant improvement after the surgery ($P < 0.001$). No implant breakage or

TaMC dislodgement was found during at least 24 mo of follow-up.

CONCLUSION

Single-stage anterior debridement and reconstruction with TaMC followed by immediate instrumentation could be an alternative method to manage the patients with spinal deformity or instability due to complicated infectious spondylitis.

Key words: Anterior reconstruction; Complicated infectious spondylitis; Instrumentation; Spinal deformity; Tantalum mesh cage

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Core tip: Complicated infectious spondylitis is a rare infection with vertebral pathological fracture and severe spinal destruction that require anterior reconstruction. The use of metallic implants for vertebral body stabilization and reconstruction following debridement at the lesion of infection remains controversial. In the present study a series of 20 patients with complicated infectious spondylitis were treated with single-stage anterior debridement and reconstruction using tantalum mesh cage (TaMC) followed by immediate instrumentation. The results demonstrated that good functional outcome and low complication rate could be achieved by a single-stage anterior debridement and reconstruction with TaMC.

Yang SC, Chen HS, Kao YH, Tu YK. Single-stage anterior debridement and reconstruction with tantalum mesh cage for complicated infectious spondylitis. *World J Orthop* 2017; 8(9): 710-718 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i9/710.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i9.710>

INTRODUCTION

Spinal infections continue to be a challenge for clinical physicians and surgeons because of their initial vague symptoms with varied manifestations, and subsequent complex progression^[1-6]. A delay or failure of diagnosis and treatment can lead to structural instability, spinal deformity, neurologic impairment, sepsis, and even death. Tuberculous spondylitis is common in almost all developing and underdeveloped regions of the world and is resurgent in developed nations. Neurologic involvement is usually gradual in onset and typically results from a kyphotic deformity with secondary spinal cord compression. Pyogenic spondylitis, either referred to as spondylodiscitis or vertebral osteomyelitis, generally results from arterial or venous hematogenous seeding, which can occur from infection in the urinary or respiratory tract, soft tissue, or elsewhere. The spine also can be seeded from infection related to the diagnostic and therapeutic procedures, or intravenous drug abuse^[7-10]. Infectious spondylitis may

be acute, subacute, or chronic. The virulence of the offending pathogens and the host condition are major determinants of clinical presentations.

Complicated infectious spondylitis indicated for anterior reconstruction is a spinal infection with vertebral pathologic fracture and severe spinal destruction. Various biological and mechanical spacers, including autograft, allograft, and titanium mesh cage (TiMC), are used to reconstruct the anterior column after corpectomy. Previously, the use of metallic implants for vertebral body stabilization and reconstruction following debridement at the lesion of infection is controversial. Recently, several reports of patients with vertebral osteomyelitis treated with cages for anterior reconstruction have been published. The results showed that TiMC did not increase the rate of recurrent or persistent infection^[11-13]. Furthermore, a direct comparison between autograft and cages showed no difference in clinical and imaging outcomes^[14]. Tantalum components are reported to be associated with an even lower incidence of subsequent infection when used in patients with periprosthetic joint infection^[15]. However, no study has investigated the use of tantalum mesh cage (TaMC) for anterior reconstruction in the treatment of complicated infectious spondylitis. Therefore, this study aimed to evaluate the clinical and radiographic results of 20 patients with complicated infectious spondylitis treated with single-stage anterior debridement and reconstruction using TaMC followed by immediate instrumentation and followed-up at least 2 years.

MATERIALS AND METHODS

A total of 20 patients (7 women and 13 men) who underwent single-stage combined extensive debridement and anterior reconstruction using tantalum mesh cages at our university hospital between January 2012 and December 2014 were included in the study. This study was approved by the ethical committee in our institution. The patients' average age was 58.4 years (range, 39 to 73 years). Their medical records including outpatient and emergency room notes, admission notes, inpatient progress and nursing notes, discharge summaries, procedure notes, surgical reports, radiology reports, pathology reports, and microbiology laboratory results were reviewed. Infectious spondylitis was diagnosed based on clinical examinations including positive physical or neurological presentations, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values, and radiographic and magnetic resonance imaging findings. Complicated infectious spondylitis was defined as at least one-level vertebral osteomyelitis with pathological fracture or severe bony destruction and adjacent discitis, based on imaging studies. All 20 patients with complicated infectious spondylitis enrolled in this study met the surgical indications of failed conservative treatment or debridement procedure, neurological compromise, and

spinal instability or kyphotic deformity. These patients wore a rigid orthosis for protection at least 3 mo after surgery. Radiographic assessment was performed before and after surgery, and at the 3-, 6-, and 12-mo visit after discharge and every year thereafter. Systemic antibiotics or anti-tuberculous drugs were administered based on sensitivity studies for identified pathogens. A 6-wk full course of intravenous antibiotics was prescribed for pyogenic spondylitis, and a 12-mo full course of antimicrobial chemotherapy for tuberculous spondylitis. All 20 enrolled patients were followed-up for at least 24 mo after undergoing single-stage anterior debridement and reconstruction surgery.

Surgical technique

All patients underwent single-stage anterior debridement and reconstruction surgery carried out by our spinal surgery team. Three patients had cervical spine infection, and 17 patients had thoracolumbar spine infection. The patients were operated under general anesthesia with endotracheal intubation. During the operation, the vital signs of the patients, including heart rhythm, blood pressure, and pulse oxygenation levels, were continually monitored by anesthesiologists. A Smith-Robinson approach was used for patients with cervical spine lesions. An anterior transthoracic or retroperitoneal approach was performed for patients with thoracolumbar spine lesions. The infected lesion was debrided radically, and all destroyed tissues were removed. The spinal cord and neural elements were also decompressed completely. Smear, bacterial, and tuberculous cultures were all performed. The local area was irrigated thoroughly with diluted povidone-iodine and normal saline solution. The length of the defect after extensive debridement was determined, and a TaMC (Zimmer, NJ, United States) was then introduced into the space between the healthy vertebral bodies for anterior support and axial loading. The cervical locked plate was used for immediate stability after anterior reconstruction in patients with cervical spine lesions. Posterior transpedicular screw instrumentation was performed in patients with thoracolumbar spine lesion. The sequence of anterior or posterior surgery depended on the spinal stability and neurological status of the individual. The wound was closed with drain insertion.

Outcome assessment

The severity of the neurological status was evaluated using the Frankel scale before and after surgery, and regular follow-up visits. Radiographic examination images were used to compare the correction of the sagittal Cobb angle before and after surgery. The Cobb angle, defined as the angle between the superior endplate of the vertebrae above the implanted TaMC and the inferior endplate of the vertebrae below, was measured on plain lateral radiographs. Clinical outcomes were assessed by asking patients to qualify their pain on a visual analog scale (VAS) using a scale of 0-10 (0



Figure 1 A 51-year-old man experienced intractable neck pain and neurologic deficit. Dynamic radiograph showed pathological fractures with kyphotic deformity of 5th and 6th cervical vertebrae.

= no pain and 10 = worst possible pain) and by careful physical examination and regular serological tests during admission and before discharge to determine the modified Brodsky criteria scores. Data of outcome assessment are presented as mean values with standard deviations or median values with interquartile ranges. The Frankel scale, sagittal Cobb angle, and VAS before and after surgery were compared and analyzed using the Wilcoxon signed-rank test. Nonparametric statistics were used because some variables did not have normally distributed data. SPSS 13.0 software (SPSS Inc., Chicago, United States) was used for data analysis. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Seventeen patients with thoracolumbar infection and 3 patients with cervical infection were enrolled in this study. Sixteen patients underwent anterior debridement with 1-level corpectomy and adjacent discectomies, 3 patients with 2 levels, and 1 patient with 3 levels. Sixteen patients underwent 2 levels above and 2 levels below instrumentation of anterior reconstruction using TaMCs after extensive debridement and corpectomy, 3 patients underwent 1 level above and 1 level below, and 1 patient underwent 3 levels above and 3 levels below (Figures 1-7). The average number of segments of resected vertebrae was 1.25 (4 in the cervical region, 6 in the thoracic region, and 15 in the lumbar region). The average length of the TaMC for anterior reconstruction was 36.9 mm. Kyphotic deformity reduced in all patients, with an average angle correction of 14.9° (Table 1).

Neurologic deficits were much improved, from the median of Frankel D before surgery to Frankel D before discharge ($P = 0.003$), and to Frankel E at the 1-year follow-up visit ($P = 0.001$). No patient experienced neurologic deterioration after the operation. Severe back pain related to infectious spondylitis significantly decreased from the average VAS of 7.4 ± 0.8 (range,

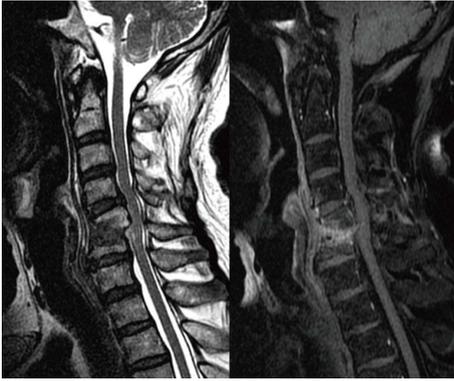


Figure 2 Sagittal T2-weighted and contrast-enhanced magnetic resonance imaging revealed C5-C6 infectious spondylitis with epidural abscess accumulation and spinal cord compression.



Figure 5 A 73-year-old woman with end-stage renal disease sustained severe back pain and intermittent high fever. Radiograph showed endplate erosion and destruction of the 2nd and 3rd lumbar vertebrae, and loss of lumbar lordotic alignment.



Figure 3 Single-stage anterior radical debridement and tantalum mesh cage implantation followed by supplemental anterior locked plate instrumentation were performed to treat infectious spondylitis and correct kyphotic deformity. Postoperative radiograph showed better alignment after single-stage anterior surgery for complicated infectious spondylitis.



Figure 6 Sagittal T1- and T2-weighted magnetic resonance imaging revealed L2-L3 infectious spondylitis with epidural abscess accumulation.

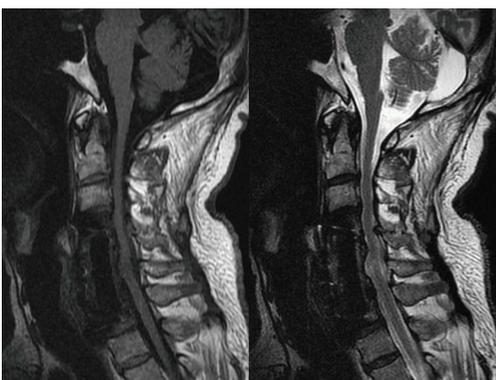


Figure 4 The follow-up sagittal T1- and T2-weighted magnetic resonance imaging demonstrated good implant position and no evidence of recurrent infection.

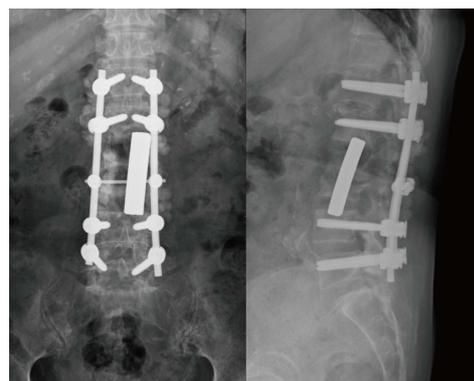


Figure 7 Single-stage anterior radical debridement and tantalum mesh cage implantation followed by supplemental posterior pedicle screw instrumentation were performed to treat infectious spondylitis and correct kyphotic deformity. The antibiotic beads were also deposited for infection control. Postoperative radiograph showed better lordotic alignment after single-stage combined anterior-posterior surgery for complicated infectious spondylitis.

6 to 9) before surgery to VAS of 3.3 ± 0.8 (range, 2 to 5) after surgery ($P < 0.001$), and to VAS of 2.2 ± 0.9 (range, 1 to 4) at the 1-year follow-up visit ($P < 0.001$). Eight patients could achieve excellent outcomes. Ten patients have good outcomes based on the modified Brodsky's criteria, and the improvement showed

significant differences 1 year after surgery ($P < 0.001$) (Table 2).

Causative bacteria were isolated in 19 (95%) of 20 biopsy cultures through either preoperative or

Table 1 Patient demographic data

Case no	Age (yr)	Gender	Infection level	Instrumented level	Length of mesh cage	Pathogen	Cobb angle correction
1	62	M	L2 and adjacent discs	T12L1 to L3L4	38 mm	OSSA	15°
2	50	M	L1 and adjacent discs	T11T12 to L2L3	35 mm	ORSA	18°
3	39	M	T11-L1 and adjacent discs	T8T9T10 to L2L3L4	56 mm	MT	25°
4	55	M	L2 and adjacent discs	T12L1 to L3L4	41 mm	SV	19°
5	48	F	L3 and adjacent discs	L1L2 to L4L5	35 mm	PA	6°
6	51	M	C5C6 and adjacent discs	C4 to C7	44 mm	ORSA	29°
7	70	F	L3 and adjacent discs	L1L2 to L4L5	33.5 mm	OSSA	12°
8	72	F	T8T9 and adjacent discs	T6T7 to T10T11	38 mm	MT	20°
9	69	F	C4 and adjacent discs	C3 to C5	24.5 mm	OSSA	22°
10	42	M	L1 and adjacent discs	T11T12 to L2L3	38 mm	OSSA	15°
11	52	M	L1 and adjacent discs	T11T12 to L2L3	38 mm	EF	9°
12	60	F	T12 and adjacent discs	T10T11 to L1L2	32 mm	No growth	8°
13	65	M	L1 and adjacent discs	T11T12 to L2L3	33.5 mm	ORSA	8°
14	59	M	L4 and adjacent discs	L2L3 to L5S1	41 mm	PA	10°
15	73	F	L2L3 and adjacent discs	T12L1 to L4L5	62 mm	EC	23°
16	58	M	T11 and adjacent discs	T9T10 to T12L1	29 mm	MT	15°
17	55	F	L1 and adjacent discs	T10T11 to L2L3	29 mm	OSSA	14°
18	64	M	C4 and adjacent discs	C3 to C5	23 mm	EC	12°
19	68	M	L1 and adjacent discs	T11T12 to L2L3	32 mm	ORSA	7°
20	56	M	L2 and adjacent discs	T12L1 to L3L4	35 mm	OSSA	11°

F: Female; M: Male; T: Thoracic spine; L: Lumbar spine; S: Sacrum; OSSA: Oxacillin-sensitive *staphylococcus aureus*; ORSA: Oxacillin-resistant *staphylococcus aureus*; MT: *Mycobacterium tuberculosis*; SV: *Streptococcus viridans*; PA: *Pseudomonas aeruginosa*; EF: *Enterococcus faecalis*; EC: *Escherichia coli*.

Table 2 Comparison of clinical outcomes and radiographic findings before surgery and after surgery

	Preop	Postop	1 yr later	P (a/b)
VAS	7.4 ± 0.8 ¹	3.3 ± 0.8 ¹	2.2 ± 0.9 ¹	< 0.001 / < 0.001
FS	D (C,E) ²	D (D,E) ²	E (E,E) ²	= 0.003 / = 0.001
MBC	F (P,F) ²	G (G,G) ²	G (G,E) ²	< 0.001 / < 0.001

¹mean ± SD; ²median (25th percentile, 75th percentile). Preop: Preoperative; Postop: Postoperative; a: Postop vs preop with Wilcoxon signed-rank test; b: Postop 1 year vs preop with Wilcoxon signed-rank test. VAS: Visual analog scale: 0 means no pain and 10 means the most pain possible. MBC: Modified Brodsky criteria: P = poor, F = fair, G = good, E = excellent; FS: Frankel scale: A = complete paralysis; B = sensory function only below the injury level; C = incomplete motor function below injury level; D = fair to good motor function below injury level; E = normal function.

intraoperative procedure. Ten of the 20 patients were infected with *Staphylococcus aureus*, including 6 with the oxacillin-sensitive strain and 4 with the oxacillin-resistant strain. Three patients had *Mycobacterium tuberculosis* infection, 2 had *Pseudomonas aeruginosa* infection, 2 had *Escherichia coli* infection, and 2 had *Streptococcus viridans* and *Enterococcus faecalis* infections. Intravenous antibiotic therapy was continuously administered for a minimum of 6 wk postoperatively based on the specific microbial sensitivities and the identified pathogenic organism. Oral antibiotics were not routinely used after discharge. At outpatient clinics, anti-tuberculous chemotherapy was given for 12 mo or longer. A full course of broad-spectrum antibiotics was administered for the patient with negative culture results. Both elevated CRP and ESR values returned to normal limits at the 1-year follow-up visit (Figure 8).

No implant breakage or tantalum mesh cage dislodgement was found. One patient who was receiving regular hemodialysis experienced refractory infection and underwent additional debridement with antibiotic bead deposition. No recurrent infections were found among the patients during the postoperative follow-up.

DISCUSSION

Infectious spondylitis has generally been regarded as medical disease. Effective antibiotic therapy is the mainstay of successful nonsurgical treatment. Surgery has historically been recommended in several circumstances: Cases refractory to appropriate conservative management, spinal cord compression resulting in neurologic deficit, progressive instability due to significant destruction, severe scoliosis or kyphosis caused by chronic infection^[16,17]. All patients in the present study sustained complicated infectious spondylitis with pathological fracture and adjacent discitis. Extensive destruction of the vertebral body resulted in a large amount of epidural abscess accumulation, progressive scoliotic or/and kyphotic deformity, severe back pain, spinal instability, and neurological impairment. A single-stage anterior or combined anterior-posterior procedure, including an anterior surgery for initially radical debridement and subsequent TaMC reconstruction, was performed to treat these patients. An additional posterior surgery was used for immediate pedicle screw instrumentation to keep physiologic alignment and secure spinal stability in patients with thoracolumbar spine infection. Anterior instrumentation using locked plate/screw one above and one below was used for

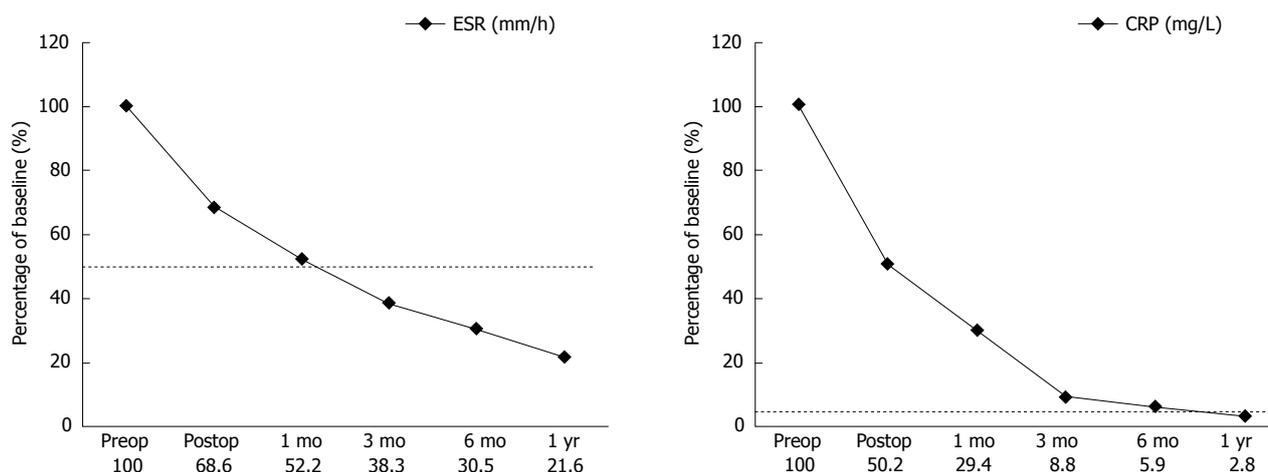


Figure 8 Percentage changes in serological values before and after single-stage anterior and/or posterior surgery in patients with complicated infectious spondylitis.

patients with cervical spine infection.

Various biological and mechanical spacers, including fibular autograft, fibular allograft, and even antibiotic-impregnated methylmethacrylate, are used to reconstruct the anterior column after corpectomy^[18-21]. Antibiotic-impregnated methylmethacrylate is sometimes formed into antibiotic beads to salvage deep wound infection in our clinical practice. The defect after corpectomy is usually repaired by an autologous bone graft from the fibula or the iliac crest, which may cause a 25% increase in permanent morbidity of the donor site^[22-25]. The advantages of allograft bone include the elimination of the harvesting surgical site, the related postoperative pain, and the added expense of a second operative procedure. However, there is still a slight chance of disease transmission using allograft. The other concern is that the sources or sufficient allograft is usually unavailable in most hospitals. The use of metallic implants for vertebral body reconstruction and stabilization following extensive debridement at the site of infection is controversial. Only few retrospective cohort studies including few cases have been previously published. Recent studies have focused on the usefulness, stability, and safety with minimal recurrence of internal fixation of metallic implants in eradicating an active spinal infection^[26-29]. In an observational cohort study at 5 tertiary care hospitals in South Korea, 153 patients with spinal infection requiring surgical management were enrolled. Among these patients, 94 (61.4%) underwent non-instrumented surgery and 59 (38.6%) underwent instrumented surgery^[30]. Clinical outcomes were evaluated using the following measures: Infection-related death, primary failure, recurrence, and sequelae. The results showed that placement of spinal instrumentation did not adversely affect the clinical outcomes. The authors concluded that concerns about infection recurrence and complications should not prevent the use of instrumentation in the management of vertebral osteomyelitis where spinal stability is necessary.

Despite the fact that there is evidence for bacterial adhesion to metal implants, the strong immunity of the highly vascularized cancellous vertebral body bone is unique, even in the presence of infection. In an *in vitro* cell culture experimental study, *S. aureus* and *Staphylococcus epidermidis* were used to evaluate qualitatively and quantitatively bacterial adherence to metallic implants including tantalum, tantalum-coated stainless steel, titanium, titanium alloy, and grit-blasted and polished stainless steel. The results showed that pure tantalum presents with a lower or similar bacterial adhesion when compared with commonly used materials in orthopedic implants^[31]. Schildhauer *et al.*^[32] compared the functions and cytokine response of human leukocytes and equally sized solid orthopedic metal implant materials (pure titanium, titanium alloy, stainless steel, pure tantalum, and tantalum-coated stainless steel) toward porous tantalum foam biomaterial. The results indicated that leukocyte activation at the surface of tantalum material induces a microenvironment, which promotes local host defense mechanism with increased phagocytosis, chemotaxis, and whole blood *S. aureus* killing rate. In a clinical study, Tokarski *et al.* compared the use of tantalum and titanium acetabular components in revision total hip arthroplasty^[15]. They concluded that tantalum components are associated with a lower incidence of subsequent infection when used in patients with periprosthetic joint infection.

TaMC derived from trabecular metal (TM) Technology has an advanced fixation surface designed for orthopedic implants. With a high coefficient of friction (0.98), it provides excellent initial scratch fit. In contrast to coatings and other surfaces, TM material has up to 80% porosity, which enhances the potential for bone ingrowth and soft tissue vascularization^[33]. Sinclair *et al.*^[34] reported an *in vivo* assessment of polyetheretherketone (PEEK) and porous tantalum cervical interbody fusion devices in a goat model. The result showed that bone growth into and around the TM implant margins was better than the PEEK devices. Ordway *et al.*^[35] examined the

implant-endplate interface using a cyclic fatigue loading protocol to model the subsidence observed *in vivo*. The TM construct demonstrated comparable axial stability and subsidence to a fibular allograft. Given the above-mentioned reasons, it could be an alternative material for anterior reconstruction in spine surgery.

A single-stage combined anterior-posterior approach, as opposed to 2-stage surgery, has advantages of a shorter anesthesia time, less anxiety for the patient and family, less blood loss, and earlier mobilization. In the current study, nineteen out of twenty (95%) patients achieved excellent outcome without complication, which was better than the previous reports. Additional anterior debridement and antibiotic bead deposition successfully treated the residual patient with refractory infection and anterior wound dehiscence. All 20 patients who received this combined surgery for their complicated infectious spondylitis recovered from the illness uneventfully. Tantalum with adequate length was used for anterior column reconstruction after radical debridement. All patients had significant improvement of neurologic function and back pain. Good recovery of the sagittal alignment was achieved with an average 14.9° correction of the Cobb angle. No complications related to the single-stage combined surgery were noted. Tokarski *et al.*^{15]} analyzed 10 clinical series involving 106 patients undergoing a single-stage procedure for their spinal infection. Deep wound infections were reported in 6.6% of patients, with most treated by debridement and secondary granulation. Superficial wound infections were found in 2.8% of patients. Patients undergoing spinal instrumentation for spinal disorders other than infection treatment had a similar incidence of postoperative infection. An incidence as high as 20% in instrumented spinal surgery was even reported in previous studies^[36,37]. Therefore, if a cooperative surgical team and care unit are available, a single-stage combined anterior-posterior surgery may be a good alternative in consideration of complications of staged surgeries.

This study has several limitations. First, only 20 cases were examined. Second, this retrospective study did not include patients receiving variant treatment strategies for comparison, and lacked randomization. A large patient population with prospectively controlled comparison groups may be required to evaluate the benefit and feasibility of this single-stage combined anterior-posterior procedure using tantalum reconstruction for complicated infectious spondylitis. Third, most of the patients in this study had received different types of treatment, either open surgery or conservative antibiotics, and then were admitted to our institute due to progressive infection at their original hospital and/or previous failed treatment. After careful examination and evaluation, a primary or revision surgery was performed in these eligible patients, which might cause selective and therapeutic bias. However, uncontrolled infection and difficulty in bony incorporation did not occur in the patients with either single-stage surgery or anterior

reconstruction using tantalum, based on the clinical results of this small patient population.

In conclusion, single-stage anterior debridement and reconstruction combined with anterior instrumentation for cervical spine and posterior instrumentation for thoracolumbar spine can be recommended to treat patients with complicated infectious spondylitis. Anterior radical debridement and TaMC implantation and associated supplemental instrument fixation provide immediate secure stability, successful infection management, neurologic impairment recovery, better physiological alignment, satisfactory pain relief, and significant improvement of daily activities. TaMC can be considered an alternative for anterior column reconstruction, which can provide biomechanical support, avoid donor site morbidity, proceed to bony incorporation, and appear to be protective against infection. However, an administration of a full course of offending pathogens specific intravenous antibiotics or chemotherapy is mandatory to maintain good long-term outcomes and eliminate the risk of recurrent infection.

COMMENTS

Background

Spinal infections challenge clinical physicians because of their varied presentation and complicated course. The use of metallic implants for vertebral body stabilization and reconstruction following debridement at the lesion of infection is controversial. Previously, no study has investigated the use of tantalum mesh cage (TaMC) for anterior reconstruction in the treatment of complicated infectious spondylitis. The primary aim of this study was to evaluate the efficacy of TaMC in patients with Complicated infectious spondylitis.

Research frontiers

The authors demonstrated that TaMC could be a good alternative for anterior reconstruction.

Innovations and breakthroughs

Single-stage anterior debridement and TaMC implantation followed by immediate instrumentation provided immediate stability, successful infection control, neurologic deficit recovery, more satisfactory alignment, adequate pain relief, and better improvement of daily activities.

Applications

Single-stage anterior debridement and TaMC implantation followed by immediate instrumentation was useful for patients with complicated infectious spondylitis. This method could avoid the complications derived from various biological spacers such as autograft and allograft.

Terminology

TaMC derived from Trabecular Metal (TM) Technology has an advanced fixation surface designed for orthopedic implants. TM material has up to 80% porosity, which enhances the potential for bone ingrowth and soft tissue vascularization.

Peer-review

This is a good study, which evaluates clinical and radiological results of patients with complicated infectious spondylitis treated with single-stage anterior debridement and reconstruction using tantalum mesh cage followed by immediate instrumentation.

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Prospective Study

Association of adiponectin gene polymorphisms with knee osteoarthritis

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Abstract**AIM**

To investigate the possible relationship of adiponectin (*ADIPOQ*) gene polymorphisms, plasma adiponectin, and the risk of knee osteoarthritis (OA).

METHODS

A total of 398 subjects, 202 knee OA patients and 196 healthy individuals, were enrolled in the case-control study. Genotyping at +45T/G (rs2241766) and +276G/T (rs1501299) loci was performed using polymerase chain reaction-restriction fragment length polymorphism. Plasma adiponectin levels were assessed using enzyme-linked immunosorbent assay. OA severity was determined using the Kellgren-Lawrence (KL) grading system.

RESULTS

No significant associations were observed in the genotype distributions and allele frequencies at two loci of +45T/G and +276G/T polymorphisms in the *ADIPOQ* between

knee OA patients and control subjects. There was a significant association between genotype distribution of +276G/T polymorphism and KL grade 2, 3 or 4 ($P = 0.037$, $P = 0.046$, $P = 0.016$, respectively). At +45T/G locus, the percentage of GG genotype was notably greater in control subjects (13.40%) compared with OA subjects (1.70%) ($P = 0.023$). Plasma adiponectin was markedly decreased in OA subjects compared with control subjects ($P = 0.03$). Likewise, circulating adiponectin in OA subjects was notably lesser than that in control subjects in GG genotype of +45T/G ($P = 0.029$) and +276G/T polymorphisms ($P = 0.012$).

CONCLUSION

Polymorphisms +45T/G and +276G/T of the *ADIPOQ* gene might not be responsible for OA susceptibility among Thais.

Key words: Adiponectin; *ADIPOQ*; Polymorphism; Knee osteoarthritis; Plasma

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Core tip: Plasma adiponectin levels were significantly lower in knee osteoarthritis (OA) than controls. No significant associations were observed in the genotype distributions and allele frequencies of *ADIPOQ* +45T/G and +276G/T polymorphisms between knee OA subjects and controls. There was a significant association between genotype distribution of +276G/T polymorphism and OA severity. In addition, plasma adiponectin in OA subjects was seemingly lower than that in control subjects in GG genotype of +45T/G and +276G/T polymorphisms. Polymorphisms +45T/G and +276G/T of the *ADIPOQ* gene might not be responsible for the susceptibility to knee OA in the Thai population.

Zhan D, Thumtecho S, Tanavalee A, Yuktanandana P, Anomasiri W, Honsawek S. Association of adiponectin gene polymorphisms with knee osteoarthritis. *World J Orthop* 2017; 8(9): 719-725 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i9/719.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i9.719>

INTRODUCTION

Osteoarthritis (OA), also known as degenerative joint disorder, is characterized by progressive cartilagenous damage, chronic synovial inflammation, development of bone spurs, subchondral cyst formation, and osteosclerosis, leading to joint disability. OA of the knee remains a main cause of mobility impairment, particularly in the elderly population and has been recognized as a major global health problem. A wide variety of potential factors including environments, biomechanics, biochemical processes and/or genetics have been demonstrated to play substantial parts in the progression

of OA. Nonetheless, the cause of OA is still a mystery. Numerous single-nucleotide polymorphisms (SNPs) related to OA have been previously investigated.

Besides storing-energy, adipogenous tissue is also recognized as a metabolic and endocrine organ with significance, complication and high activity. Hormones secreted from adipose tissue are named after adipokines that associate with metabolic processes and inflammatory reaction as well as performance cytokine-like function including anti- and pro-inflammatory effects^[1-3]. In human chromosome 3q27, *ADIPOQ* gene encodes one essential adipokine - adiponectin which contains 244 amino acid residues. It is synthesized in differentiated adipocytes and maintains high levels in blood circulation. The function and effect of adiponectin have been clearly elaborated in anti-diabetic and anti-atherogenic properties. It is still controversial whether adiponectin may have a contributing role in the development of OA. Recently, adiponectin was identified in cartilage, osteophytes, meniscus, synovial membrane and infrapatellar fat pad taken from the knees of OA patients, with the highest concentrations found in the last two^[4]. Previous investigations demonstrated that circulating and synovial adiponectin concentrations were negatively correlated with the radiographic severity in OA subjects^[5,6]. In chondrocytes, adiponectin could modulate cartilage destruction through increasing tissue inhibitor of metalloproteinase-2 and decreasing interleukin-1 β (IL-1 β)^[7]. Accumulating documentation proposes that adiponectin might act as a protective cytokine in OA.

As an essential component of the etiology of OA, candidate genes encoding proteins about metabolism of the articular cartilage and inflammation of synovial membrane have been proved with the pathogenesis of OA. It is ascertained that a number of SNPs involving in OA surrounding genes of estrogen receptor alpha^[8], interleukin-6^[9] and matrix metalloproteinase-3 (MMP-3)^[10]. However, until recently, the study of adiponectin gene polymorphisms in OA patients has received little attention. There are many genetic variations of the human adiponectin gene reported, including several non-synonymous mutations. Some metabolic disorders have been recognized to be related with the two most commonly investigated polymorphisms of *ADIPOQ*, +45T/G and +276G/T SNPs^[11,12]. Additionally, Qi *et al.*^[13] found that greater circulating adiponectin concentration in control subjects carried more T allele at +276G/T locus. We hypothesized that the adiponectin gene would play a part in the development of OA. Thus, the objective of the present investigation is to determine the association between +45T/G or +276G/T *ADIPOQ* polymorphisms and OA susceptibility and plasma adiponectin in knee OA subjects.

MATERIALS AND METHODS

This study was approved by the Institutional Review

Board on Human Research of the Faculty of Medicine, Chulalongkorn University. The present study was conducted in compliance with the guidelines of the Declaration of Helsinki. All subjects gave written informed consent prior to their participation in the study.

Study population

The current study recruited 202 primary knee OA patients (average age 68.80 ± 7.80 years, range from 50-84 years), including 136 female and 66 male subjects. Diagnostic criteria of the American College of Rheumatology were used to identify knee OA subjects. We precluded individuals who had other chronic inflammatory diseases or immunological abnormalities, or preceding knee trauma or surgery. Kellgren-Lawrence (KL) classification system was assigned to determine the severity of knee OA into KL grade 1, 2, 3, or 4 corresponding to radiographic examination^[14]. Furthermore, 196 healthy individuals (average age 65.20 ± 6.20 years, 128 female and 68 male) without any symptoms and signs and previous history of OA were used as control subjects.

DNA isolation and ADIPOQ gene polymorphisms

Peripheral venous blood specimens of 3 mL were collected from each participant by standard venipuncture. Genomic DNA was extracted from buffy coats by using the commercially available Illustra Blood Genomic Prep Midi Flow Kit (GE Healthcare, Buckinghamshire, United Kingdom) and was maintained at -20°C until analysed. +45T/G and +276G/T polymorphisms of adiponectin gene were detected by polymerase chain reaction (PCR) restriction fragment length polymorphism (PCR-RFLP). PCR amplifications were conducted for the +45T/G (rs2241766) SNP by using the published primer set^[15]: forward, 5'-TCCTTTGTAGGTCCCAACT-3' and reverse, 5' GCAGCAAAGCCAAAGTCTTC-3'. The PCR for +45T/G SNP was performed with the following protocols: 95°C for 15 min, repeated by 35 amplification cycles at 95°C for 30 s, 56°C for 30 s, and 72°C for 1 min, and a last extension at 72°C for 7 min. After digestion with the restriction enzyme *BspH1* (New England Biolabs, Beverly, MA) in 37°C water bath for 16 h, the PCR amplified 503 base pair length sequence was cleaved into 375 and 128 base pair segments (T allele of +45T/G). PCR amplifications were conducted for the +276G/T (rs1501299) SNP by using the published primers set^[15]: Forward primer 5'-ACACTGATATAAACGCCATGAA-3' and reverse primer 5'-GCAGCAAAGCCAAAGTCTTC-3'. The PCR for +276G/T (rs1501299) SNP was performed with the following protocols: 95°C for 10 min, repeated by 40 amplification cycles at 95°C for 30 s, 48°C for 1 min and 72°C for 1 min, and a last extension at 72°C for 7 min. After digestion with the restriction enzyme *BglI* (New England Biolabs, Beverly, MA) in 37°C water bath for 16 h, the PCR amplified 168 base pair length sequence was cleaved into 147 and 21 base pair segments (G allele of +276G/T). The digested sequences were resolved by electrophoresis in 2.5% agarose gel or 12%

polyacrylamide gel. The gels were stained with ethidium bromide and analysed by exposure to ultraviolet light on a transilluminator.

Assessment of plasma adiponectin

Following blood sample collection, the plasma were centrifuged and kept promptly at -20°C till analysis. Plasma adiponectin concentrations were assessed by a commercially available sandwich enzyme-linked immunosorbent assay kit (DuoSet ELISA Development kit for human adiponectin, R and D Systems, Minneapolis, MN). Based on the guidelines of manufacturer, 100 μL of samples or standards in reagent diluent were added into a 96-well plate which was precoated with capture antibody overnight at room temperature (RT). After incubating for 2 h at RT and washing three times with washing buffer, 100 μL of the specific detection antibody was pipetted and kept for 2 h at RT. After thoroughly four washes with washing buffer, 100 μL of streptavidin-HRP (1:200) was pipetted to each well and kept for 20 min at RT to avoid in direct light. One hundred slightly of substrate solution was pipetted and kept for another 20 min. Finally, 50 μL of stop solution was pipetted to terminate reactions. The optical density (OD) of each well was determined immediately using a micro-plate reader. The readings at 450 nm were subtracted at 570 nm to correct for optical imperfections in the plate. Adiponectin value was assessed using a linear standard calibration curve constructed from a series of adiponectin standard.

Statistical analysis

All data were analysed were with SPSS version 22.0 software (SPSS Inc., Chicago, IL) and GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). The Hardy-Weinberg equilibrium analyses of two SNPs were determined by the χ^2 test to examine the differences in allele frequency and genotype distribution between OA group and control group. Odds ratios (ORs) and 95% confidence intervals (CIs) of genotypes and alleles were assessed by using the Medcalc[®] (Medcalc[®] Software, Mariakerke, Belgium) statistical software program. Their haplotypes and linkage disequilibrium (LD), D' and r^2 were conducted with Haploview software version 4.1 (Broad Institute Cambridge, MA). Unpaired Student's *t*-test and one-way analysis of variance were utilised to analyse quantitative data of two and more than two independent groups. Genotype distribution and allele frequency of *ADIPOQ* in OA patients and control subjects was calculated by the χ^2 test. The statistical review of the study was performed by a biomedical statistician. *P* values < 0.05 were considered as statistical difference.

RESULTS

The distributions of the genotypes in the control and OA groups conformed to the Hardy-Weinberg equilibrium. The genotype and allele frequency of +45T/G *ADIPOQ* polymorphisms were present in Table 1. No statistically significant differences were observed in the

Table 1 Genotype distributions and allele frequencies of adiponectin gene +45T/G (rs2241766) single-nucleotide polymorphism in control and osteoarthritis groups

+45T/G SNP (rs2241766)		Control n (%)	OA n (%)	OR (95%CI)	P
Genotype	TT	96 (48.98)	84 (41.6)	1	-
	TG	75 (38.27)	93 (46)	1.417 (0.929-2.162)	0.106
	GG	25 (12.75)	25 (12.4)	1.143 (0.611-2.139)	0.676
Allele	T	267 (68.11)	261 (64.6)	1	-
	G	125 (31.89)	143 (35.4)	1.170 (0.872-1.571)	0.295

OA: Osteoarthritis; SNP: Single-nucleotide polymorphism.

Table 2 Genotype distributions and allele frequencies of the adiponectin gene +276G/T (rs1501299) single-nucleotide polymorphism in control and osteoarthritis groups

+276G/T SNP (rs1501299)		Control n (%)	OA n (%)	OR (95%CI)	P
Genotype	GG	102 (52)	106 (52.5)	1	-
	GT	77 (39.3)	76 (37.6)	0.950 (0.626-1.442)	0.809
	TT	17 (8.7)	20 (9.9)	1.132 (0.561-2.283)	0.729
Allele	G	281 (71.68)	288 (71.29)	1	-
	T	111 (28.32)	116 (28.71)	1.020 (0.750-1.387)	0.901

OA: Osteoarthritis; SNP: Single-nucleotide polymorphism.

Table 3 Based on radiographic severity of osteoarthritis, genotype distribution of adiponectin gene +45T/G polymorphism in osteoarthritis patients

OA severity	Genotype			P	³P
	TT	TG	GG		
KL system					
Grade 2	27	30	8		
Grade 3	29	29	8	NS	
Grade 4	28	34	9	NS	NS

P value for difference in distribution of genotype between grade 2 and grade 3 or grade 4. ³P value for genotype distribution between grade 3 and grade 4. OA: Osteoarthritis; KL: Kellgren-Lawrence; NS: Not significant.

Table 4 Based on radiographic severity of osteoarthritis, genotype distribution of adiponectin gene +276G/T polymorphism in osteoarthritis patients

OA severity	Genotype			P	³P
	GG	GT	TT		
KL system					
Grade 2	20	29	5		
Grade 3	41	22	8	0.037	
Grade 4	45	25	7	0.046	NS

P value for difference in distribution of genotype between grade 2 and grade 3 or grade 4. ³P value for genotype distribution between grade 3 and grade 4. OA: Osteoarthritis; KL: Kellgren-Lawrence; NS: Not significant.

genotype and allele frequencies between knee OA and control groups. The T allele frequency was 68.11% in control group and 64.60% in OA group, and the G allele frequency was 31.89% in control subjects and 35.40% in OA group ($P = 0.295$). For the +276G/T polymorphism, there was no difference in the genotypic distribution and allelic frequency between knee OA participants and control subjects (Table 2). The G allele frequency was 71.68% in control group and 71.29% in OA group, and the T allele frequency was 28.32% in control group and 28.71% in OA group. There were no remarkable differences in the +45T/G and +276G/T loci haplotype distributions. The correlation coefficient of the frequencies r^2 is 0.033 in Linkage disequilibrium (LD) in these two polymorphisms.

The association between genotypes of the +45T/G *ADIPOQ* gene polymorphism and radiographic severity of OA patients was shown in Table 3. The genotypic distribution and allelic frequency of the +45T/G SNP was not significantly different among various groups

of OA severity. Corresponding to the genotypes of the +276G/T *ADIPOQ* SNP, however, there were significantly different between KL grade 2 and KL grade 3 at +276G/T genotypes ($P = 0.037$), as well as between KL grade 2 and KL grade 4 ($P = 0.046$) (Table 4). The allele frequency of +276G/T polymorphism was not significantly different.

Circulating adiponectin concentrations of control group and knee OA group were shown in Figure 1. Circulating adiponectin values in OA group were notably lesser than those of the control group ($2.58 \pm 0.60 \mu\text{g/mL}$ vs $2.78 \pm 0.68 \mu\text{g/mL}$, $P = 0.033$). Further analysis of plasma adiponectin based on gender was shown in Figure 2. Plasma adiponectin of female subjects was seemingly greater than that of male subjects in both controls and OA patients ($P < 0.001$).

Figure 3 demonstrates plasma adiponectin concentrations of various genotypes of +45T/G and +276G/T loci. Plasma adiponectin levels of GG genotype were statistically higher than those of the TT genotype at

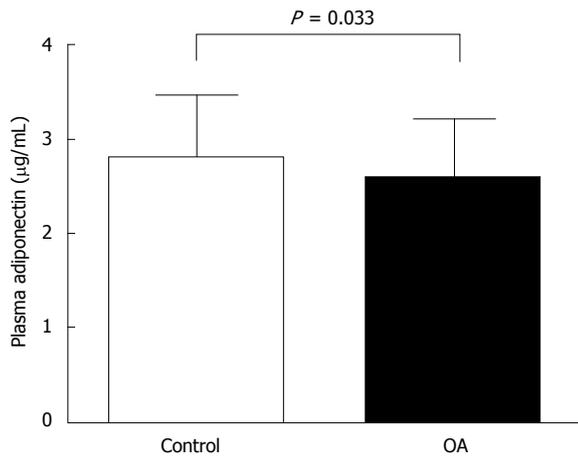


Figure 1 Adiponectin levels in plasma between control and osteoarthritis groups. OA: Osteoarthritis.

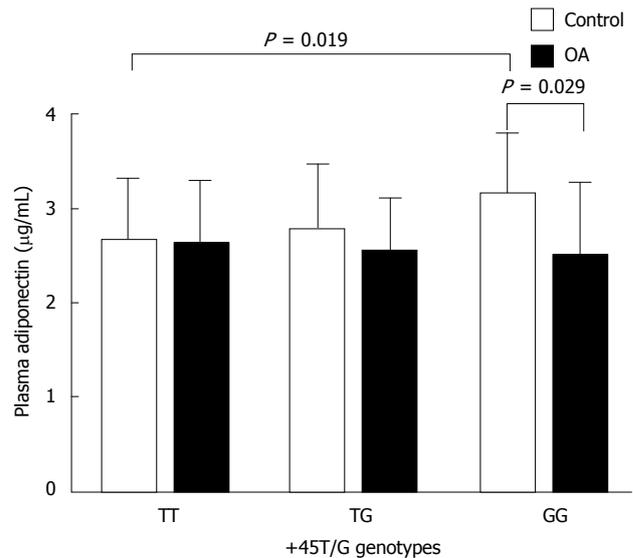


Figure 3 Genotypes of +45T/G locus and their plasma adiponectin levels in control group and osteoarthritis group. OA: Osteoarthritis.

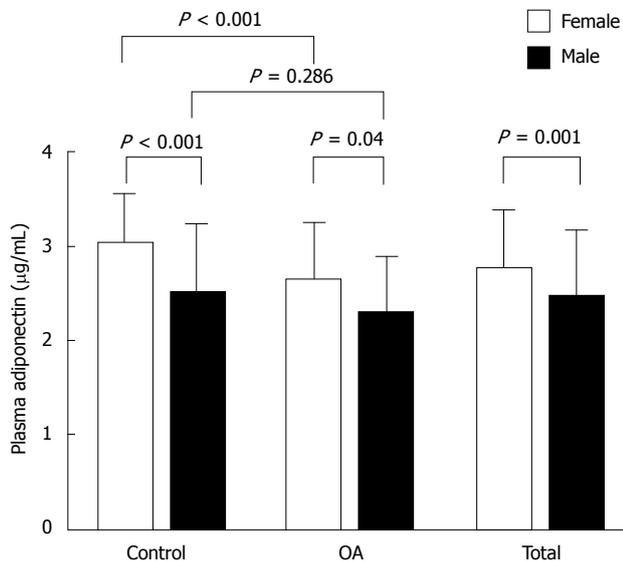


Figure 2 Comparison of plasma adiponectin levels between female and male in control group osteoarthritis group and total subjects. OA: Osteoarthritis.

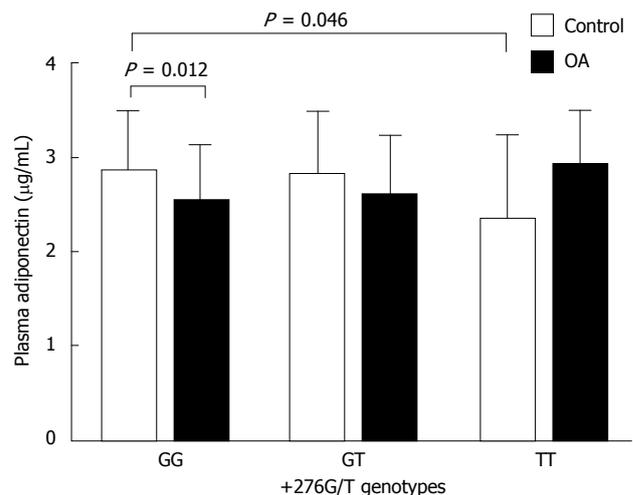


Figure 4 Genotypes of +276G/T locus and their plasma adiponectin levels in control group and osteoarthritis group. OA: Osteoarthritis.

the +45T/G polymorphism of control group ($3.16 \pm 0.63 \mu\text{g/mL}$ vs $2.66 \pm 0.66 \mu\text{g/mL}$, $P = 0.019$). In the GG genotype of the +45T/G locus, the circulating adiponectin levels of control group were significantly greater than those of OA group ($P = 0.029$). In control group, the mean value of plasma adiponectin in TT of +276 G/T was lowest among three genotypes (2.34 ± 0.88 , 2.81 ± 0.66 , $2.84 \pm 0.63 \mu\text{g/mL}$, respectively). In the +276G/T polymorphism, plasma adiponectin levels were more elevated in GG genotype when compared with those in TT genotype of healthy individuals ($P = 0.046$). In GG genotype of +276 G/T locus, the plasma adiponectin of control group was significantly greater than that of OA group ($P = 0.012$) (Figure 4).

DISCUSSION

Adiponectin is a novel adipocyte-derived hormone with various biological functions. Most previous studies have

suggested that circulating adiponectin levels have been found to be decreased in patients with OA. The genetic mechanism of low adiponectin level and its significance in the pathogenesis of OA needed to be determined. The purpose of the current investigation was to investigate the relationship between 2 single nucleotide polymorphisms, +45T/G (rs2241766) and +276G/T (rs1501299), in *ADIPOQ* gene with the risk of OA in Thai population. Moreover, we emphasized on the impact of the 2 SNPs on plasma adiponectin values. We postulated that the *ADIPOQ* SNPs could serve as genetic parameters that affected the risk of OA.

This study is the first to explore the possible relationship between +45T/G and +276G/T polymorphisms of the *ADIPOQ* with the susceptibility of knee OA. The population of this study was ethnically homogeneous

according to the Hardy-Weinberg equilibrium, which makes the possibility of confounding ethnic heterogeneity less possible. Compared with other diseases, OA is a polygenic disease on the basis of the epidemiologic and genetic studies.

Adiponectin is derived from adipocytes, has anti-inflammatory and anti-atherogenic effects as well as multiple beneficial effects on metabolism^[16]. Studies indicate that adiponectin modulates the function and phenotypes of macrophages in chronic inflammation^[3], suppressed the production of TNF-alpha^[2]. Moreover, it was shown that adiponectin up-regulated tissue inhibitor of metalloproteinases-2 (TIMP-2)^[17] and down-regulated IL-1 β -induced MMP-13^[7]. Until now, there are two-loci polymorphisms in adiponectin gene have been researched extensively, +45T/G SNP located in exon 2 and +276G/T SNP located in intron 2. The two loci polymorphisms have been identified to associate with amount of diseases related with metabolism and inflammation. Our findings indicated that the percentage of alleles and the genotypic distributions were not statistically different between knee OA participants and control subjects. Interestingly, based on knee OA severity, *ADIPOQ* genotype at +276G/T was significant difference between KL grade 2 and grade 3 or 4, suggesting that OA patients with GG genotype are more likely to develop, or be more severe OA than those with GT and TT genotype. The association of *ADIPOQ* polymorphisms with circulating adiponectin concentration is in line with the previous finding that +276G/T polymorphism was significantly associated with serum adiponectin in Chingford study by Kyriakou *et al.*^[18].

It has been widely studied that the relationship between plasma adiponectin levels and the +45T/G and +276 G/T polymorphisms. Our study revealed that plasma adiponectin level in OA group was significantly lower than control group. Additionally, the GG genotype at +45T/G and +276 G/T polymorphisms in knee OA patients was associated with lower circulating adiponectin concentration. Different body fat distribution may have a contributory role on adiponectin expression and response in obesity individuals with low-grade inflammatory reaction^[19]. Therefore, genetic variation in the *ADIPOQ* could regulate adiponectin level in the circulation.

How the +276G/T polymorphism affects the *ADIPOQ* gene function and expression remains questionable. The changed genotype at a specific polymorphism locus could not alter amino acid sequence or structure of the protein. In other words, no obviously biological function might not be precluded. As a matter of fact, it has been demonstrated by Yang *et al.*^[20] in *ADIPOQ* gene. On the other hand, linkage disequilibrium could exist at this SNP to influence its gene with other mutation sites. A recent study reported that the single nucleotide mutation at +276G/T locus arised linkage disequilibrium with inserted "A" nucleotide at +2019 SNP of adiponectin gene three prime untranslated region (3' UTR) which

was known as an important part to affect synthesis and degradation of adiponectin mRNA^[21]. Furthermore, it has been demonstrated that mRNA stability would be affected by 3'UTR polymorphisms of other researched genes^[22]. The discrepancy persists in several studies regarding to the association of the SNPs with OA. The susceptibility of candidate genes for OA has previously been demonstrated by some studies, but variants will be controversial by other researchers. This study included a relatively small number of participants in this single-center trial study. It is necessary to conduct additional observations under administration of multiple centers with a larger increased sample size. Multiple risk factors contribute to OA including mechanical stress, inflammation, obesity, aging, and genetic alteration. The susceptibility of OA could vary in different populations. Environmental factors may influence the genetic contributions to the susceptibility of OA.

Taken together, our study suggested that the +45T/G and +276G/T polymorphisms were not related with the risk of knee OA in our Thai population. The knee OA patients with the GG genotype at the +276G/T locus seemed to have a higher potential risk in the severity of OA than those having the GT and TT genotypes. The GG genotypes at SNP +45T/G and +276G/T loci were associated with plasma adiponectin concentration in healthy controls and knee OA patients. Further studies will be needed to clarify the relationship of two single nucleotide polymorphisms in larger sample size and different ethnic cohort on knee joint or other joints to yield a better understanding of these polymorphisms in the development of OA.

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COMMENTS

Background

The understanding of genetic factors in the pathogenesis of osteoarthritis (OA) is still incomplete. There is growing awareness of the role of adiponectin in knee OA. Understanding the polymorphisms of adiponectin might help explain why these polymorphisms play roles in the development of knee OA.

Research frontiers

Adiponectin +45T/G and +276G/T polymorphisms and plasma adiponectin levels have been studied in patients with knee OA, including healthy controls.

Innovations and breakthroughs

This is a novel study in that it addresses the polymorphisms and plasma of adiponectin in patients with knee OA, including healthy controls. The authors

found that Plasma adiponectin levels were significantly lower in knee OA than controls. There were no significant differences in the genotype distributions and allele frequencies of *ADIPOQ* +45T/G and +276G/T polymorphisms between patients with knee OA and controls.

Applications

Understanding the role of adiponectin +45T/G and +276G/T polymorphisms in OA could help find possible biomarkers of susceptibility of OA. It could also serve as predictive parameter for disease severity of knee OA.

Peer-review

The study is interesting.

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Osteoarthritis action alliance consensus opinion - best practice features of anterior cruciate ligament and lower limb injury prevention programs

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Abstract

AIM

To identify best practice features of an anterior cruciate ligament (ACL) and lower limb injury prevention programs (IPPs) to reduce osteoarthritis (OA).

METHODS

This consensus statement started with us performing a systematic literature search for all relevant articles from 1960 through January 2017 in PubMed, Web of Science and CINAHL. The search strategy combined the Medical Subject Heading (MeSH) and keywords for terms: (1) ACL OR "knee injury" OR "anterior cruciate ligament"; (2) "prevention and control" OR "risk reduction" OR "injury prevention" OR "neuromuscular training"; and (3) meta-analysis OR "systematic review" OR "cohort study" OR randomized. We found 166 different titles. The abstracts were reviewed for pertinent papers. The papers were reviewed by at least two authors and consensus of best practice for IPP to prevent OA was obtained by conference calls and e-mail discussions. All authors participated in the discussion.

RESULTS

The best practice features of an IPP have the following six components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper technique; (4) sufficient dosage; (5) minimal-to-no additional equipment; and (6) balance training to help prevent injuries. Exercises focused on preventing ankle sprains, hamstring injuries and lateral trunk movements are important. Plyometric exercises should focus on correcting knee valgus movement.

Exercises should focus on optimizing the hamstring to quadriceps strength ratio. In order for IPP to be successful, there should be increased education and verbal feedback along with increased athletic compliance. Additional equipment is not necessary. Balance training alone does not significantly reduce injuries, but is beneficial with other exercises. Not enough evidence to recommend stretching and agility exercises, with no ill effects identified. Therefore, we suggest making these optional features.

CONCLUSION

Best practice features for ACL and lower limb IPPs to help prevent OA contain six key components along with two optional.

Key words: Anterior cruciate ligament; Lower limb; Injury prevention program; Knee injury

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Core tip: Sports participation can provide health benefits, but also increase the injury risk to the lower limbs especially the anterior cruciate ligament. Many different types of injury prevention programs (IPPs) exist to train athletes to reduce inherent risk factors. The aim of this review is to provide a comprehensive analysis of both systematic and meta-analyses studies to identify the best practice features (lower extremity and core strengthening, plyometrics, continual feedback to athletes regarding proper technique, sufficient doses, minimal-to-no additional equipment, and balance training along with optional components of stretching and agility exercises) of an IPP to help protect the athlete.

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INTRODUCTION

The osteoarthritis action alliance (OAAA) is a broad coalition of public health leaders and stakeholders committed to elevating osteoarthritis (OA) as a national health priority and promoting effective policy solutions that aim to address the individual and national toll of OA. The authors of the paper are members of the OAAA prevention working group. Our goal is to prevent the onset of OA through effective injury prevention and weight management strategies. One of our strategies is to promote widespread implementation of activity-specific rules and policies for organized sports, recreation and school athletics to prevent joint injuries that can lead to OA. We believe that implementing

anterior cruciate ligament (ACL) and lower limb injury prevention programs (IPPs) will prevent OA of the knee.

Sports participation can generally enhance one's health benefits *via* regular physical activity. However, there is an increased risk for injuries that occurs in athletics. Lower limbs injuries are very common.

ACL injuries are common in a high-risk sport occurring in 2.1% of college female soccer players per season^[1] and 12.3% of female college soccer players report a previous ACL tear^[1]. The annual ACL injury incidence does vary with reported rates for amateur athletes (ranging from 0.03% to 1.62% in studies of at least moderate sample size), which are lower than professional sports but higher than national surveys^[2].

An injury to the ACL has both significant short-term (time away from sport) and long-term implications. In particular, injury to the ACL of the knee significantly increases a person's risk for (OA) in the injured knee^[3,4]. In particular, an ACL injury significantly increases a person's risk for OA in the injured knee with around 20% of ACL-injured knees having moderate or severe radiologic changes (Kellgren and Lawrence grade III or IV)^[3]. OA is a chronic, painful, and disabling disease, and it is prevalent in 1 in 3 people around 10-15 years after an ACL injury regardless of treatment (operative or non-operative)^[3,5]. Therefore we believe the best practice is to prevent knee injuries and ACL injuries.

Studies suggest that a beneficial effect exists when utilizing both lower limb and ACL IPPs^[6,7]. Prevention programs that incorporate a variety of strategies to target modifiable risk factors can be crucial in reducing the number of ACL injuries sustained. The number of athletes needed to treat to prevent one ACL tear varies with estimates at 89-128^[7-9] depending on age of participants and inclusion of all ACL tears or non-contact ACL tears only. It is estimated that an ACL reconstruction lifetime cost to society is US \$38121^[10]. IPP for high risk sports for those 12-25 years of age (IPP for HR 12-25) is estimated to prevent 842 lifetime cases of OA per 100000 individuals and 584 total knee replacements per 100000 are subsequently averted^[11]. IPP for HR 12-25 would avert US\$ 693 of direct healthcare costs per person per lifetime. As well, other studies have found cost-savings from IPP from prevention of ACL surgeries not just the savings from OA prevented^[12-15].

The purpose of this consensus statement is to provide a comprehensive evaluation of the literature to identify the best practice features of an ACL and lower limb IPP and determine essential components that are required to help protect the athlete from sustaining such traumatic injuries, thereby reducing OA. Multiple systematic reviews and meta-analyses have attempted to identify the essential components required for an effective ACL IPP^[9,16-31]. Based on a comprehensive review of this literature, OA Action Alliance injury prevention experts recommend that the following six core components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper

technique; (4) sufficient doses; (5) minimal-to-no additional equipment; and (6) balance training along with optional components of stretching and agility exercises be included in a structured warm-up to maximize effectiveness of ACL and lower extremity IPP's for youth athletes.

MATERIALS AND METHODS

We performed a systematic literature search for all relevant articles from 1960 through January 2017 in PubMed, Web of Science and CINAHL. The search strategy combined the Medical Subject Heading (MeSH) and keywords for terms: (1) ACL OR "Knee injury" OR "anterior cruciate ligament"; (2) "prevention and control" OR "risk reduction" OR "injury prevention" OR "neuromuscular training"; and (3) meta-analysis OR "systematic review" OR "cohort study" OR randomized.

We found 166 different titles. The abstracts were reviewed for pertinent papers. In addition, we performed a manual search of references from reports of randomized controlled trials (RCTs), prior meta-analyses and review articles to identify additional relevant studies. Articles published by the authors of this paper were reviewed for relevant citations. The authors reviewed the search and suggested other papers. All were found in the search criteria.

To be included the paper needed to be a randomized control trial, systematic review or meta-analysis on the effectiveness of IPP for the prevention primarily ACL injury or secondary lower limb injury prevention.

The papers were reviewed by at least two authors and consensus of best practice for IPP to prevent OA was obtained by conference calls and e-mail discussions. All authors participated in the discussion.

RESULTS

Based on a comprehensive review of this literature, OA Action Alliance injury prevention experts recommend that the following six core components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper technique; (4) sufficient doses; (5) minimal-to-no additional equipment; and (6) balance training along with optional components of stretching and agility exercises be included in a structured warm-up to maximize effectiveness of an ACL and lower extremity IPP's for youth athletes.

Lower extremity and core muscle strength training

We note that hamstring/quadriceps ratio is a noted risk factor for ACL injuries^[32]. Hence, these muscle group are considered to be an important risk factors for an ACL injury^[16,21,25,32-34]. Eccentric hamstring exercises such as Russian/Nordic exercises should be incorporated as it has been proven to increase hamstring/quadriceps strength ratio and improve eccentric hamstring torque and isometric strength^[18,25]. Core strengthening, such as

planks, aid in preventing injuries^[16,19,23,25,35-40]. It is key to have continual feedback to ensure proper technique with the use of body-weight exercises that focus on the trunk and hamstring strength^[26,41].

Plyometrics

Plyometrics is an essential component in an IPP. Studies have shown that oth balance and plyometric training reduces peak valgus knee moments^[25], this improves in an athlete's motor control during side-stepping and/or single leg landing tasks. Sports specific Neuromuscular Training (NMT) that focuses on jumping and landing tasks improves ground reaction force and stance time as well as unanticipated cutting maneuvers are important^[26,27]. Since excessive medial knee displacement is considered to be a risk factor for an ACL injury, it is important for NMT to include exercises that involve the entire kinetic chain of the lower limb which can be individualized for the team and practice facility^[12,26]. Plyometric exercises in programs have included jumping forwards and backwards, jumping side to side, tuck and scissor jumps, and single leg squats^[18].

Continual feedback

Prevention programs applying both proprioception and technique modification are effective in reducing ACL injuries^[26,31,42,43]. Education and verbal feedback from athletic trainers regarding proper technique has shown to decrease peak vertical ground forces from landing (soft landing with bent knee, knee in alignment with the second toe, and proper deceleration techniques) and is a large contributor to the success of IPP's^[8,27,34,44]. An external focus (EF) for the acquisition and control of complex motor skills required for sport with positive over negative feedback is recommended^[45].

Sufficient doses

IPP need time to take effect therefore at least 6 wk (10 to 15 min at least 3 d per week) should be given for lead time (ideally during a preseason) and then continued during the season with less frequency (1-2 times a week)^[8,26]. NMT programs performed for longer times per day and more frequently demonstrated greater NMT prophylactic effects^[46] but lower compliance. Combining pre-season and during season is the most effective process to reduce ACL injuries rather than either NMT programs alone^[46].

Besides the frequency of IPP's, compliance rates play a major role. Coaches are more likely to perform a 10 min IPP than 20 min or longer^[47]. High compliance rates showed 35% lower risks and 39% risk reduction rate compared to intermediate compliance rate^[46,48]. Moderate to strong evidence exists to support the importance of compliance especially consistent attendance by involved athletes and commitment to the completion of sessions throughout the intervention period contributed to the effectiveness of the IPP^[48,49]. There are fewer ACL, acute knee, and lower extremity

injuries when there is higher compliance rates with the IPP^[27,48,50]. We recommend a shorter 10 min program started in the pre-season and continued through the season every week as part of the standard warm-up.

Minimal-to-no additional equipment

A number of neuromuscular warm-up strategies do not require the acquisition of additional equipment, such as a balance board, to produce an effective IPP^[35]. Drawbacks of some IPP's is the need for additional equipment, most notably many teams lack this equipment and resources may preclude compliance among participants of IPP^[16,35]. Utilizing additional equipment has not shown significant reduction in lower limb injuries^[35]. Therefore, we recommend that the best practice IPP have no additional equipment needs.

Balance exercises

Some studies have found prevention programs that only apply balance training did not significantly reduce the overall lower limb injury rate reduce or to modify risk factors for ACL injuries despite good athletic adherence to the intervention^[25,42,51]. However, there have been randomized control trials that have shown that balance exercises might be efficacious in preventing other lower extremity, such as ankle ligamentous injuries^[25,35]. Balance exercises demonstrated a 41% reduction in ACL injury rate compared to a 66% reduction by preventive NMT without balance exercises^[18]. The effectiveness of balance exercises can be enhanced when utilized in conjunction with proprioceptive exercises^[17]. We recommend that balance training be done in conjunction but not alone to prevent ACL injuries.

Stretching exercises

Current evidence suggests that stretching alone may confer no injury prevention benefit^[35]. A review found that greater durations during an IPP that static stretching was performed was associated with a lower risk for non-contact ACL injuries^[30]. We note that one study greatly affected their analysis^[30]. There is not enough evidence to support static stretching in ACL injury prevention, although dynamic stretching may be beneficial for other reasons, including perceptions about flexibility^[30,35,42]. In conclusion, additional research is needed to understand how stretching influences risk for ACL injury. We recommend stretching as an optional exercise, with dynamic stretching being emphasized over static stretching.

Agility exercises

There is not enough evidence to support agility exercises in ACL injury prevention. However, there is evidence to suggest that the addition of this component provides beneficial effects of reducing non-contact ACL injury rates in sport-specific training by increasing the emphasis and duration of agility training^[26,30]. In order to improve lower extremity neuromuscular control/

balance, specific drills targeted at improving running technique and coordination could be targeted^[25].

DISCUSSION

Unfortunately, ACL injuries are commonly encountered in various sporting activities. The mechanism of ACL injury can be categorized as contact and non-contact^[17]. Contact ACL injuries are non-preventable, but utilizing lower limb and ACL IPP's can prevent non-contact ones. Prevention of such injuries is essential given the long-term effects and high economic costs for the patient and health care system^[42]. Much of literature focuses on female athletes as equivocal data exists for male athletes^[42]. This is because there is a paucity of literature available and controversial data on the effectiveness of IPP's modifying risk factors for ACL injuries and injury reduction rates^[42]. However, it is firmly established that IPP's successfully reduce noncontact ACL injury incidence rates in female adolescent athletes^[27].

Current evidence supports that the implementation of NMT and decrease in ACL tear incidence is age-related^[20]. The change in biomechanics and the onset of ACL injuries indicate that there is a potential optimal time to start these programs. This would be before the onset of changes in biomechanics and increase in ACL injuries^[20]. Therefore, initiation of IPP should be during early adolescence prior to these changes^[20].

Regardless, it is imperative that IPP's incorporate a wide variety and combination of strategies to help target ACL injury prevention. The comprehensive review of both systematic and meta-analyses studies are discussed in order to identify the best practice features of an ACL and lower limb IPP and determine the six essential components: (1) lower extremity and core strengthening; (2) plyometrics; (3) continual feedback to athletes regarding proper technique; (4) sufficient doses; (5) minimal-to-no additional equipment; and (6) balance training along with optional components of stretching and agility exercises that are required to help protect the athlete from sustaining such traumatic injuries.

Lower extremity and core muscle strength training

Of the lower extremity components, hamstring injuries are fairly commonly. The hamstrings are noted to be an antagonist of the quadriceps and provide a protective posterior force on the tibia^[18]. The ACL's anteromedial bundle is under the most tension during the last 30° of knee extension, therefore this posterior force could be protective by decreasing anterior translation^[18]. The quadriceps muscle contraction *via* the patella tendon-tibia shaft angle determines the anterior shear force that is generated during knee extension as well as during the contact phase of landing^[18]. Inherently, there exists an aberrant ratio of hamstrings to quadriceps neuromuscular activation^[18,26,27,35]. In order to reduce such forces, programs should incorporate exercises

such as isometric warm-up exercises, hamstring flexibility, and eccentric strength training (Russian/Nordic hamstring exercises), walking lunge, and single toe raise (gastrocnemius/soleus exercises) increase the muscle power to stabilize the knee to reduce injuries^[17,18,25,35].

Core strength is another important factor in reducing the risk of other injuries^[35]. Evidence supports that core muscle weakness may raise the risk of groin strain and knee joint injuries^[18,35]. Athletes who injured their ACLs were noted to have increased lateral trunk flexion and knee abduction angles^[18]. Exercises incorporating planks (front and side), sit-ups and abdominal curl are important^[18,35].

Another risk factor that should be targeted is excessive knee valgus motion. Certain movements in a sport adds stress to the medial passive and active stabilizing knee structures that predisposes one to an ACL injury^[26]. Specific NMT of the entire kinetic chain of the lower limb that are targeted for individual sports and their specific conditions of play are particularly required^[26]. For example, female basketball players exhibit increased medial knee displacement than female soccer players due to increased internal ACL loading^[26]. Therefore, it is important to have sport specific NMT focusing on jumping and landing tasks as well as the stop phase of a sidestep cutting maneuver for basketball that are based on ground reaction force and stance time data^[26].

Furthermore, the importance of ankle injuries can not be ignored. There is sufficient evidence that balance exercises might be effective in preventing ankle ligament injuries^[52]. Exercises that focus on the dynamic balance and strengthening such as single leg balance exercises. This can be performed by standing on one leg while throwing a ball with a partner, resisting a push from a partner while balancing on one leg, hopping across a line on the field or court, and one legged squat exercises should also be added^[35]. A program involving a combination of balance, eccentric hamstring, plyometrics and strength exercises could be efficacious in preventing lower limb injuries^[25]. Therefore, there is consensus that a multifaceted exercise program that is aimed at reducing general lower limb injuries is efficacious especially when combining strengthen and proximal control training^[18,25].

Plyometrics

NMT programs utilizing plyometric exercises and a preseason component were noted to be most beneficial^[10,26]. Plyometric exercises often incorporate side-stepping and/or single leg squats, jumping forwards and backwards, jumping side to side, and tuck and scissor jumps^[18,25]. This is to target the elevated knee abduction moment as well as to increase the knee flexion range by focusing on increasing power, muscle strength, and speed and improving motor control to reduce the peak knee valgus moments^[8,12,17,18,25].

Evidence shows that there is a 17%-26% reduction in ground reaction force on landing after 6-9 wk of training along with asymmetrical landing patterns reducing the side to side asymmetry landing force^[18]. This is especially important considering that high ground reaction forces are identified as one of the risk factors for future non-contact ACL injuries in female athletes^[18]. Overall, individual components of NMT programs such as plyometrics, strengthening, and proximal control training have been estimated to lead to ACL injury risk reduction of 61%, 68%, and 67% respectively^[18].

Continual feedback

Continual feedback on proper technique by the certified athletic trainer or sports physical therapist has been shown to be efficacious in reducing ACL injuries. The benefit may best be seen in sports with emphasis on landing and cutting maneuvers by altering landing patterns in frontal plan^[18,26], with the use of plyometric exercises to teach proper landing technique. Vocal cues during plyometric exercises such as "land light like a feather" can emphasize soft landing with the proper positioning of knees bent, patellar alignment with the second toe, and proper deceleration^[8,18,27]. Emphasis on biomechanical technique correction and individualized feedback that athletes receive appears to be a central element among the most successful programs that reduce ACL injury rate^[34].

Sufficient doses

For a NMT program to be successful, frequency and duration as well as adherence to the program is vital in reducing ACL injuries. The actual number of completed training sessions is likely more valuable than the prescribed number of sessions when considering the effectiveness of programs^[53,54]. Evidence supports prevention program should be performed two (2) or more times a week for a minimum of six weeks^[26]. Duration longer than 6 wk does not necessarily improve the effectiveness of the programs^[34]. Current analyses suggest performing preventive NMT interventions less than 20 min per session once a week during in-season can reduce 38%-39% of ACL injury risk^[46]. Fewer than two NMT session per week during the in-season without previous 6 wk pre-season NMT workouts of more than one session per week is less likely to demonstrate the prophylactic effects on ACL injury reduction than two or more sessions for 6 or more weeks^[46]. In addition, the IPP studies with statistically significant reductions in ACL injury rates had athletes performing preseason neuromuscular training^[53,54]. Therefore, it is recommended that a NMT program be performed for 10 to 20 min (higher compliance is seen with the shorter 10 min) at least two days per week in the preseason and at least 1 session per week during the season.

Additionally, better compliance is needed for sufficient training effects to reduce injuries^[35]. Compliance is a major issue and one should monitor the compliance for

the training program to ensure the desired protective transformations in reaction times, fatigue resistance and the correct movement patterns is obtained^[26,55]. Adjustment to the program may be needed if compliance diminishes to fit the individual team needs. There is an inverse dose-response relationship seen between NMT compliance and incidence rates of ACL injury^[12,49,50]. More specifically, it was noted that athletes with a low or moderate compliance rate had a risk of injuring their ACLs 4.9 and 3.1 times greater, respectively, than their counterparts who had high compliance rates^[49]. It is also speculated that the decrease in player compliance as the season progresses may be due to reduction of player attendance at training sessions over the season^[55]. In order for an ACL IPP to be effective, the overall compliance rate needs to be more than 66%^[49].

The importance of player level compliance in addition to team compliance is sometimes underestimated^[55]. It is possible that motivational barriers and facilitators among coaches over the entire season may need to be further investigated in order to maintain a high compliance rate for the NMT program^[55]. Consistent attendance by involved athletes and commitment to the completion of NMT throughout the season contributes to the effectiveness of the IPP^[49]. We recommend addressing issues of compliance with coaches and administration to determine reasons for reduced compliance and in order to correct these barriers.

Minimal-to-no additional equipment

A number of neuromuscular warm-up strategies do not require the acquisition of additional equipment^[35]. Balance work (using balance boards) and neuromuscular exercises (without balance boards) revealed that ankle sprains were reduced by 36% and 50%, respectively^[35]. However, neuromuscular strategies alone can reduce injuries without requiring the need to purchase additional equipment which would require resources many teams do not have available to them^[35]. Since a NMT programs can be performed with similar outcomes with and without additional equipment, we recommend no additional equipment.

Balance exercises

We recognize that in one review balance was associated with worse outcomes from IPP but this association was only with total hours of balance training and this was skewed by the inclusion of one study with an excessive amount of balance training^[30]. Balance exercises are considered effective when used in conjunction with other types of exercises for IPP^[18,26,35,42,51,56]. There is strong evidence for the prevention of ankle ligament injuries for the use of neuromuscular control and balance exercise, in addition a multifaceted program for the prevention of lower limb injuries^[25]. Balance programs may reduce ankle injuries, but the effects could be enhanced by utilizing proprioceptive exercises^[17,25,30].

Additionally, balance training may be required to

build proximal segment stability in order to further enhance trunk control^[18]. An asymmetrical landing pattern and landing favoring one foot is a risk factor for ACL injury which can be altered by incorporating balance training along with plyometrics^[18]. Balance training demonstrated improvement in the center of pressure measurements and a reduction in GRF during a single leg landing^[18]. Balance and plyometric training improve an athlete's motor control during tasks like sidestepping and/or single leg landing, reducing peak valgus knee moments (a risk factor of non-contact ACL injuries)^[25]. Therefore, NMT programs that incorporate plyometrics, and strengthening exercises have demonstrated effectiveness in reducing ACL injury risk factors^[16,17].

Stretching exercises

Stretching during warm-up routine before exercise has been historically advocated to prevent injury^[35]. However, current evidence time and again does not support static stretching alone for injury prevention benefit^[35]. Although studies have shown that static and dynamic stretching may have a positive impact on reducing injury rates when performed in an ACL prevention program^[30]. Previous studies have found that static stretching has no overall impact on preventing general musculoskeletal athletic injuries, but may have some relationship with reducing ligamentous injuries^[30]. Perhaps a beneficial effect in ACL injury reduction could be due to static stretching modifying the structural properties of ligamentous tissues^[30]. One downside of eliminating stretching from an IPP is athletes believe stretching is an essential part of an IPP and removal might decrease compliance^[57].

Agility exercises

Agility exercises are activities that improve the ability to move and change direction under control both quickly and effectively^[30]. Increasing the emphasis and duration of agility training in an IPP is beneficial in reducing non-contact ACL injury rates^[30,35,43]. Lower extremity mechanics during landing and cutting tasks are affected by a fatigue-producing agility training programs^[30]. Therefore, timing of the agility training intervention may be important. Specific agility exercises like shuttle run, diagonal run, bounding run or zigzag running with pressure technique should be supplemented by landing technique with feedback so that the players learn to avoid the high-risk landing and cutting positions^[26,35,43].

Limitations

A comprehensive review of literature containing both systematic and meta-analysis studies contain different limitations. The combination of mixed design studies can lead to difficult interpretations and incorrect results^[17]. Furthermore, the heterogeneous treatment protocols with exercise programs having varying intensity levels is another concern^[17]. Most of the studies can be

generalized to only the young female population as there is a dearth of studies on the males^[18]. Additionally, the limitations of systematic review include those inherent in determining the results of studies of varying design (*e.g.*, frequency, duration, and start of training); how the training was performed; who supervised; the components of the training program; and how exposure data was determined^[7,27,46,49]. To identify the exact essential exercise for IPP that are responsible for the reduction of injury incidence is not possible because of these inconsistencies. Furthermore, different types of neuromuscular training were applied to different sports, ages and study designs which makes the analysis challenging to identify imperative aspects of neuromuscular training^[7,46].

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COMMENTS

Background

Sports participation can increase the risk for injuries to the lower limbs especially the anterior cruciate ligament (ACL). When utilizing injury prevention program (IPP)'s, a variety of strategies to help target risk factors can be crucial in reducing the number of knee and ACL injuries, and therefore future knee osteoarthritis (OA). A comprehensive review of multiple systematic reviews and meta-analyses have identified the essential components to be lower extremity and core strengthening, plyometrics, continual feedback to athletes regarding proper technique, sufficient doses, minimal-to-no additional equipment, and balance training along with optional components of stretching and agility exercises to be included in a structured warm-up to maximize effectiveness of an ACL and lower extremity IPP's for youth athletics. The authors believe that participating in 10 min of IPP most days of the week that contain these features will diminish knee OA and reduce health care costs.

Research frontiers

The authors recommend future studies looking at compact 10-15 min programs in multiple groups and ages followed out for many years to determine the reduction of knee OA and health care costs.

Innovations and breakthroughs

IPP's have been important in modifying inherent risk factors in athletes to help reduce the number of ACL injuries and subsequent OA. Retrieved literature has provided an in depth overview of the various techniques that are pertinent in the various strategies utilized in IPP's.

Applications

This review suggests that IPP's should contain the six strategies in order to be effective in preventing athletes from sustaining ACL and lower limb injuries and subsequent OA. These should become incorporated into every high-risk sports training program.

Terminology

IPP's that incorporate a variety of strategies in NMTs to help target risk factors can be crucial in reducing the number of ACL and lower limb injuries sustained and subsequent OA.

Peer-review

The authors provide comprehensive study on lower limb injury prevention.

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Using humeral nail for surgical reconstruction of femur in adolescents with osteogenesis imperfecta

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Informed consent statement: According to the ethical approval, there was no need for informed consent from individual patients in retrospective study (all data were retrieved from medical records).

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Abstract

Osteogenesis imperfecta (OI) is a rare inherited connective tissue disorder caused by mutation of collagen which results in a wide spectrum of clinical manifestations including long bone fragility fractures and deformities. While the treatment for these fractures was recommended as using intramedullary fixation for minimizing stress concentration, the selection of the best implant in the adolescent OI patients for the surgical reconstruction of femur was still problematic, due to anatomy distortion and implant availability. We are reporting the surgical modification by using a humeral nail for femoral fixation in three adolescent OI patients with favorable outcomes.

Key words: Osteogenesis imperfecta; Adolescent; Humeral nail; Femoral fracture; Femoral bowing deformity

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Core tip: This case report presented the satisfactory clinical outcome of the adolescent osteogenesis imperfecta patients suffering from femoral fracture or bowing deformity which had been treated with the modification of humeral nail as intramedullary implant.

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INTRODUCTION

Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disorders with the common clinical presentation of excessive bone fragility caused by mutations in collagen^[1]. Clinical manifestations of OI are wide spectrum and could be vary from lethal forms in the perinatal period to the subtle forms, which could be hardly identified and comparable to a normal person. However, the common orthopaedic problems in the OI patients, that is related to the excessive fragility, are frequent fractures, progressive deformity of long bones and impaired ambulation. The treatment of OI requires a multidisciplinary approach including both medical treatment, such as using bisphosphonates therapy to increase bone mineral density and reduce long bone fractures rate^[2-4], and surgical treatment for fracture fixation or deformity correction^[4].

Regarding surgical management of OI, the treatment goals are to minimize the incidence of fracture, restore bone axis and avoid bone bowing^[4]. The recommended surgical implant in OI was a load-sharing intramedullary (IM) device, with the largest diameter as possible, due to the better biomechanical property in fragile bone over plate construct^[1] and avoid plate-related complications, such as bony resorption from stress shielding, implant failure, and subsequent fracture at the plate ending^[5,6]. However, the surgical fixation in OI, especially in adolescent OI patients with femoral fracture or nonunion, are still problematic due to particular abnormal femoral anatomy (such as short limb, non-anatomical alignment secondary to previous injury, and narrow and non-linear medullary canal with superphysiologic bowing)^[1] resulting in implant selection difficulty which was suitable for medullary canal size and bone length. Although there is an advanced surgical system, like a telescopic rod, which is specifically designed for OI patients with many different sizes that allow fixation in all age groups, this implant is not available everywhere, including our country. Moreover, the traditional implant standard pediatric IM devices such as single Rush pin might not be appropriate in these adolescent OI patients due to its small size and inability to provide rotational stability^[6-8]. Recently, there has been a few studies which reported that the small IM interlocking nail, such as humeral nail, could be used in femoral fixation in normal adolescent patients due to the advantages of the entry point lateral to tip of greater trochanter resulting in avoiding iatrogenic vascular injury and being the IM locking device with smaller diameter and shorter length than conventional femoral

nail which was appropriate for small-sized adolescent femoral anatomy^[9,10]. Therefore, this humeral nail should be also suitable for femoral fixation in adolescent OI patients. This study aimed to demonstrate the outcome of adolescent OI patients with femoral fracture or deformity and treated with humeral nail fixation.

CASE REPORT

Case 1

A 12-year-old girl with type I OI presented with progressive left femur deformity (August, 2013). Her height and weight were 138 cm and 51 kg. Initially, she had been diagnosed as type I b (Silence classification)/Tarda B (Shapiro classification) and received treatment since age of 7 years. Three years ago (2010), she had been treated with corrective osteotomy and Ender nail fixation for left femur bowing deformity and the fracture was united uneventfully. However, she had experienced the progressive deformity on her left thigh without pain on weight bearing. The radiographs showed anterolateral femoral bowing due to femoral varus and flexion deformity with 8.5-mm medullary canal diameter (Figure 1A).

Preoperative planning for progressive left femoral deformity was discussed. The goal of treatment was rigid fixation with load-sharing intramedullary (IM) device^[1]. The IM instrument options were K-wire, Rush pin, and telescoping IM device. K-wire and Rush was suitable only for small children with small IM canal due to the size of implant. Telescoping IM device was suitable for older children with larger IM canal, although this device was not available in our country. Therefore, we decided to use humeral IM nail for femoral osteotomy stabilization in this case due to two reasons. Firstly, the humeral nail was the interlocking nail that was available in smaller size and shorter length than conventional femoral nail. Thus, the humeral nail would be better in biomechanical property than single Rush pin. Secondly, the humeral nail geometry was rather straight than femoral nail resulting in the more lateral entry point for humeral nail insertion at the lateral to the tip of greater trochanter, and so avoiding the iatrogenic vascular injury on piriformis fossa.

Surgical technique: The patient was placed in lateral decubitus position under general anesthesia (GA). Multi-level corrective osteotomy was performed with drill and osteotome. Then the femur was reduced to acceptable alignment. The entry point was made at the tip of greater trochanter (GT), and the medullary canal was gently prepared by hand reaming using 6-mm and 7-mm T-reamer. Then a 7-mm diameter Expert humeral nail (Synthes®, Inc.) with 290-mm length was inserted following by proximal blade and distal locking screw insertion under fluoroscopic guidance. One additional wiring was performed due to iatrogenic cortical crack on the osteotomized fragment (Figure 1B). The operative time was 4 h, and the total length of hospital stay was 6

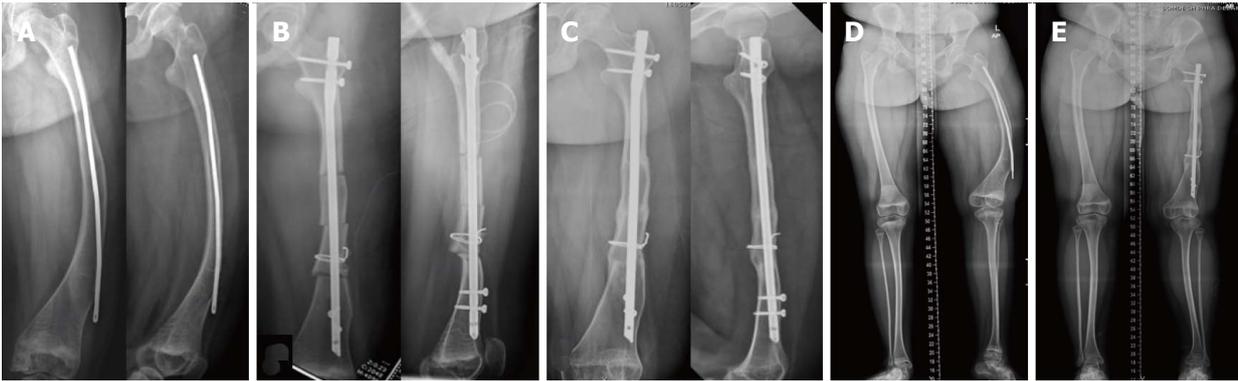


Figure 1 Clinical presentation of case 1. A 12-year-old girl with type I osteogenesis imperfecta presented with progressive bowing of left shaft femur after ender nail fixation for 3 years. Plain radiographs of left femur in anteroposterior and lateral views on preoperative period (A), immediately after multi-level osteotomy and internal fixation with humeral nail (B), 9-mo after humeral nail fixation (C), preoperative scanogram (D) compared with 1-year postoperative scanogram (E).

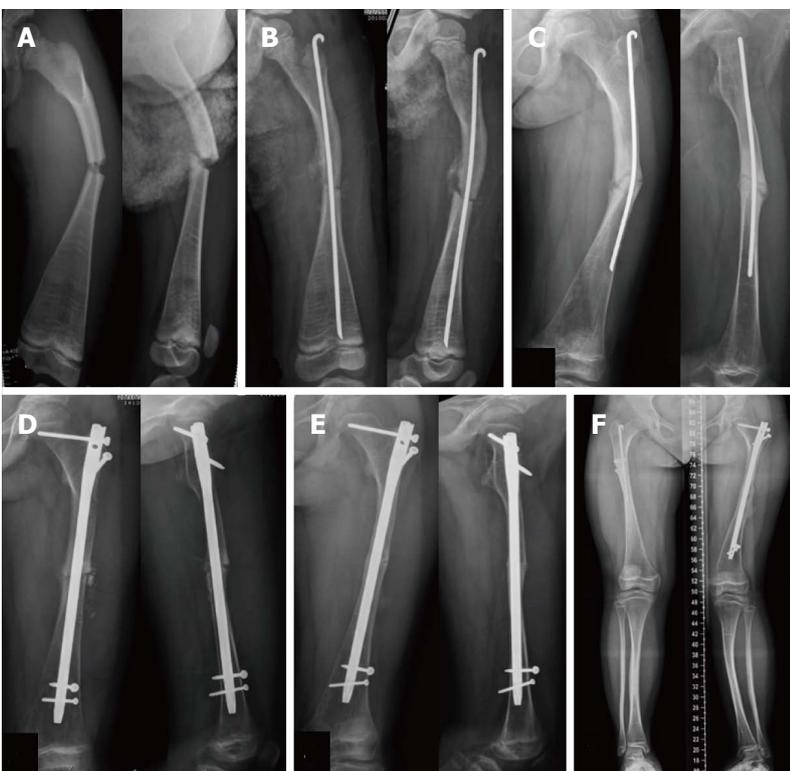


Figure 2 Clinical presentation of case 2. A 12-year-old girl with type III osteogenesis imperfecta presented with limping and pain on full weight bearing after Rush pin fixation for 4 years. Plain radiographs in anteroposterior and lateral views after injury (A), immediately after Rush pin fixation (B), 4 years after Rush pin fixation (C), immediately after humeral nail fixation (D), 9 mo after humeral nail fixation (E), and 1-year postoperative scanogram after humeral nail fixation (F).

d. Estimated blood loss was 350 mL.

1D and E).

Postoperative care and rehabilitation: The postoperative protocol was initially 6-wk toe touch weight bearing with gait aids following by progressive weight bearing as tolerated. The patient reported clinical union (pain-free full weight bearing without tenderness on osteotomy site) at 6 mo postoperatively, and the radiographic union was completed at 9 mo postoperatively (Figure 1C). On 3-year postoperative follow-up period, the patient had normal hip range of motion and function. The radiographs showed no evidence of avascular necrosis of femoral head (Figure

Case 2

A 12-year-old girl with type III OI presented with left femoral shaft oligotrophic nonunion with failed Rush pin fixation (2014). Her height and weight were 122 cm and 25 kg. She had been diagnosed as type III (Silence classification)/Tarda A (Shapiro classification) after birth and treated with intravenous bisphosphate therapy since the age of 3 mo. On 2010, at the age of 7 years, she sustained left femoral shaft fracture and had been treated with single Rush pin fixation (Figure 2A and B). After surgery, she was lost to follow-up for 3 years

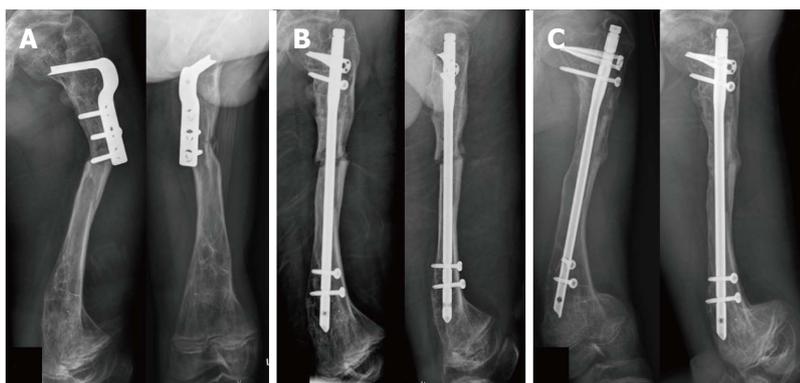


Figure 3 Clinical presentation of case 3 during the first operation. A 16-year-old male with type III osteogenesis imperfecta presented with subtrochanteric peri-implant fracture of left femur after corrective osteotomy and fixation with osteotomy plate for 10 mo. Plain radiographs in anteroposterior and lateral views after injury (A), immediately after humeral nail fixation (B), and 8 mo after humeral nail fixation (C).

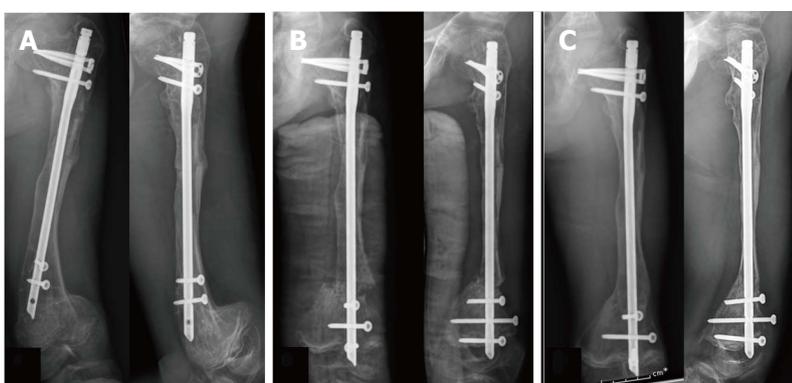


Figure 4 Clinical presentation of case 3 during the second operation. A 16-year-old male with type III osteogenesis imperfecta presented with progressive deformity of left distal femur after first humeral nail fixation for 10 mo. Plain radiographs in anteroposterior and lateral views on preoperative period (A), immediately after corrective osteotomy with humeral nail fixation (B), and 9 mo after humeral nail fixation (C).

(2011-2014) and then came back to our clinic 4-year postoperatively with limping and mild pain on full weight bearing. The radiographs showed that the fracture was still non-united with progressive bending of Rush pin (Figure 2C), and the medullary canal diameter was 9.2 mm. Therefore, the revision operation was planned as Rush pin removal with nonunion resection and humeral nail insertion with local bone graft.

Surgical technique: The patient was placed on lateral decubitus position under general anesthesia. The Rush pin was removed from old surgical scar. The nonunion site was opened directly with subvastus approach. Nonunion fibrous tissue was resected and previous bony callus was harvested for local bone graft. The humeral nail insertion was performed, with the same technique as above, using previous Rush pin entry point at the tip of GT. A 8-mm diameter M/DN Humeral Intramedullary nail (Zimmer, Warsaw, IN) with 255-mm length was applied and locked proximally and distally. Then local bone graft was inserted around the fracture site (Figure 2D). The operative time was 3.5 h, and the total length of hospital stay was 5 d. Estimated blood loss was 300 mL.

Postoperative care and rehabilitation: The patient was allowed 6-wk toe touch weight bearing followed by progressive weight bearing as tolerated. The clinical union was achieved within 6 mo and the radiographic union was completed within 9 mo postoperatively (Figure 2E). On 2-year postoperative follow-up period, the patient had normal function without pain on FWB. The radiographs showed no evidence of avascular necrosis of femoral head (Figure 2F).

Case 3

A 16-year-old male with type III OI presented with left subtrochanteric peri-implant fracture after falling on the ground (September, 2014). His height and weight were 130 cm and 27 kg. He was diagnosed as type III (Silence classification)/Congenita A (Shapiro classification) during antenatal care period, and treated with intravenous bisphosphate therapy since the age of 19 mo. He had previous bilateral leg deformity and had been treated with bilateral femoral and tibial corrective osteotomy. The radiographs showed displaced left subtrochanteric fracture below osteotomy plate with varus angulation, and bilateral distal femur extension deformity (Figures 3A, 4A, and 5A). The left and right medullary canal

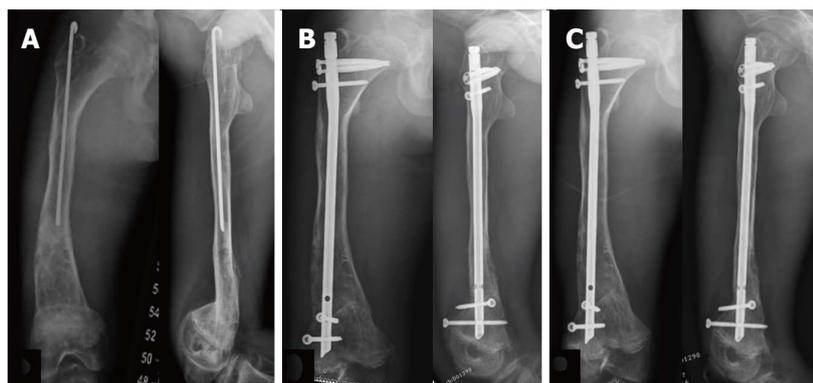


Figure 5 Clinical presentation of case 3 during the third operation. A 17-year-old male with type III osteogenesis imperfecta presented with progressive deformity after Rush pin fixation right shaft femur at early childhood. Plain radiographs in anteroposterior and lateral views on preoperative period (A), immediately after corrective osteotomy with humeral nail fixation (B), and 6 mo after humeral nail fixation (C).

diameters were 8.6 and 9.0 mm respectively.

Surgical technique: After preoperative planning was discussed, bilateral staged femoral reconstructions were planned as: (1) osteotomy plate removal and humeral nail insertion (August, 2014) (Figure 3B); (2) corrective hinged osteotomy left distal femur with humeral nail (June 2015) (Figure 4B); and (3) corrective osteotomy right distal femur with humeral nail (March, 2016) (Figure 5B). All operations were performed using the same technique as mentioned above with Expert humeral nail (Synthes®, Inc.). The operative times were 2.5, 3.5, and 3 h respectively. The lengths of hospital stay were 4, 4, and 3 d. Estimated blood loss were 200, 500, and 350 mL, respectively.

Postoperative care and rehabilitation: After the first and second operation on left femur, due to bilateral deformity, the patient was allowed for 8-wk wheel chair mobilization, and followed by weight bearing as tolerated with full weight bearing after 3 mo postoperatively. The subtrochanteric fracture and osteotomy site both showed clinical union and radiographic union at 3-mo and 8-mo postoperatively (Figures 3C and 4C). After the third operation on his right femur, the postoperative protocol was the same as case no.1 and no.2 due to complete fracture healing with good alignment on left femur. The clinical and radiographic union were shown at 3-mo and 5-mo postoperatively, respectively (Figure 5C). At the most recent follow-up (postoperative 10 mo after the third operation), the patient showed normal hip range of motion with pain-free weight bearing. No avascular necrosis of femoral head was found.

DISCUSSION

OI is a heritable disorder of collagen synthesis that commonly presents as bone fragility with multiple long bone fractures and deformities. These bony problems usually require surgical management for fracture fixation or reconstruction by the load-sharing IM device. However, the surgical fixation in OI patients, especially

in the older children with femoral fracture or deformity, is very difficult due to the abnormal femoral anatomy resulting in implant selection problems such as a mismatch with conventional femoral IM nail, the poor fixation stability of standard pediatric IM device (Rush pin), and the high cost of advanced telescopic rod. This study aimed to present the usefulness of humeral nail fixation as a surgical tool for femoral reconstruction in adolescent OI patients.

The humeral nail application for femoral fixation in adolescent OI patients has many advantages. Firstly, humeral nail implant, which is available in smaller diameter and shorter length than conventional femoral IM nail, is more suitable with these patients' femoral anatomy with narrow medullary canal and short limb. Secondly, humeral nail geometry has narrow width and is easier to insert into the lateral transtrochanter area^[9] which can avoid the risk of iatrogenic injury to greater trochanter physis^[11] or medial femoral circumflex artery^[12]. Thirdly, due to the interlocking nail property, the humeral nail would offer superior biomechanical benefits than the standard Rush pin fixation as better in rotational stability and leg length control, especially for the patients with multilevel corrective osteotomy.

However, there were also some limitations for using humeral nail for femoral reconstruction in adolescent OI patients. First, most of the humeral nail designs had only 90-100 degree of the cephalomedullary angle for proximal locking blade/screw, which was more varus than the neck-shaft angle of the femur and resulting in suboptimal fixation for proximal femur. Therefore, we recommended carefully adjustment of the proximal blade/screw position to achieve the best position and longest length as possible for the stable femoral head and neck fixation (Figures 2-5). Second, the required length for distal locking screw was usually longer than normal due to the wider width of distal femur than distal humerus, thus it was necessary to prepare the extra-length distal locking screw or using the other types of screw, such as 3.5 mm or 4.5 mm cortical screw, instead. Lastly, due to the abnormal femoral anatomy and using humeral nail design, we recommended

performing the rotational alignment examination by intraoperative checking hip rotation in every cases.

The results of this study showed that using humeral nail implant in femoral fixation was possible and could be used in proximal, middle or distal location. Moreover, this option could be indicated for fixation of fracture and nonunion, or corrective osteotomy. Our study also demonstrated the favorable outcome with 100% fracture healing [the mean clinical union time of 4.2 mo (range 3-6 mo) and the mean radiographic union time of 7.8 mo (range 5-9 mo)] and without the implant-related complications such as infection, nonunion, or AVN. Therefore, we concluded that the humeral nail application for femoral fixation in adolescent OI patients would be one of the possible options with satisfactory outcomes.

COMMENTS

Case characteristics

Three adolescent patients with underlying osteogenesis imperfecta presented with progressive femoral deformity (case 1) or nonunion (case 2) or peri-implant fracture and bilateral distal femur deformity (case 3).

Clinical diagnosis

Case 1: Varus and flexion deformity on left femur without local tenderness. Case 2: Antalgic gait with pain on weight bearing, and local tenderness on the fracture site. Case 3: Moderate swelling, local tenderness on left thigh, and limited movement by pain with bilateral distal thigh deformity.

Differential diagnosis

Progressive deformity associated with osteogenesis imperfecta (OI), fracture or osteotomy nonunion, infection, implant irritation.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Case 1: Radiographs showed anterolateral femoral bowing deformity. Case 2: Radiographs showed persistent radiolucent line on fracture site and progressive Rush pin bending. Case 3: Radiographs showed displaced subtrochanteric fracture below osteotomy plate with bilateral distal femur deformity.

Treatment

Case 1: Ender nails removal and multi-level corrective osteotomy with humeral nail. Case 2: Rush pin removal, and open reduction and internal fixation with humeral nail and local bone graft. Case 3: Bilateral staged femoral reconstructions; (1) osteotomy plate removal and humeral nail insertion; (2) corrective hinged osteotomy left distal femur with humeral nail; and (3) corrective osteotomy right distal femur with humeral nail.

Related reports

The recommended surgical treatment of long bone fracture in OI patients is load-sharing intramedullary fixation to avoid plate-related complications (implant failure, peri-implant fracture, etc.). However, the femoral reconstruction in these adolescent OI patients was difficult due to the abnormal femoral anatomy (short limb, abnormal alignment from previous fracture or bowing, and narrow medullary canal), and the unavailability of the specific IM implant.

Term explanation

OI is a rare genetic disorder of the synthesis of collagen that mainly affects the bone, and commonly presents as recurrent fracture and deformity.

Experiences and lessons

The humeral nail application for femoral fixation in adolescent OI patients should be performed with careful preoperative planning, gentle fracture manipulation, and strict postoperative rehabilitation protocol.

Peer-review

The authors demonstrated excellent results for treatment of femur deformity in OI adolescents with humeral nail. The paper is well written and instructive.

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Hernia mesh prevent dislocation after wide excision and reconstruction of giant cell tumor distal radius

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Abstract

Giant cell tumor (GCT) remains as major health problem. GCT which located at the lower end of the radius tends to be more aggressive. Wide excision and reconstruction of the wrist in stage 3 of distal radius GCT lesion is an optimal modality to prevent tumor recurrence. However, dislocation often occurs as its complication. We are reporting patient with GCT of distal radius treated with wide excision and reconstruction using nonvascularized fibular graft and the addition of hernia mesh. Circumferential non-absorbable polypropylene hernia mesh was applied, covered radioulnar joint and volar aspect of radius, and served as additional support to prevent dislocation. During five years and two months of follow-up, we found no dislocation in our patient. Furthermore, good functional outcome was obtained. Our finding suggests that the addition of hernia mesh after wide excision and reconstruction with nonvascularized fibular graft may benefit to prevent dislocation and provides an excellent functional outcome.

Key words: Giant cell tumor; Wide excision; Fibular graft; Hernia mesh; Dislocation

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Core tip: Dislocation after wide excision and reconstruction

with nonvascularized fibular graft on giant cell tumor (GCT) distal radius often occur and becomes a problem for the patient. This case report presented the outcome of a patient with GCT of distal radius and treated with wide excision and nonvascularized fibular graft with the addition of non-absorbable polypropylene hernia mesh. Circumferential non-absorbable polypropylene hernia mesh may prevent the occurrence of dislocation and provides an excellent functional outcome.

Wiratnaya IGE, Budiarta IGBAM, Setiawan IGNY, Sindhughosa DA, Kawiyana IKS, Astawa P. Hernia mesh prevent dislocation after wide excision and reconstruction of giant cell tumor distal radius. *World J Orthop* 2017; 8(9): 741-746 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i9/741.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i9.741>

INTRODUCTION

Giant cell tumor (GCT) is an aggressive lesion with a high rate of recurrence^[1]. Most GCTs are located in the epiphyseal regions of long bones, however studies reported that GCT in the lower end of the radius more aggressive and possess higher tendency for local recurrence^[2,3]. Treatments for GCT of distal radius include curettage followed by bone graft or cementing, en-bloc excision and reconstruction either with nonvascular or vascular fibular autograft, ulnar translocation, endoprosthesis, or amputation^[4-6].

Wide excision is the optimal surgical treatment modality to prevent tumor recurrence in stage 3 of distal radius GCT lesion. However, reconstruction of wrist after wide excision of distal radius remains a challenging task. Most patients are active young adults who demand cosmetically acceptable and functionally adequate wrist. Nonvascularized proximal fibular graft without arthrodesis still used for reconstruction with excellence function, but dislocation of radiocarpal joint often occur as its complication after surgery^[7]. Here we try to prevent dislocation of radiocarpal joint by using hernia mesh.

CASE REPORT

A 28-year-old female presented with lump and pain on the left wrist since one year. The lump was getting bigger, and the pain was felt while flexing the wrist. On examination, the lump was observed on the distal end of the radius with tissue exposure on the dorsal side (Figure 1). The skin was shiny, tense, tenderness with ill-defined margins. The wrist's range of movements was restricted with intact neurovascular status. Left wrist anteroposterior and lateral radiograph revealed extensive local bony destruction along with significant soft-tissue expansion (campanacci grade 3) (Figure 2). She was suspected with GCT of the left distal radius. However, she refused open biopsy and went to bone setter. She came



Figure 1 Clinical photograph of the patient.



Figure 2 Preoperative X-ray of the patient.

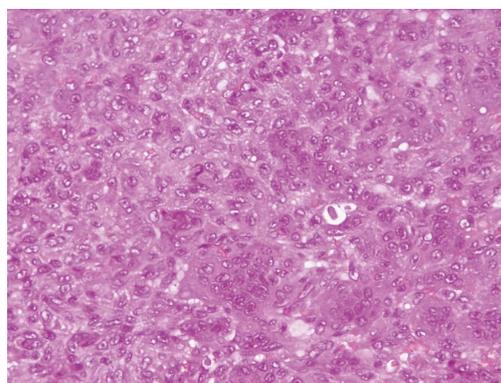


Figure 3 Histopathology examination of the tumor. Multinucleated giant cells were observed from the examination with background of mononuclear cells.

back to the outpatient clinic and then an open biopsy was performed. Histopathology examination revealed GCT of bone (Figure 3).

We did wide excision (Figure 4) with a posterior approach along with intracapsular resection (Figure 5) and osteotomy 9 cm proximal from styloid of radius (Figure 6). Flexor, extensor tendon, radial, ulnar artery, median and ulnar nerve were able to preserve. Subsequently, the lateral approach was used for harvesting entire proximal fibula including the head of fibula and bicep tendon with a length of 4 cm. The



Figure 4 Intra-operative photograph of wide excision with posterior approach.



Figure 6 Intra-operative photograph showing large defect due to wide excision.



Figure 5 Excision of tumor.

common peroneal nerve was identified and osteotomy 10 cm from the head of fibula was done (Figure 7).

The harvested fibula was fixed to the radius with 3.5 locking plate. The tip of fibula should lie for the radial styloid and its articular surface articulated with scaphoid. The dorsal radiocarpal capsule was sutured with bicep tendon, and the transplanted fibula stabilized to ulnar with 1.6 K wire. To prevent dislocation of the radioulnar and radiocarpal joint, circumferential non-absorbable polypropylene hernia mesh was applied circularly. At the distal part, the mesh was sutured to the remain of the capsule and the ligament of os carpalia at the volar, while at the proximal part the mesh was sutured to the periosteum and the surrounding soft tissue, attached



Figure 7 Proximal fibula harvested via lateral approach. The asterisk showing the intact of peroneal nerve (A) including head of fibula and bicep tendon (B).

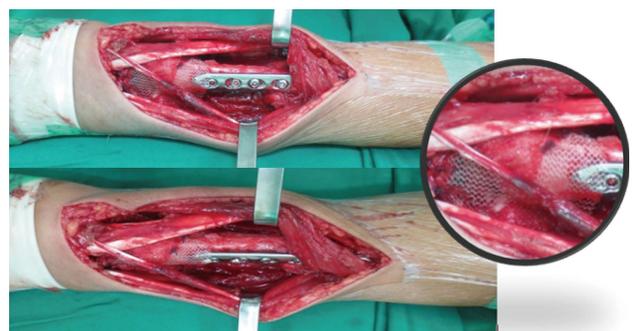


Figure 8 Fibular graft implantation fixed with 3.5 locking plate and covered with hernia mesh on radioulnar joint and volar aspect of radius. The inset showing the hernia mesh.

to fibular graft. The mesh covered the radioulnar joint (Figure 8). This hernia mesh is used to provide additional support to weakened or damaged tissue in this area. Afterward, X-ray examination was performed (Figure 9). A short arm splint in 30° wrist extension was applied. Splint and pins were removed six weeks post



Figure 9 The post operative X-ray after wide excision of giant cell tumor of distal radius (A) and defect in fibula (B).



Figure 10 The follow-up X-ray 5 years after the wide excision of giant cell tumor distal radius and fibular autograft and after removal of plate and screw.



Figure 11 The clinical picture of functional outcome after five years of follow-up. The pictures showing a range of motion of 75%-99% of normal side, and grip strength of 100% compared with normal hand.

operation and gentle range of motion was advised.

Four months post operation we evaluate her functional outcome by using Mayo Wrist Score and obtained a good result. Evaluation with quick dash score also obtained a good result. The total disabilities involving the arm, shoulder and hand (DASH) score was 9.2. During five years and two months of follow-up, no subluxation was observed in our patient (Figure 10). The total Mayo Wrist Score was 90. The patient did not feel any pain, returned to regular employment, range of motion of 75%-99% of normal side, and grip strength of 100% compared with normal hand (Figure 11).

DISCUSSION

En bloc excision method leaving a large defect in excision area, thus reconstruction on this site is necessary. Various techniques have been described for reconstruction, including iliac crest graft, centralization of ulna, distal radial allograft, vascularized or non-vascularized fibular graft, and prosthesis. Non-vascularized fibular autograft is one reconstruction technique to fill the defect caused by the wide excision. It was first used in 1945 for congenital absence of radius. The fibula was chosen since its size and shape are similar with distal radius^[8]. Later,

fibular transplant was used by various authors for tumors of the lower end of radius.

Nonvascularized fibular autograft possesses more advantages compared with other procedures. It has low morbidity of the donor site, satisfactory functional result, and free of major complications although some minor complications exist^[7,9,10]. A study by Saini *et al*^[11] in twelve patients with GCT of distal radius treated with wide excision of tumor and ipsilateral nonvascularized fibular autograft obtained the average of grip strength was 70% (24%-86%) compared with normal contralateral side and well preserved of forearm supination and pronation movement. However, a complication in term of subluxation occurs in 3 cases.

Subluxation is a commonly-occurring complication in defect reconstruction with nonvascularized fibular autograft method. With the addition of hernia mesh, the patient in our case did not develop any dislocation or subluxation, but the incidences reported in the literature are quite high. A study by Saikia *et al*^[7] (2010) obtained 10 cases of subluxation from the total of 24 GCT of distal radius cases treated with en bloc resection and arthroplasty reconstruction of autogenous non-vascularized ipsilateral fibular graft. Seven of them occur 3-12 mo after surgery. A study by Dhammi *et al*^[12] in 16 patient with GCT of lower end radius treated with similar method reported 10 cases suffered from wrist subluxation out of 16 patients, with follow-up duration ranges from two to five years. Saraf *et al*^[13] reported subluxation on 2 patients from 15 patients which caused significant pain, deformity, and loss of function.

Fibular graft with appropriate length is a method to prevent subluxation of wrist joint after the reconstruction was performed. Saikia *et al*^[7] ensure the appropriate length obtained with the addition of 2-3 mm longer than the required length, which is the resection tumor and safe margin, so that the compression at the host-graft junction during fixation with DCP was achieved and subluxation could be prevented. K-wire fixation used to stabilized wrist joint. However, this method did not ensure the prevention of subluxation.

We perform modification with a different approach than previous technique that is the addition of hernia mesh to prevent subluxation or dislocation. Circumferential hernia mesh which covered radioulnar joint and volar aspect of the radius was applied to stabilize the graft. Furthermore, the tensile strength of the mesh may withstand the local pressure forces, hence prevent the occurrence of dislocation or subluxation. During five years and two months of follow-up, no subluxation was observed in our patient. The total Mayo Wrist Score was 90. The patient did not feel any pain, returned to regular employment, the range of motion of 75%-99% of normal side, and grip strength of 100% compared with normal hand.

In conclusion, the complication in the form of subluxation did not occur in our case. Reconstruction method with the addition of hernia mesh to prevent subluxation provides an excellent functional outcome.

COMMENTS

Case characteristics

A 28-year-old female with lump which getting bigger in the last one year and pain on left wrist, aggravated by flexion of the wrist.

Clinical diagnosis

Swelling on the distal end of radius, the skin condition was shiny, tense, tenderness with ill-defined margins, and tissue exposure on the dorsal side.

Differential diagnosis

Aneurysmal bone cyst and tuberculosis of bone.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Anteroposterior and lateral radiograph of the left wrist showed extensive local bony destruction along with significant soft-tissue expansion (campanacci grade 3).

Pathological diagnosis

Multinucleated giant cells with a background of mononuclear cells, appropriate for giant cell tumor (GCT).

Treatment

Wide excision and reconstruction using non vascularized fibular graft with the addition of hernia mesh.

Related reports

GCT located in the lower end of the radius tend to be more aggressive and has a higher tendency for local recurrence. The optimal surgical treatment to prevent tumor recurrence in stage 3 of GCT distal radius is wide excision along with non-vascularized fibular autograft to repair the large defect in excision area. Subluxation is a commonly-occurring complication in defect reconstruction with nonvascularized fibular autograft method. The addition of hernia mesh may advantageous to prevent the subluxation, affecting the functional outcome of the patient.

Term explanation

GCTs are benign tumors which have a tendency for aggressive characteristics and ability to metastasize. The disabilities of the arm, shoulder and hand (DASH) score is an outcome instrument for measuring upper-extremity disability and symptoms.

Experiences and lessons

The addition of hernia mesh after wide excision and reconstruction using nonvascularized fibular graft of GCT of distal radius prevent the complication in term of subluxation and offer excellent functional outcome.

Peer-review

The authors present a very interesting paper on the reconstruction of the wrist after radius bone excision for a GCT.

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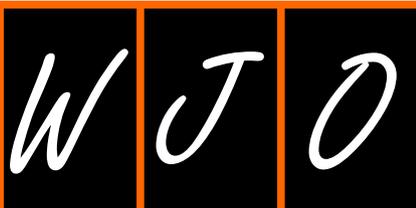
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Nuclear medicine imaging in osteonecrosis of hip: Old and current concepts

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Abstract

Osteonecrosis (ON) is caused by inadequate blood supply leading to bone death, which results in the collapse of the architectural bony structure. Femoral head is the most common site involved in ON. Magnetic resonance imaging (MRI) is a commonly used imaging modality to detect early ON. When MRI is inconclusive, bone scan is helpful in detecting ON during early phase of the disease. As newer nuclear medicine equipment, like single photon emission computed tomography/computed tomography (CT) and positron emission tomography/CT, are emerging in medical science, we review the role of these imaging modalities in ON of femoral head.

Key words: Osteonecrosis; Avascular necrosis; Bone scan; Magnetic resonance imaging; Photon emission computed tomography scan; Single photon emission computed tomography/computed tomography

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Core tip: Early diagnosis and treatment remains the key to hip preservation in osteonecrosis (ON). Till date magnetic resonance imaging (MRI) is considered as the gold standard diagnostic modality for ON. However with the improvement in nuclear imaging technique, the disease can be diagnosed even at a very early stage. Available literature suggests that single photon emission computed tomography/computed tomography (CT) bone scan and

¹⁸F-fluoride photon emission computed tomography/CT have similar or better results in comparison to MRI in ON of the femoral head. They also provide both morphological and metabolic information in the disease part and hence can indicate whether the disease is active or healed.

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INTRODUCTION

Osteonecrosis (ON) is caused by inadequate blood supply leading to bone death, which results in the collapse of the architectural bony structure. ON can be due to interruption of the vascular supply as a result of local trauma or non-traumatic systemic conditions^[1]. In general, symptomatic patients present with pain and reduced range of motion. Initially, pain is due to increase in intramedullary pressure resulting from medullary bone marrow edema. However, clinical diagnosis is often difficult due to lack of specific symptoms during the initial period. Common sites for ON include the femoral head, humeral head, knee, femoral and tibial metadiaphysis, scaphoid, lunate and talus^[2]. Femoral head is the most common site involved in ON^[1]. In the femoral head, site of necrosis is immediately below the weight bearing articular surface of the bone, *i.e.*, the anterolateral aspect of the femoral head. Early recognition of the disease is essential for better patient management.

RADIOLOGICAL IMAGING IN ON

The clinical findings and imaging studies are the primary modalities used to diagnose and stage ON. In radiology, the imaging modalities to detect ON are conventional radiographs, computed tomography (CT) and magnetic resonance imaging (MRI). In nuclear medicine imaging, the imaging modalities are planar bone scintigraphy, single photon emission computed tomography (SPECT) only bone scintigraphy, SPECT/CT bone scintigraphy and ¹⁸F-fluoride positron emission tomography/CT (PET/CT) bone scan. Different staging systems have been developed based on the severity of symptoms and imaging findings. Knowledge of degree of involvement in ON of femoral head helps in selecting the optimal treatment and also predicting the prognosis. In general, the most important feature of the staging system is the initial collapse of the cortex of femoral head. Before collapse, the necrotic lesion in the cortex can undergo repair and the damage may be reversible; after collapse, the damage is irreversible^[1].

Conventional radiographs

Being the least expensive and most widely available method, imaging evaluation of ON usually begins with



Figure 1 X-ray pelvis anteroposterior view shows collapsed right femoral head with sclerosis and subchondral lucencies, suggestive of osteonecrosis of right femoral head.

conventional radiography. Ideally, both frontal and frog-leg lateral projections should be obtained. The typical radiographic appearance shows patchy areas of lucency with surrounding sclerosis^[2]. The surrounding sclerotic margin correlates with the host bone response to wall off the areas of necrosis. X-rays may also show early articular collapse (Figure 1). However, radiography has low sensitivity during early stages.

CT

In early femoral head ON, a CT scan may show alteration of the normal "asterisk" that is formed due to condensation of the compressive and tensile trabeculae. Although, CT has lower sensitivity in detection of early changes than scintigraphy or MR imaging, it is helpful for detecting articular collapse location and extent in epiphyseal ON^[3-5].

MRI

MRI is considered the most sensitive and specific imaging modality in detection of ON^[6,7]. Generally, early fatty marrow necrosis is not associated with changes in signal intensity on MR studies. Death of cellular marrow components initiates tissue reaction, which results in appearance of a reactive interface between live and necrotic marrow areas. The hallmark of early avascular necrosis lesions is clear delineation of normal-appearing epiphyseal area with either a low-signal-intensity band on T1-weighted images or a rim of sclerosis on radiographs^[2]. The rim of sclerosis is often crescentic or wedge shaped. The interface appears as a low-signal-intensity band with a sharp inner face and a blurred outer face on MRI^[8]. A "double-line" sign on T2 weighted MRI has been demonstrated in 65%-85% of cases of early ON^[8]. This double-line sign consists of an outer low signal intensity rim of sclerosis and a second inner high signal intensity representing the reparative granulation tissue of the reactive interface. However, some authors have attributed the outer low signal intensity rim to a potential chemical-shift artifact^[9].

In a minority of patients, the area of ON may also show intrinsic characteristics such as hemorrhage

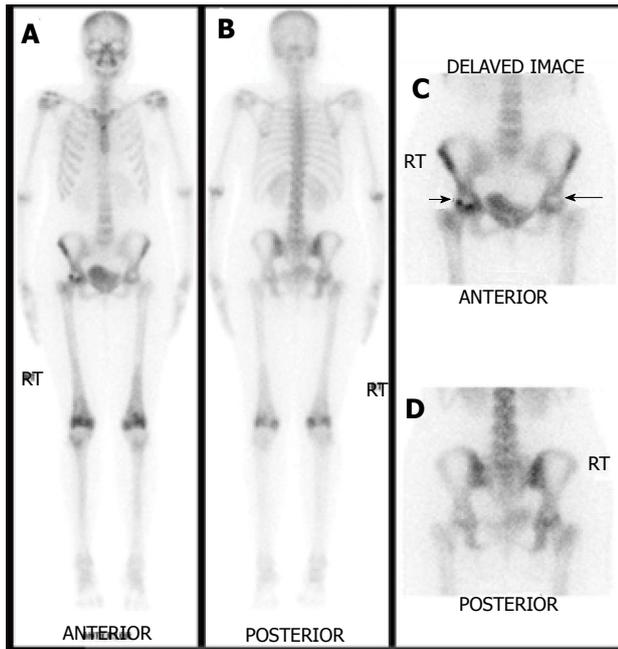


Figure 2 A 30-year-old female treated with chemotherapy for breast cancer was referred for ^{99m}Tc -MDP bone scan to evaluate cause of disabling hip pain. Whole body (A and B) and delayed images (C and D) demonstrate photopenic areas in bilateral femoral heads (arrows) with increased osteoblastic activity surrounding the photopenic region in the right femoral head, suggestive of bilateral avascular necrosis. Increased osteoblastic activity in bilateral distal femora is likely due to biomechanical stress reaction due to altered gait.

(high signal intensity on T1- and T2-weighted), cystic changes (low signal intensity on T1-weighted and high signal intensity on T2-weighted images), and fibrous tissue (low signal intensity with all pulse sequences). Non-specific diffuse marrow signal abnormality may be seen in patients with sickle cell anemia and Gaucher's disease. On a contrast enhanced MR study, typically, there is lack of enhancement of the necrosed area. A peripheral rim of enhancement corresponding to the zone of creeping substitution granulation tissue is generally seen^[2]. In advanced disease, lesions show low signal intensity on T1 weighted and variable signal intensity on T2 weighted images. However, previous studies have demonstrated that signal changes on MR imaging may not be evident despite histologic evidence of ON^[10-12]. It has been shown that signal changes caused by the death of marrow cells from ischemia on T1- and T2-weighted images may not occur until 5 d after interruption in the blood supply^[10]. Hence, MRI may be false negative in the early phase of ON.

NUCLEAR MEDICINE IMAGING IN ON

Planar technetium-99m methylene diphosphonate bone scintigraphy

Technetium-99m methylene diphosphonate (^{99m}Tc -MDP) bone scintigraphy is one of the most commonly performed nuclear medicine studies. It is highly sensitive in detection of different benign and malignant bone pathologies^[13]. The skeleton is made up of inorganic

calcium hydroxyapatite crystals. The tracer uptake in a bone scan primarily identifies areas of osteoblastic activity. ^{99m}Tc -MDP binding occurs by chemisorption in the hydroxyapatite component of the osseous matrix. However, blood flow is the other most important factor influencing uptake of the radiotracer. As low as 5% change in bone turnover can be detected on bone imaging, whereas 40%-50% of mineral must be lost to detect lucency within the bone on radiographs and CT^[14].

Three phase bone scan is usually performed in patients with suspected ON. In the three phase study, a bolus of ^{99m}Tc -MDP is injected intravenously with the concerned body parts under the gamma camera. The first phase of the study includes immediate dynamic images after radiotracer injection acquired for 60 s. The second phase or blood pool or soft tissue phase is acquired after approximately 5-10 min of radiotracer administration and delayed phase after 2-3 h.

As ON is an evolving process, the appearance on bone scan depends on the stage of the disease. In the acute phase of ON, no radiotracer is delivered to the bone tissue. Therefore, initially for 7-10 d after the event, ON generally appears on bone imaging as a photopenic area (Figures 2 and 3). After 1-3 wk, increased radiotracer uptake is seen in a subchondral distribution due to osteoblastic activity at the reactive interface around the necrotic segment^[15]. Imaging with pinhole collimator is useful as it increases the resolution. Overall sensitivity of bone scintigraphy for diagnosis of ON of femoral head is from 78% to 91%^[16-18]. This variation in sensitivity is probably due to different etiology of ON of femoral head. For example, sensitivity is high in ON following femoral neck fracture due to sudden and nearly complete cut off of blood supply resulting in large, well defined cold lesion on bone scintigraphy. However, in chronic processes like steroid induced ON, typical cold lesion may not be identified and scintigraphy usually demonstrates increased tracer localization due to microcollapse and repair. Some studies have shown that bone scan is superior to conventional MRI in early detection of ON^[19]. However, a planar bone scan has its own limitations of low specificity due to difficulty in distinguishing ON from fractures, transient osteoporosis or other conditions^[1]. Although MRI is considered the diagnostic modality of choice in patients with femoral head ON, bone scan remains a valid alternative with fractured femoral neck with a metallic fixation device. Moreover, it is also helpful when involvement of multiple sites is suspected in patients with risk factors such as sickle cell disease.

SPECT bone scintigraphy

SPECT imaging is a nuclear medicine modality which produces cross-sectional images similar in presentation to CT and MRI in radiology. On planar bone scintigraphy, earliest and most evident finding of ON, *i.e.*, photopenic region in the femoral head may be obscured by the superimposed acetabular and other surrounding bone activity^[20]. This overlying increased activity could be



Figure 3 Coronal single photon emission computed tomography (A), coronal computed tomography (B) and coronal fused single photon emission computed tomography/computed tomography images (C) of the patient mentioned in Figure 2 localizes the photopenic defects to head of bilateral femora. The lucent areas with surrounding sclerosis in both femoral heads on low dose computed tomography (CT) component of single photon emission computed tomography/CT (B) increase the diagnostic confidence and specificity.

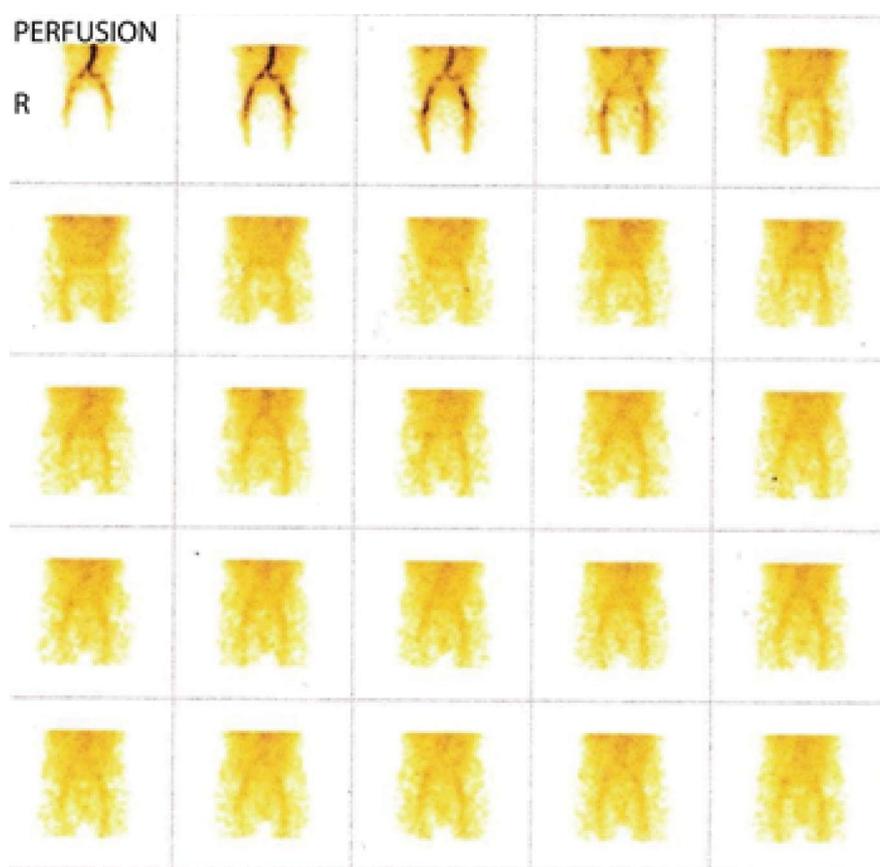


Figure 4 Perfusion phase of three-phase ^{99m}Tc-MDP bone scan of a patient with right side hip pain shows symmetrical flow of tracer in bilateral hips.

due to osteoarthritis, fracture, inflammatory arthritis, etc., and results in false negative test results. As SPECT provides three-dimensional images, it is possible to separate the femoral head from other overlying bony structures (Figures 4-6). Siddiqui *et al*^[21] demonstrated that both MRI and bone SPECT are complementary to each other in detecting subclinical avascular necrosis in asymptomatic renal allograft recipients. Ryu *et al*^[20] showed that bone SPECT imaging is more sensitive than MRI in early detection of femoral head ON in renal transplant recipients. Their study revealed 100%

sensitivity of SPECT in detection of ON of the femoral head, compared to 66% for MRI. Several other studies have shown that in ON of the femoral head, the sensitivity of MRI ranges from 85% to 100% and that of SPECT bone imaging ranges from 85% to 97%^[22-24]. Hence, SPECT bone scan could be equally informative in patients with suspicion of ON of the femoral head.

SPECT/CT bone scintigraphy

Hybrid SPECT/CT provides both anatomical and metabolic information (Figures 2 and 3)^[13]. CT component is helpful

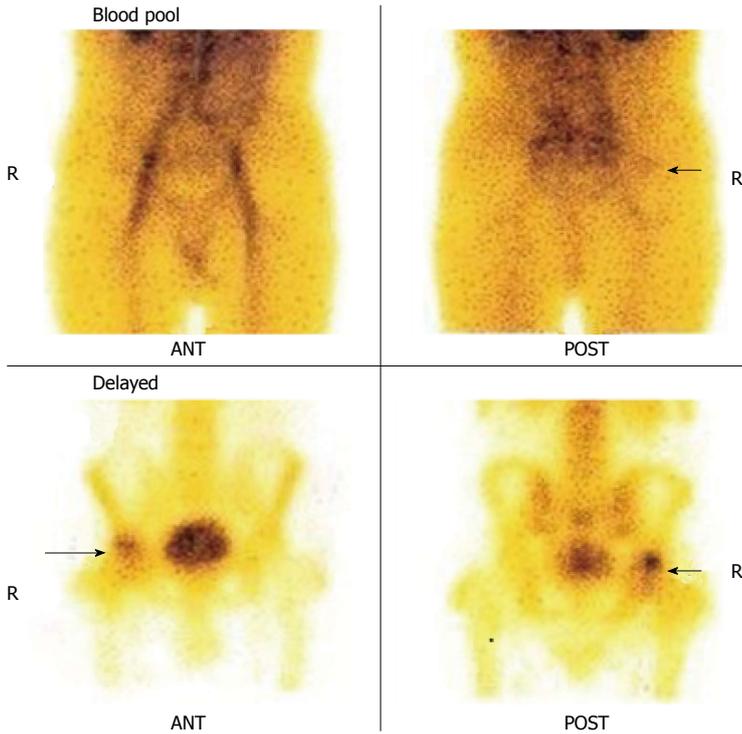


Figure 5 Blood pool images of the patient (as mentioned Figure 4) show minimally increased tracer uptake in the region of right hip. The delayed images show increased tracer uptake in the right hip region with no definite photopenic area.

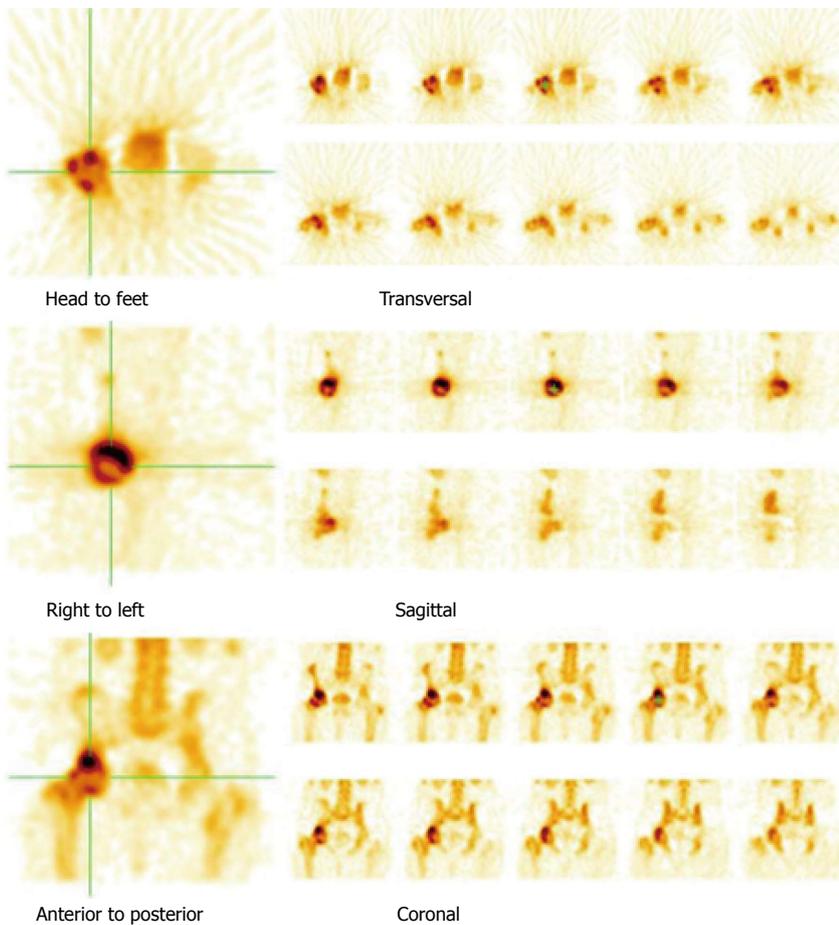


Figure 6 The single photon emission computed tomography images of the patient (as mentioned in Figure 4) show definite central photopenia with surrounding increased tracer uptake in the right femoral head (not evident on planar delayed images), suggestive of osteonecrosis of the right femoral head.

in localization and characterization of increased osteoblastic activity seen on planar or SPECT only images. CT scan added to SPECT can detect subtle collapse of the femoral head, which may not be easily visible on plain radiographs. In addition, morphological imaging may detect other underlying pain generators, which may explain the symptoms. Although SPECT-only bone scintigraphy has high sensitivity, its specificity is low. Luk *et al*^[25] showed that SPECT/CT has similar sensitivity (100%) as SPECT bone scintigraphy, but better specificity compared to SPECT imaging alone (88% vs 82%) for the diagnosis of ON of the femoral head. In another study, SPECT/CT was found superior to planar and SPECT only bone scan for the diagnosis of ON. SPECT/CT demonstrated diagnostic accuracy of 95%, sensitivity of 98% and specificity of 87% compared to diagnostic accuracy of 67%, sensitivity of 75% and specificity of 40% for planar bone scan^[26].

¹⁸F-fluoride PET bone scan

With wider use of PET/CT and reintroduction of the ¹⁸F-fluoride bone scan, its role in ON has been evaluated by researchers. ¹⁸F-fluoride is a positron-emitting radiotracer^[13]. After diffusion through capillaries into bone extracellular fluid, ¹⁸F-ions exchange with hydroxyl groups in hydroxyapatite crystals to form fluorapatite^[13]. ¹⁸F-fluoride PET has several advantages over ^{99m}Tc-MDP bone scan. ¹⁸F-fluoride has approximately 100% first-pass extraction in bone, allowing the estimation of bone blood flow. Further, its uptake in bone is two-fold higher than that of ^{99m}Tc-MDP. Moreover, it is not protein bound, which leads to faster blood clearance and better target-to-background ratio. In addition, PET/CT imaging has higher resolution compared to SPECT/CT leading to better appreciation of the characteristic photopenic region on PET/CT. Hence, ¹⁸F-fluoride bone scan has high sensitivity compared to ^{99m}Tc-MDP bone scan^[13]. Quantification is another technical advantage of PET/CT imaging. Additional CT features theoretically results in high specificity of ¹⁸F-fluoride PET/CT in ON of femoral head.

Typically, a ring sign, *i.e.*, circular pattern uptake surrounding a photopenic region is noted on ¹⁸F-fluoride PET/CT studies^[27]. The central photopenia represents the necrotic area, whereas the surrounding uptake area probably reflects reactive bone formation around the necrotic area or microcollapse. A study by Gayana *et al*^[28] revealed higher sensitivity and accuracy of ¹⁸F-fluoride PET/CT compared to MRI in ON of the femoral head. Recently, one group showed that metabolic information obtained from ¹⁸F-fluoride PET/CT is useful to predict femoral head collapse in ON^[27]. A semi-quantitative parameter like SUVmax is used for quantifying bone metabolism. They concluded that SUVmax increases with stage progression and collapse of femoral head was observed within 12 mo after ¹⁸F-fluoride PET in patients with SUVmax more than 6.45. This finding could be very useful in predicting femoral head collapse in ON and may lead to early management change.

CONCLUSION

Imaging plays a crucial role in early diagnosis of ON of the femoral head. Although MRI is a commonly used modality in detecting ON, nuclear medicine imaging technology has improved tremendously in recent years. Although there is scarcity of literature, new imaging modalities like SPECT/CT bone scan and ¹⁸F-fluoride PET/CT have similar or better results in comparison to MRI in ON of the femoral head. In addition, they provide both morphological and metabolic information.

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Basic Study

Bone regeneration with osteogenic matrix cell sheet and tricalcium phosphate: An experimental study in sheep

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Abstract**AIM**

To determine the effects of a cell sheet created from sheep bone marrow and tricalcium phosphate (TCP) on osteogenesis.

METHODS

Bone marrow cells were harvested from a sheep and cultured in a minimal essential medium (MEM) containing ascorbic acid phosphate (AsCP) and dexamethasone (Dex). After 2 wk, the formed osteogenic matrix cell sheet was lifted from the culture dish using a scraper. Additionally, harvested bone marrow cells were cultured in MEM only as a negative control group, and in MEM with AsCP, Dex, and β -glycerophosphate as a positive control group. For *in vitro* evaluation, we measured the alkaline phosphatase (ALP) activity and osteocalcin (OC) content in the media of the cultured cells from each group. For *in vivo* analysis, a porous TCP ceramic was used as a scaffold. We prepared an experimental group comprising TCP scaffolds wrapped with the osteogenic matrix cell sheets and a control group consisting of the TCP scaffold only. The constructs were

implanted subcutaneously into athymic rats and the cell donor sheep, and bone formation was confirmed by histology after 4 wk.

RESULTS

In the *in vitro* part, the mean ALP activity was 0.39 ± 0.03 mg/well in the negative control group, 0.67 ± 0.04 mg/well in the sheet group, and 0.65 ± 0.07 mg/well in the positive control group. The mean OC levels were 1.46 ± 0.33 ng/well in the negative control group, 3.92 ± 0.16 ng/well in the sheet group, and 4.4 ± 0.47 ng/well in the positive control group, respectively. The ALP activity and OC levels were significantly higher in the cell sheet and positive control groups than in the negative control group ($P < 0.05$). There was no significant difference in ALP activity or OC levels between the cell sheet group and the positive control group ($P > 0.05$). TCP constructs wrapped with cell sheets prior to implantation showed bone formation, in contrast to TCP scaffolds alone, which exhibited poor bone formation when implanted, in the subcutaneous layer both in athymic rats and in the sheep.

CONCLUSION

This technique for preparing highly osteoinductive TCP may promote regeneration in large bone defects.

Key words: Cell sheet; Osteogenesis; Sheep; Bone marrow; Mesenchymal stromal cell

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Core tip: An osteogenic matrix cell sheet derived from sheep bone marrow enhances osteogenic differentiation. We found that the osteogenic matrix cell sheets on tricalcium phosphate discs efficiently promotes bone formation.

Kira T, Akahane M, Omokawa S, Shimizu T, Kawate K, Onishi T, Tanaka Y. Bone regeneration with osteogenic matrix cell sheet and tricalcium phosphate: An experimental study in sheep. *World J Orthop* 2017; 8(10): 754-760 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i10/754.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i10.754>

INTRODUCTION

Massive bone defects that result from trauma or tumor resection, osteomyelitis, or osteonecrosis require bone grafting and represent a great burden in clinical practice. Although an autologous bone graft transferred as either vascularized or non-vascularized tissue remains the gold standard to treat bone defects, the graft procedure is associated with complications at donor sites^[1,2]. Allografts carry high risks of infections, immunological rejection, and poor rate of bone-healing^[3]. Although artificial bone material possesses some osteoinductive

and osteoconductive activities, its osteogenic potential is limited^[4].

Bone marrow mesenchymal stromal/stem cells (BMSCs) are capable of differentiating into osteoblasts, chondrocytes, or adipocytes *in vitro* and are widely applied in bone tissue engineering^[5]. They are preferably combined with scaffolds to prevent the BMSCs from flowing out of the target site^[6].

We previously developed a new technique of BMSC transplantation using osteogenic matrix cell sheets (OMCSs) derived from rat BMSCs to induce osteogenesis^[7]. Because these OMCSs do not require a scaffold and maintain intercellular networks with the extracellular matrix that they produce, these sheets can be used in various graft sites in animal models^[8,9]. Furthermore, these OMCSs produce growth factors, such as bone morphogenetic protein and vascular endothelial growth factor. Therefore the OMCSs represent an ideal candidate for promoting new bone formation. However, no studies have investigated *in vivo* osteogenesis of OMCSs in a large animal model.

This study aimed to investigate whether OMCSs could promote *in vivo* osteogenesis in a sheep model. The sheep is a frequently used model for orthopedic research for several reasons: The bone size is large enough to allow complex orthopedic procedures to be performed and for medical devices and biomaterials to be tested; the lifespan of the animal is short enough for age-related studies in diseases such as osteoarthritis and osteoporosis to be performed; and bone remodeling in sheep is comparable to that in humans^[10,11].

MATERIALS AND METHODS

BMSC preparation

BMSCs were obtained from the humeral head of a 2-year-old male Corriedale sheep (40.0 kg body weight; Japan Lamb, Hiroshima, Japan) by bone marrow aspiration under general anesthesia with intravenous atipamezole (20 µg/kg IV, ZENOAQ, Fukushima, Japan) and induction with intravenous ketamine (2 mg/kg IV, Daiichi Sankyo Propharma, Tokyo, Japan). The aspirated cells were collected in two 75-cm² culture flasks (Falcon; BD Biosciences, Franklin Lakes, NJ, United States) containing 15 mL of regular medium comprising minimal essential medium (Nacalai Tesque, Kyoto, Japan) supplemented with 15% fetal bovine serum (Gibco Life Technologies, Carlsbad, CA, United States) and antibiotics (100 U/mL penicillin and 100 µg/mL streptomycin; Nacalai Tesque). Cells were cultured in a humidified atmosphere of 95% air and 5% carbon dioxide at 37 °C. After reaching confluence (at approximately day 14), the primary cultured cells were released from the culture substratum using trypsin-EDTA (Nacalai Tesque).

OMCS preparation and cell culture

To create OMCSs, the cells released from the primary culture were seeded at 2×10^3 cells/cm² in culture dishes



Figure 1 Macroscopic appearance of a sheep osteogenic matrix cell sheet (A), the cell sheet was easily detached from the culture surface using a scraper (B and C). Macroscopic appearance of β -tricalcium phosphate (TCP) wrapped with a bone marrow cell sheet.

for subculture in regular medium containing 10 nmol/L dexamethasone (Dex, Sigma, St. Louis, MO, United States) and 0.28 mmol/L l-ascorbic acid phosphate magnesium salt n-hydrate (AscP, Wako Pure Chemical Industries, Kyoto, Japan) until they reached confluence (at approximately day 14). After two rinses with PBS (Gibco), the cell sheet was lifted using a scraper. The cell sheet was easily detached from the culture dish by gentle scraping in PBS, starting from the periphery of the sheet (Figure 1A). As positive and negative controls for osteoblastic differentiation, respectively, released cells were also seeded at the same cell density and cultured in osteoinductive medium (containing 10 nmol/L Dex, 0.28 mmol/L AscP, and 10 mmol/L β -glycerophosphate) or in regular medium (without Dex, AscP or β -glycerophosphate) until they reached confluence.

***In vitro* study**

Alkaline phosphatase activity measurement: Alkaline phosphatase (ALP) activity was measured in cells cultured in 12-well plates (Falcon), as reported previously^[12]. For each condition, six wells were evaluated. ALP activity is represented as the amount of *p*-nitrophenol released after 30 min of incubation at 37 °C. The measurements were repeated twice.

Osteocalcin measurement: The Osteocalcin (OC) content of the culture medium was measured by an ELISA developed in a previous study^[13]. Briefly, conditioned medium was collected at day 12 and an aliquot (100 μ L) of 1:10 diluted medium was analyzed. The OC measurements evaluated four wells for each group, and the measurements were repeated twice.

***In vivo* study**

Construction of tricalcium phosphate scaffold wrapped with a OMCS: Sterilized porous beta tricalcium phosphate (TCP) ceramics (Superpore; discs: 5 mm in diameter and 2 mm thick; 60% porosity) were purchased from Pentax (Tokyo, Japan). Constructs with OMCSs were prepared by wrapping the OMCS around the TCP immediately previous to transplantation (Figure 1B and C).

Construct implantation in the subcutaneous layer of athymic rats and the cell donor sheep:

TCP constructs were implanted into the subcutaneous layer on the backs of athymic 7-wk-old male F344/NJcl-rmu/rmu rats (CLEA Japan Inc., Tokyo, Japan) as described previously^[7,14]. Additionally, constructs were implanted subcutaneously into the abdomen of the cell donor sheep under the general anesthesia conditions described above. We also prepared control groups in which TCP discs were implanted subcutaneously into athymic rats and at a different site in the sheep. For each group, six constructs were implanted into one recipient rat to produce the subcutaneous implantation model, and all constructs were implanted into the cell donor sheep. After 4 wk, the implanted constructs were harvested and bone formation was histologically evaluated. The harvested discs were fixed in buffered formalin (Wako Pure Chemical Industries). Each disc was embedded in paraffin after decalcification, cut through the middle of the disk, and then stained with hematoxylin and eosin for histological evaluation.

Animal care and use statement

The care and handling of the rats and the sheep used in this study was approved by the animal care committee of our institute and met the standards of the National Institutes of Health.

Statistical analysis

The ALP activity values and OC levels are presented as mean and SD. One-way analysis of variance with *post-hoc* multiple comparisons using Tukey's test was conducted to determine statistical significance. Values of $P < 0.05$ were considered statistically significant.

RESULTS

***In vitro* study**

In the *in vitro* study, the mean ALP activity was 0.39 ± 0.03 mg/well in the negative control group, 0.67 ± 0.04 mg/well in the sheet group, and 0.65 ± 0.07 mg/well in the positive control group (Figure 2). The mean OC levels were 1.46 ± 0.33 ng/well in the negative control group, $3.92 \pm$

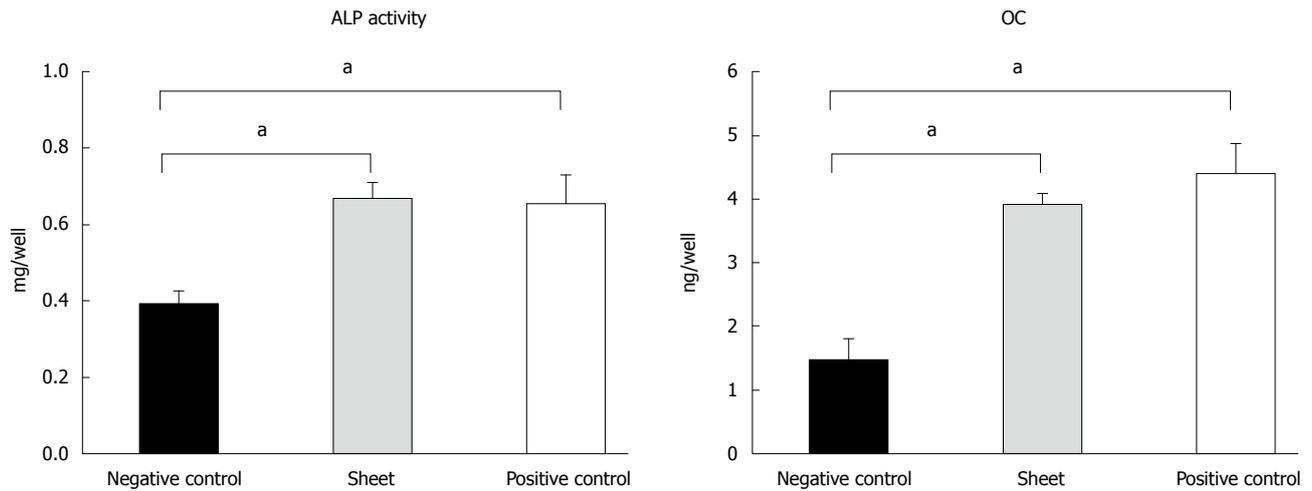


Figure 2 Alkaline phosphatase activity (A) and osteocalcin levels (B) in the culture medium of the bone marrow cell sheet, positive control and negative control groups in the *in vitro* study. ^aThe alkaline phosphatase (ALP) activity and osteocalcin (OC) levels in the cell sheet and positive control groups were significantly higher than those in the negative control group.

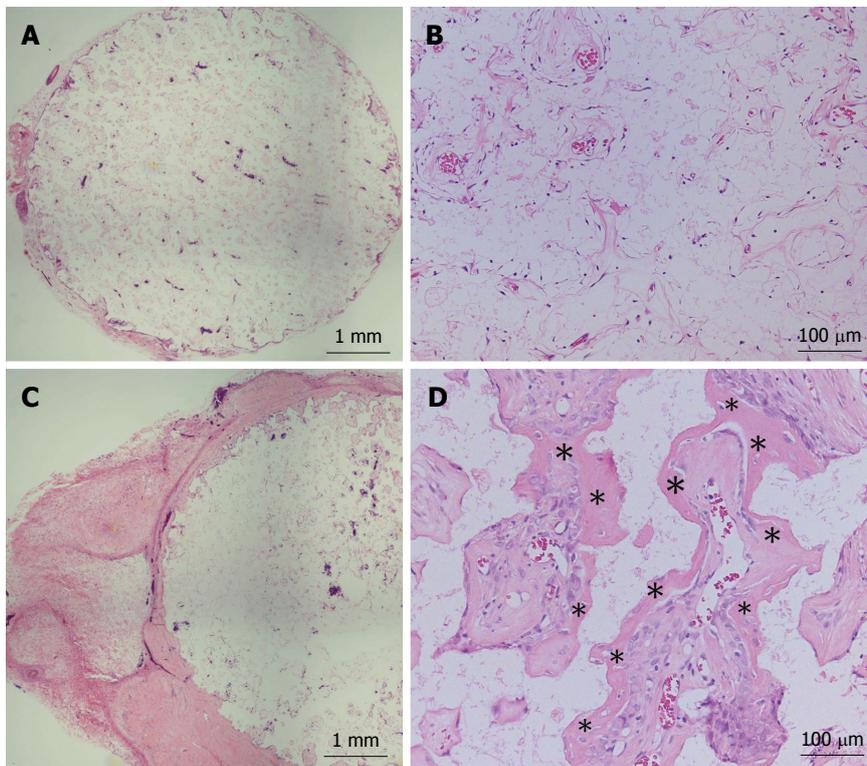


Figure 3 Hematoxylin and eosin-stained sections at 4 wk after implantation into the subcutaneous layer of athymic rats. A low-magnification image of a β -tricalcium phosphate (TCP) disc without the cell sheet shows poor bone formation (A and B). Conversely, a high level of bone formation is visible in and around TCP wrapped with an osteogenic matrix cell sheet cultured in minimum essential medium containing ascorbic acid and dexamethasone (C and D). Asterisks indicate bone tissue.

0.16 ng/well in the sheet group, and 4.4 ± 0.47 ng/well in the positive control group, respectively. The ALP activity and OC levels were significantly higher in the cell sheet and positive control groups than in the negative control group ($P < 0.05$). There was no significant difference in ALP activity or OC levels between the cell sheet group and the positive control group ($P > 0.05$).

***In vivo* study**

Figures 3 and 4 show representative histological sections of constructs subcutaneously implanted at 4 wk into athymic rats and the cell donor sheep, respectively. The low-magnification images show higher levels of bone formation in the TCP-cell sheet construct sections than in sections of TCP discs without the cell sheet, in

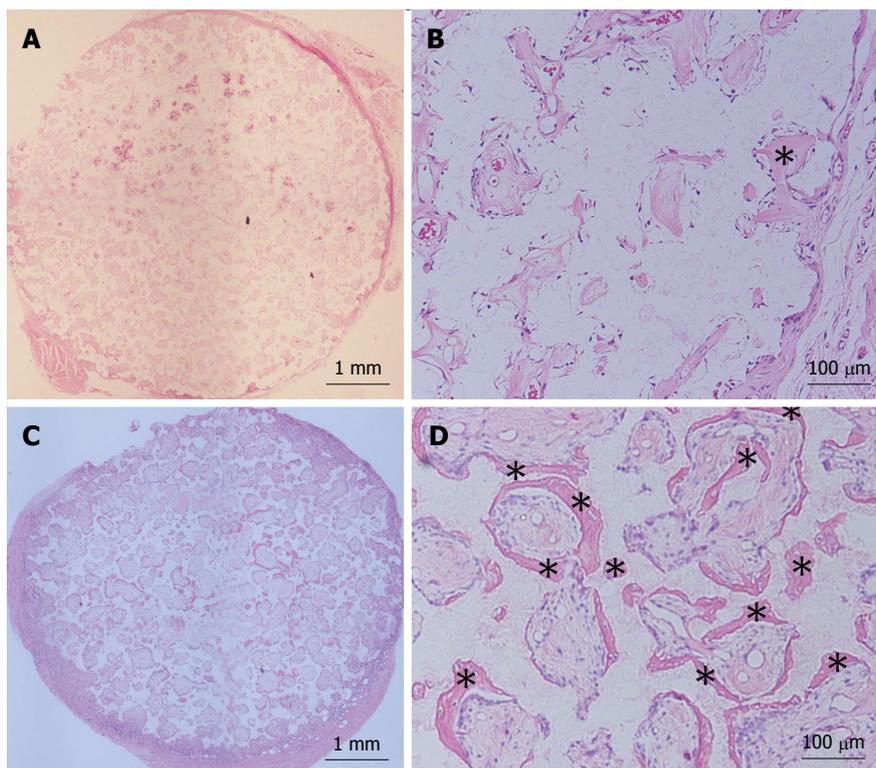


Figure 4 Hematoxylin and eosin-stained sections at 4 wk after implantation into the subcutaneous layer of the donor sheep. A low-magnification image of a β -tricalcium phosphate (TCP) disc without the cell sheet shows poor bone formation (A and B) whereas relatively high level of bone formation is visible in and around TCP wrapped with an osteogenic matrix cell sheet cultured in minimum essential medium containing ascorbic acid and dexamethasone (C and D). Asterisks indicate bone tissue.

the subcutaneous layer of both athymic rats and sheep.

DISCUSSION

Our study demonstrates that we can successfully use large animal models to derive and culture OMCS, and that TCP constructs wrapped with sheep OMCSs lead to bone formation after implantation. This is important, as sheep bone healing is more comparable to that of humans than rodents used in previous models.

Even though BMSCs alone have osteogenic potential, their implantation as a cell suspensions leads to an uneven distribution and weak adhesion of cells to the bone surface, potentially leading to cell defluviu from the target site^[15]. In contrast, cell sheets bear intact cell-cell junctions and an extracellular matrix, which provide mechanical support to the cell and thereby maintain the viability of the cells at the transplanted site^[16]. Furthermore, prior culture with medium that includes agents that potentiate bone formation, such as Dex and AscP, allows for already pre-determined cells to be implanted^[17], which have a better chance of laying down additional matrix and integrating with the transplant site than cells that are still actively engaged in proliferation.

BMSCs including osteoblasts and osteoprogenitor cells are bone-forming cells that express various osteoblastic markers such as OC, and exhibit ALP activity^[18,19]. ALP is considered a relevant biochemical marker in

osteoblast differentiation. The activity and correct localization of ALP are necessary for bone development and differentiation^[20,21]. OC is considered a late marker of osteogenic differentiation and its expression at high levels indicates maturation and terminal differentiation of osteoblasts^[22]. Others have suggested that Dex may inhibit OC expression through direct binding of the Dex-activated glucocorticoid receptor to negative glucocorticoid response elements in the OC promoter^[23]. However, we observed enhanced OC expression in OMCSs compared with the negative control group^[23]. The effect of Dex is dependent on its concentration and on the stage of cellular differentiation. The Dex concentration used in this study (10 nmol/L) is considered an appropriate concentration for the differentiation of BMSCs committed to the osteogenic lineage. The ALP activity and OC levels observed in the OMCS suggest that the osteogenic differentiation ability of the BMSCs was enhanced by AscP and Dex.

OMCSs can be easily detached from the plastic dish and transplanted subcutaneously with or without a scaffold, and has osteogenic potential to form new bone tissue. The TCP scaffold also has osteoinductive properties in bone; however, minimal osteogenesis was observed inside the TCP without the cell sheet in athymic rats, presumably because of the small number of osteoprogenitor cells available for integration into the disc in the subcutaneous layer. Conversely, substantial amounts of new bone was found inside the TCP that had

been wrapped with an OMCS. We suggest that these transplanted sheep cells from the OMCSs migrated into the TCP disc, proliferated, differentiated into osteoblasts, and mineralized, and thus induced bone formation.

Results similar to those for athymic rats were obtained for implantation in the cell donor sheep. We have previously investigated cell sheets derived from rodent bone marrow and reported their efficacy for osteogenesis, angiogenesis and reconstructive surgery^[8,9,24,25]. We found that severe fracture and nonunion could be united by the implantation of OMCSs^[9,24] and that OMCSs can enhance early bone tunnel healing in a tendon graft model^[8]. Furthermore, we show that a vascularized tissue-engineered bone scaffold composed of OMCSs wrapped around vascular bundles within a TCP mediates abundant vascularization and osteogenesis^[25]. Although these studies reported that OMCS transplantation is useful for bone reconstruction, large animal studies are required to further support the potential of OMCS transplantation for clinical application. Guo *et al.*^[26] created cell sheets using canine cells, and showed that cell sheets exhibited normal activity and a preserved extracellular matrix and multi-layer cell structure, and displayed osteogenic induction. They used AscP (vitamin C) to create cell sheets from bone marrow mesenchymal stem cells, whereas we used a combination of AscP and Dex to create our cell sheets. Culturing cell in the medium containing AscP and Dex can stimulate osteogenic differentiation and complete cell sheet formation; therefore, using induction medium containing AscP and Dex may be more suitable for creating cell sheets for application in bone reconstruction surgery^[17].

We chose a sheep model because sheep have bone properties similar to those of humans, with similar bone turnover and remodeling activities^[27-29]. Furthermore, their size allows for the simultaneous implantation of many TCP constructs^[30-33], and the subcutaneous implantation approach used in this study permitted the implantation of multiple TCP constructs in one sheep. Thus, the results of these *in vivo* studies suggest that human OMCSs can induce high levels of osteogenesis in TCP.

There were a few limitations in our study. First, we only used 2-mm-thick TCP. In future studies, we aim to use thicker TCP discs to assess their osteogenic ability when transplanted with OMCSs. Second, the experimental period in the present study was relatively short. Therefore, a longer follow-up study is required to investigate whether the implanted TCP remains in the sheep or is broken down and resorbed by the newly formed tissue. Third, we did not confirm whether the bone that formed in the TCP construct was derived from host cells or donor cells. Finally, we need to verify osteoinductive and osteoconductive ability of human OMCSs. Concerning these points, further study will be necessary.

COMMENTS

Background

Osteogenic matrix cell sheets (OMCSs) created from bone marrow mesenchymal

stromal/stem cells (BMSCs) can be used to aid fracture nonunion, delayed bone union, or bone defects in rodent models. However, there has been no report as to whether OMCSs can also successfully induce bone formation in a large animal model. Here, the authors investigated whether OMCSs could promote *in vivo* osteogenesis in a sheep model.

Research frontiers

OMCSs are easily created from BMSCs and can be transplanted without the requirement for a scaffold. OMCSs have a high osteogenic potential, because the cells are supported by a rich extracellular matrix and various growth factors required for bone formation. As such, OMCSs are thought to be an ideal graft material for bone regenerative medicine.

Innovations and breakthroughs

Over the past decade, the utility of OMCSs for bone reconstruction has been verified in rat models of bone repair. However, rat bone does not contain Haversian canals, and thus the mode of remodeling differs to that of humans. In the current study, the authors used a sheep model to explore the osteoconductive and osteoinductive potential of sheep-driven OMCSs as sheep bone formation and repair is similar to that of human bone.

Applications

The authors suggest that OMCSs in combination with bone prostheses could be manipulated to intricately shape bony defects, and will be particularly relevant in areas where the osteogenic potential for regeneration is poor, such as in older patients or patients with bone disorders.

Terminology

TCP: Tricalcium phosphate is a calcium salt of phosphoric acid with the chemical formula $\text{Ca}_3(\text{PO}_4)_2$. TCP is grafted into the bone defect, but has lowered osteogenic potential; BMSCs: Bone marrow mesenchymal stromal/stem cells. BMSCs can be induced to differentiate into osteogenic, chondrogenic, adipogenic or other cell lineages with the appropriate media conditions. Furthermore, BMSCs secrete various growth factors, such as bone morphogenetic protein, basic fibroblast growth factor, transforming growth factor, vascular endothelial growth factor, as well as matrix proteins, including osteocalcin, and alkaline phosphatase. These cells are routinely used as a cell source for musculoskeletal tissue engineering purposes; OMCSs: Osteogenic Matrix Cell Sheets are BMSCs cultured with dexamethasone and ascorbic acid phosphate. The cells undergo differentiation and matrix production, producing a cell sheet structure that can be collected as a single cell sheet. These sheets offer *in vitro* osteogenic potential and *in vivo* bone formation with/without the aid of an additional scaffold.

Peer-review

The manuscript is an interesting biotechnological application of bone marrow-derived cell sheets to induce subcutaneous osteogenesis in a rat and a sheep model. The manuscript is of interest in its field and has novelty since it explores the use of these cell sheets in a large animal model, the sheep, which outcomes are fairly more comparable to humans than the usual rodent models.

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Case Control Study

Neuropathic pain-like symptoms and pre-surgery radiographic severity contribute to patient satisfaction 4.8 years post-total joint replacement

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Abstract

AIM

To investigate a comprehensive range of factors that contribute to long-term patient satisfaction post-total joint replacement (TJR) in people who had undergone knee or hip replacement for osteoarthritis.

METHODS

Participants ($n = 1151$) were recruited from Nottinghamshire post-total hip or knee replacement. Questionnaire assessment included medication use, the pain-DETECT questionnaire (PDQ) to assess neuropathic pain-like symptoms (NP) and TJR satisfaction measured on average 4.8 years post-TJR. Individual factors were tested for an association with post-TJR satisfaction, before incorporating all factors into a full model. Data reduction was carried out using LASSO and receiver

operator characteristic (ROC) curve analysis was used to quantify the contribution of variables to post-TJR satisfaction.

RESULTS

After data reduction, the best fitting model for post-TJR satisfaction included various measures of pain, history of revision surgery, smoking, pre-surgical X-ray severity, WOMAC function scores and various comorbidities. ROC analysis of this model gave AUC = 0.83 (95%CI: 0.80-0.85). PDQ scores were found to capture much of the variation in post-TJR satisfaction outcomes: AUC = 0.79 (0.75-0.82). Pre-surgical radiographic severity was associated with higher post-TJR satisfaction: OR_{satisfied} = 2.06 (95%CI: 1.15-3.69), $P = 0.015$.

CONCLUSION

These results highlight the importance of pre-surgical radiographic severity, post-TJR function, analgesic medication use and NP in terms of post-TJR satisfaction. The PDQ appears to be a useful tool in capturing factors that contribute to post-TJR satisfaction.

Key words: Osteoarthritis; Patient satisfaction; Total joint arthroplasty; Neuropathic pain; Surgery outcomes

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Core tip: The growing number of total joint replacement (TJR) surgeries performed worldwide every year means that research in this area has the potential to impact millions of people. These results highlight the importance of a number of factors with regards to post-TJR satisfaction. The pain-DETECT questionnaire for neuropathic pain-like symptoms (NP) appears to be a useful tool in capturing factors that contribute to post-TJR satisfaction. Individuals with NP pre- or post-TJR could be indicated using this short questionnaire and referred for further testing and treatment to improve outcomes at every stage of their osteoarthritis treatment process.

Warner SC, Richardson H, Jenkins W, Kurien T, Doherty M, Valdes AM. Neuropathic pain-like symptoms and pre-surgery radiographic severity contribute to patient satisfaction 4.8 years post-total joint replacement. *World J Orthop* 2017; 8(10): 761-769 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i10/761.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i10.761>

INTRODUCTION

A total joint replacement (TJR) is the only treatment for clinically severe osteoarthritis (OA). A TJR should be considered in individuals with marked symptoms of OA which significantly limit activity and participation and reduce quality of life if conservative treatments (*e.g.*, exercise, weight loss if overweight, analgesic medication) are insufficient^[1]. In the United Kingdom alone 160000 TJR are performed every year^[2]. Generally very good

outcomes are reported post-TJR^[3] but pain can remain a concern for some individuals. According to one study, 27% of people who had undergone total hip replacement (THR) and 44% of people who had undergone a total knee replacement (TKR) had joint pain 3-4 years after surgery^[4]. This pain can be inflammatory, nociceptive or neuropathic in nature^[5].

Patient satisfaction post-TJR has been the subject of some studies^[6-10] which have focused only on pain and function post-TJR^[11]. Pre-operative radiographic severity, co-occurrence of painful conditions, a history of revision surgery, other comorbidities, and pain catastrophizing have also been linked to post-TJR outcomes in the literature but not all in the same cohort^[7,12-15].

Neuropathic pain-like symptoms (NP) are caused by changes or damage to the nervous system, which can result from chronic nociceptive input (as seen in chronic pain states) and nerve damage during surgery^[5,16,17]. NP has been reported in people with OA and post-TJR^[4,18]. However, to our knowledge, currently no studies have investigated the role of NP on patient satisfaction post-TJR.

As TJR is currently the only long-term treatment for OA, if its effectiveness can be improved with better understanding of the individual differences in post-operative outcomes, this must be addressed. Due to the high number of TJR carried out in the United Kingdom and worldwide, research in this area has the potential to impact many individuals.

The aim of the present study was to investigate a comprehensive range of factors that contribute to long-term patient satisfaction post-TJR in people who had undergone knee or hip replacement for OA.

MATERIALS AND METHODS

Participants

The North Nottinghamshire Research Ethics Committee approved the study protocol (REC number: 07/Q2501/22). Participants who had undergone a TJR for OA were recruited from secondary care in Nottinghamshire ($n = 1151$) and gave written, informed consent. All participants had symptomatic and radiographic OA prior to TJR surgery. Between 2008 and 2011, nurse-administered questionnaires were completed by participants ($n = 1219$) on average 18 mo after surgery. These questionnaires included information on demographic variables, pain scores, TJR satisfaction and medication use. A subsequent follow-up postal questionnaire was sent to those who consented to further involvement in the study. This questionnaire was very similar in design to the baseline questionnaire. There was an average of 3.3 years between the first and second questionnaires. When the baseline and follow-up responses of participants who completed both questionnaires were compared there were no significant differences in age ($P < 0.38$), sex ($P < 0.89$), BMI ($P < 0.07$) or WOMAC pain scores ($P < 0.51$). There was not a significant difference in satisfaction levels ($P =$

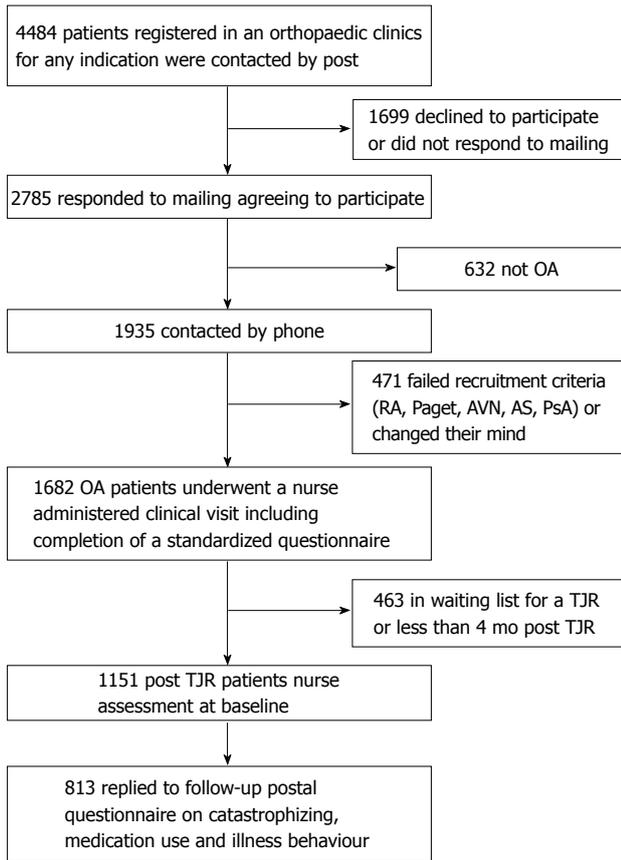


Figure 1 Flow-chart of participant recruitment for the current study.

0.22). Individuals had not been phenotyped for pain pre-surgery but pre-operative radiographic severity grade has been linked previously to TJR outcomes^[12]. The study design is presented in Figure 1.

Statistical analysis

Statistical review of this study was performed by a biomedical statistician. The statistics package R (version 3.0.2) was used to run logistic regression analyses to measure associations between TJR satisfaction and potential risk factors.

To select the risk factors contributing to post-TJR satisfaction, the least absolute shrinkage and selection operator method (LASSO) was used. LASSO is a feature selection method which, given a set of input measurements and an outcome measurement (in this case post-TJR satisfaction), fits a linear model^[19]. We employed a LASSO-regularised regression model as implemented by the R package "glmnet"^[20] (<http://cran.r-project.org/web/packages/glmnet/index.html>) using a logistic link function and the fitted LASSO coefficients derived were used.

Receiver operating characteristic (ROC) analysis was used to quantify the contribution of variables in the above models. The discrimination ability of the models was examined using the "PredictABEL" package for R (<http://cran.r-project.org/web/packages/PredictABEL/index.html>).

Trait definitions for statistical analysis

Neuropathic pain-like symptoms at the operated joints (knees or hips): The PDQ is a validated instrument for assessing NP. Scores range from 0-35, with > 12 indicating possible NP and ≥ 19 indicating likely NP^[21].

Pain severity: A visual analogue scale (VAS) was used to categorise individuals with high or low pain intensity at the operated joint (knee or hip). Scores range from 0-10, with ≥ 6 used to categorise high pain intensity.

TJR satisfaction: Individuals were asked to state how satisfied they felt with their TJR using an ordinal scale of "very satisfied", "not very satisfied" and "dissatisfied". For logistic regression analysis, individuals were dichotomised between: (1) "very satisfied"; and (2) "not very satisfied" and "dissatisfied".

Radiographic severity: The extent of joint damage evident by X-rays was categorised by assessment of pre-surgery knee and hip radiographs by a single observer. For knees, the Kellgren-Lawrence (K/L) grading system was used. Scores range from 0-4, with ≥ 3 classified as severe and 2 classified as not severe (K/L < 2 no OA)^[22]. An association with minimum joint space width (JSW) pre-surgery and pain post-surgery has been reported in a separate cohort^[12]. The minimum JSW was therefore used to classify hip OA, with minimum JSW ≤ 2.5 mm (which is a standard cut-off)^[23] being classified as radiographically severe. For bilateral surgery the joint with the most severe radiographic score was used.

Pain catastrophizing: The 13-item Pain Catastrophizing Scale (PCS) is a measure of the tendency to exaggerate the threat of a perceived harmful stimulus^[24]. Scores range from 0-52 and the highest tertile was used as a cut-off point to classify individuals as high catastrophizers, as previously described^[25].

WOMAC pain, stiffness and function: The OA-specific Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire includes questions about pain (scored from 0-20), stiffness (scored from 0-8) and function (scored from 0-76)^[26]. WOMAC function scores were categorised according to an OMERACT-defined PASS score of "acceptable function" (a score of ≤ 22) to allow a clinical guideline to be used in this study to put the importance of post-TJR satisfaction into a clinical context^[27,28].

Medication use

Questionnaire responses were used to classify participants as taking over-the-counter analgesics (OTC), opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or other prescription medications which can be used to treat pain, as previously described^[25].

Table 1 Descriptive statistics categorised by total joint replacement satisfaction status and their contribution to the risk of dissatisfaction post-total joint replacement

Trait		Very satisfied (n = 861)	Not very satisfied (n = 227)	Dissatisfied (n = 63)	OR not very satisfied/ dissatisfied (95%CI) ¹
Demographic and morphometric	Age ± SD (yr)	73.2 ± 8.6	73.0 ± 8.8	72.2 ± 9.1	1.00 (0.98-1.01)
	% female	57.4	56.8	47.6	0.85 (0.65-1.12)
	BMI ± SD (kg/m ²)	29 ± 5.2	29.4 ± 5.1	30.7 ± 5.9	1.03 (1.00-1.06) ^a
Type of surgery	THR (n = 494)	407 (82.4%)	74 (15.0%)	13 (2.6%)	0.58 (0.44-0.77) ^e
	TKR (n = 591)	410 (69.4%)	136 (23.0%)	45 (7.6%)	2.02 (1.50-2.71) ^e
	THR + TKR (n = 66)	44 (66.7%)	17 (25.8%)	5 (7.6%)	1.63 (0.95-2.78)
Pre-operative X-ray	Years since most recent surgery	4.26	3.96	4.58	0.99 (0.96-1.03)
	Radiographically severe OA	92.10%	93.40%	96.50%	0.49 (0.27-0.87) ^a
History of surgery	Previous arthroscopic knee surgery ³	20.00%	26.40%	34.90%	1.65 (1.21-2.25) ^e
	Revision surgery	5.70%	9.30%	14.30%	2.36 (1.44-3.86) ^e
Psychological	% depression	15.9	22.0	28.6	1.64 (1.17-2.30) ^e
	PCS score (0-52)	8.2	12.8	19.7	1.06 (1.05-1.08) ^e
	Top tertile of PCS ²	20.80%	37.00%	55.60%	3.40 (2.52-4.59) ^e
Use of medication	% opioid	21.7	39.5	41.3	2.37 (1.77-3.18) ^e
	% OTC	49.0	64.5	61.9	1.33 (0.84-2.12)
	% NSAIDs	7.8	12.3	3.2	1.83 (1.38-2.42) ^e
	% other prescription analgesics	12.2	20.0	23.8	1.85 (1.29-2.66) ^e
Measures of pain	PDQ score (0-35)	4.8	10.1	14.3	1.15 (1.13-1.18) ^e
	Possible Neuropathic Pain (PDQ > 12)	10.00%	33.90%	57.10%	5.91 (4.22-8.29) ^e
	Likely Neuropathic Pain (PDQ ≥ 19)	6.50%	18.10%	34.90%	7.66 (4.80-12.22) ^e
	VAS (0-10)	3.1	5.8	7.0	1.35 (1.29-1.41) ^e
	HighVAS (> 5)	30.80%	61.20%	76.20%	6.47 (4.80-8.73) ^e
	WOMAC pain (0-20)	5.2	8.5	10.9	1.28 (1.23-1.33) ^e
	WOMAC stiffness (0-8)	2.9	4.1	4.4	1.62 (1.49-1.76) ^e
Comorbidities	WOMAC function (0-76)	25.7	38.0	47.8	1.07 (1.06-1.08) ^e
	% heart disease/angina	16.7	19.4	27.0	1.34 (0.95-1.89)
	% stroke	5.1	9.3	12.7	2.09 (1.26-3.44) ^e
	% hypertension	52.3	50.2	57.1	0.95 (0.72-1.25)
	% asthma/COPD	13.8	15.4	14.3	1.07 (0.73-1.57)
	% irritable bowel syndrome	10.2	14.5	11.1	1.44 (0.96-2.17)
	% diabetes	11.8	15.0	19.0	1.28 (0.86-1.90)
	% gout	7.5	11.9	11.1	1.50 (0.95-2.37)
	% osteoporosis	11.0	10.1	19.0	1.23 (0.80-1.88)
	% cancer	15.9	19.8	17.5	1.29 (0.91-1.83)
% current smoker	6.5	11.0	14.3	1.93 (1.22-3.07) ^e	

¹All ORs are adjusted for age, sex and BMI; ²Individuals in the top tertile of scores for the PCS questionnaire were classified as high catastrophizing; ³This classification includes any previous arthroscopic knee surgery. ^a*P* < 0.05, ^e*P* < 0.01, ^e*P* < 0.001. PCS: Pain Catastrophizing Scale; BMI: Body mass index.

Comorbidities

Comorbid conditions are commonly seen in people with OA, and people with OA are more likely to develop comorbid conditions such as cardiovascular disease and diabetes^[29]. A list of comorbidities was included in the questionnaire. Participants were asked to indicate which of these conditions they had been previously diagnosed with by a doctor.

RESULTS

The descriptive characteristics, stratified by TJR satisfaction status, are shown in Table 1. One fourth of study participants (290) were dissatisfied or not very satisfied with the outcome of their surgery. The study was thus powered (80%, *P* < 0.05) to detect associations with odds ratios of 1.75 or higher for binary traits with a prevalence of 10% or higher in the satisfied group, such as neuropathic pain (Table 1).

On univariate analysis, the majority of the variables

tested were found to be significantly associated with satisfaction post-TJR. This includes a higher BMI, various measures of pain (such as PDQ scores, high pain intensity and WOMAC pain scores), WOMAC function scores and pain catastrophizing (Table 1). Additionally, THR participants reported higher levels of being very satisfied (82.4%) than TKR patients (69.4%) (Table 1). Some factors were highly correlated with each other, such as PDQ scores and high pain intensity, PDQ scores and WOMAC pain scores and WOMAC pain scores and high pain intensity (*P* < 0.001 for all).

Given the large number of factors associated, many of them correlated with each other, we performed data reduction, using LASSO to identify which factors remain important contributors to post-TJR, post-THR and post-TKR satisfaction. After data reduction, the factors that remained in all three groups were: BMI, WOMAC function scores, PDQ scores, high pain intensity, severe pre-surgery radiographic OA and a past stroke. The full results of these analyses are shown in Table 2. Some

Table 2 The best fitting and pain-DETECT questionnaire models showing the contribution of factors to post-total joint replacement, post-total hip replacement and post-total knee replacement satisfaction

	Full/best fitting model	pain-DETECT questionnaire scores
Total joint replacement satisfaction	2.207 + (-0.013-PCS) + (0.189-sex) + (-0.398-TKR) + (0.016-BMI) + (-0.027-WOMAC function) + (-0.042-WOMAC stiffness) + (-0.012-past knee surgery) + (-0.056-PDQ) + (-0.483-highVAS) + (-0.380-revision surgery) + (0.352-severe pre-surgical radiographic OA) + (-0.066-OTC) + (-0.113-opioid) + (-0.010-current smoker) + (-0.218-stroke) + (0.051-hypertension) + (0.062-IBS) + (-0.055-gout) + (-0.123-depression)	2.796 + (-0.142-PDQ) + (-0.015-age) + (0.382-sex) + (0.004-BMI)
Total hip replacement satisfaction	2.985 + (0.014-years since surgery) + (-0.018-age) + (0.036-BMI) + (-0.036-WOMAC function) + (0.599-past knee surgery) + (-0.018-PDQ) + (-0.725-high VAS) + (-0.723-revision surgery) + (0.779-severe pre-surgical radiographic OA) + (-0.248-OTC) + (-0.119-opioid) + (-0.429-other medications for pain relief) + (-0.442-current smoker) + (-0.014-stroke) + (-0.514-depression) + (-0.022-cancer)	4.788 + (-0.121-PDQ) + (-0.038-age) + (0.036-sex) + (0.008-BMI)
Total knee replacement satisfaction	2.425 + (-0.018-PCS) + (0.190-sex) + (0.00045-BMI) + (-0.015-WOMAC function) + (-0.130-WOMAC stiffness) + (-0.076-PDQ) + (-0.313-high VAS) + (0.009-severe pre-surgical radiographic OA) + (-0.143-stroke) + (0.072-hypertension) + (0.334-IBS) + (-0.120-gout)	1.072 + (-0.146-PDQ) + (0.003-age) + (0.467-sex) + (0.011-BMI)

differences were observed in the factors that contribute to satisfaction post-THR and post-TKR, most notably a history of a revision surgery for THR and the WOMAC stiffness score for TKR. In both cases PDQ and VAS scores contribute significantly after adjustment for all other factors.

Higher pre-operative radiographic severity was also significantly associated with increased odds of TJR satisfaction: $OR_{\text{satisfied}} = 2.06$ (1.15-3.69), $P = 0.015$.

It was investigated whether patient satisfaction was related to measures of healthcare usage, specifically the use of analgesic medication. Strong associations were found between dissatisfaction and an increased likelihood of the use of some prescription analgesics (opioids and other prescription medications which can be used to treat pain) and OTC analgesics, but not prescription NSAIDs (Table 1). After adjustment for possible NP, high pain catastrophizing and high pain intensity (VAS) these associations become non-significant except in the case of opioids and OTC analgesics [$OR_{\text{dissatisfied}} = 1.68$ (1.21-2.34), $P = 0.002$; $OR_{\text{dissatisfied}} = 1.44$ (1.06-1.97), $P = 0.020$, respectively].

Post-TJR satisfaction is strongly associated with a measure of acceptable function post-TJR, according to OMERACT-defined PASS scores in the literature^[27,28]. This definition of acceptable function, according to a clinical guideline, was a very strong contributor to post-TJR satisfaction in this study after adjusting for age, sex and BMI: $OR_{\text{satisfied}} = 9.88$ (95%CI: 6.58-14.85), $P < 0.001$. This association remained significant after further adjustment for possible NP, high pain catastrophizing and high pain intensity: $OR_{\text{satisfied}} = 4.82$ (95%CI: 3.08-7.55), $P < 0.001$.

With regards to comorbidities, a history of stroke was associated with an increased risk of dissatisfaction post-TJR, as was being a current smoker (vs ex-smokers and people who have never smoked); $P < 0.01$ for both, see Table 1.

It was quantified how much these models contribute to satisfaction. The results of ROC analysis of the best-fitting model for each surgery group are shown in

Table 2 and Figure 2. The results show that the list of identified factors explains an AUC of 0.83 of patient satisfaction for post-TJR, 0.84 for post-THR and 0.83 for post-TKR. This, however, includes a large number of factors and it was investigated whether one of the factors may capture the effects of most of the other factors.

Possible NP, classified using PDQ scores, was seen in 17.3% of participants in this study. However, in the dissatisfied group the prevalence of possible NP was 3.8 times higher than in the very satisfied group $OR_{\text{possNP}} = 5.91$ (4.22-8.29), $P < 0.001$ and the prevalence of likely NP was 5.4 times higher: $OR_{\text{likNP}} = 7.66$ (4.80-12.22), $P < 0.001$ (see Table 1). Possible NP was less common in THR than TKR participants (11.9% and 22.3%, respectively) (Table 1). Likely NP has been reported previously to be present only in a small proportion of individuals post-TJR^[4] using as a definition a PDQ > 19. However strong differences exist in satisfaction at various lower cut-offs which explains why pain-DETECT scores capture such a large proportion of patient satisfaction in these data (Figure 3).

Given this strong effect we hypothesised that PDQ scores, being strongly correlated with pre-surgery X-ray scores (Spearman's rho = -0.13, $P < 0.001$) and associated with post-TJR pain intensity [$OR_{\text{highpainintensity}} = 1.35$ (1.30-1.40), $P < 0.001$], may capture much of the variation in post-TJR satisfaction outcomes, and indeed we find that this is the case. According to ROC analysis of PDQ scores (adjusted for age, sex and BMI), there is a significant contribution to post-TJR, post-THR and post-TKR satisfaction when this model is used (Table 2 and Figure 2). AUC values of 0.75 and over were reached in all three groups, even without the inclusion of any of the other available measures.

DISCUSSION

This study incorporated a comprehensive range of factors and shows that a number of factors including pain, comorbidities, smoking, history of revision surgery

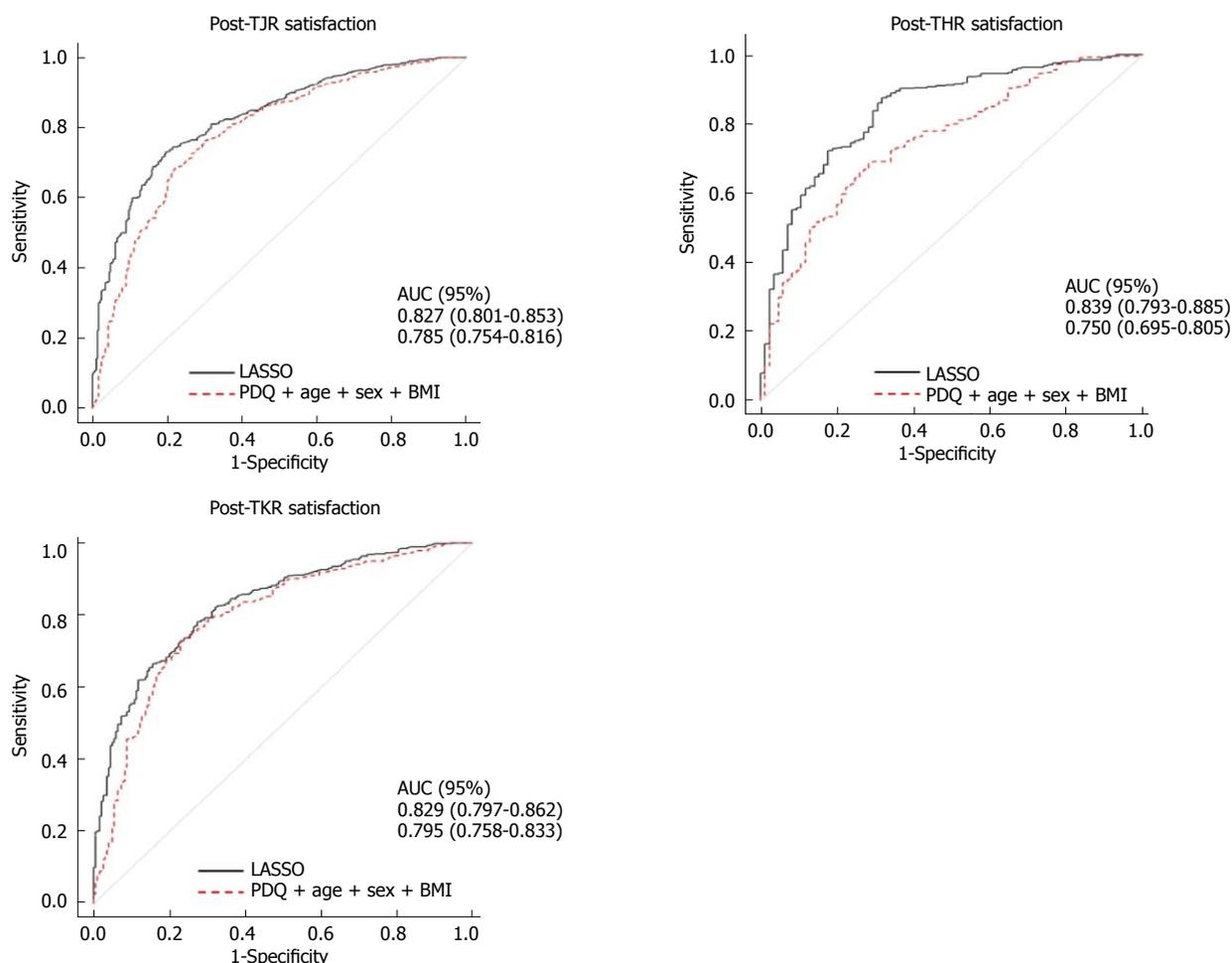


Figure 2 Receiver operator characteristic curves adjusted for age, sex and body mass index to show the amount of post-surgery satisfaction predicted by preoperative radiographic severity, pain-DETECT questionnaire scores and the best fit model. A: Post-TJR (THR and TKR combined); B: Post-TKR; C: Post-THR. TJR: Total joint replacement; THR: Total hip replacement; TKR: Total knee replacement.

and pre-surgical radiographic severity contribute to post-TJR satisfaction 4.8 years after surgery. Scores measuring the presence of NP appear to capture a large proportion of the variation seen.

Patient satisfaction is an outcome measure which is simple to use and accounts for the complex aspects of TJR^[30]. It has been recommended that patient satisfaction should be incorporated into assessments of post-TJR outcomes^[30]. Our results suggest that although post-TJR satisfaction is influenced by a large number of factors, it is well summarised by one single instrument, namely PDQ scores.

The proportion of possible NP identified in this study falls within the range reported by previous studies on NP post-TJR (reviewed in^[31]) particularly when differences in methodology and sample composition are taken into consideration^[4,15,32-37]. At first sight the importance of NP post-TJR detailed here appears to contrast with the report by Wylde *et al*^[4] who suggested that NP is a minor component of post-TJR pain.

The current data indicate that people who undergo TJR with only modest radiographic structural damage are more likely to report NP post-surgery. Although

this might suggest that the NP was also present pre-surgery, we lack the pre-operative pain assessments necessary to confirm if that is the case. In addition, pain may derive from other sources, such as bone marrow lesions, that are not evident on radiographs and may still be present post-surgery^[38]. Central nervous system involvement in OA, such as seen in NP, seems likely when the inconsistent correlation between pain and radiographic severity and the non-linear relationship between nociception and pain experienced are considered^[17] supporting the findings in this study.

In this study we fitted prediction models for patient dissatisfaction using all the contributing risk factors selected by LASSO. These models are fairly complicated in terms of the number of variables and therefore may not be applicable in clinical practice. However, we also show that PDQ scores have almost as much predictive value as the best fitting models. Therefore, in terms of clinical application our data suggest that assessing NP symptoms using the PDQ will help identify patients at highest risk of surgery dissatisfaction.

One key limitation to this study is the lack of pre-surgical pain data. However, Phillips *et al*^[39] found

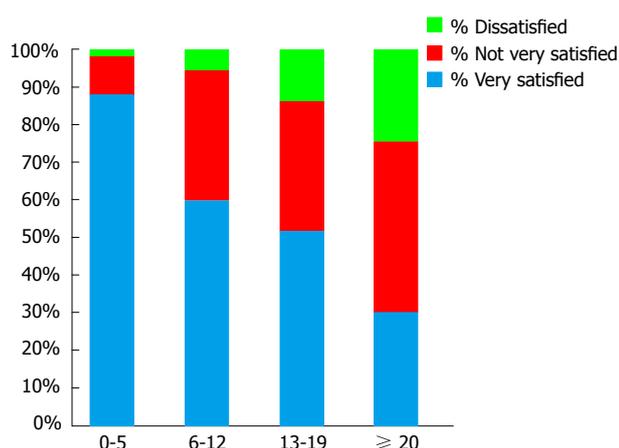


Figure 3 Proportion of post-total joint replacement patients reporting to be dissatisfied, not very satisfied or very satisfied depending on their pain-DETECT score.

that it was not possible to reliably predict post-TKR outcomes from pre-operative pain intensity and PDQ scores^[39], whereas Dualé *et al.*^[16] have reported a higher risk of NP post-surgery if peripheral NP is present pre-surgery. Although the self-administered PDQ allows data collection from a large number of individuals it does not provide definitive evidence of NP^[40]. Nonetheless, one study showed a correlation between PDQ scores and periaqueductal grey matter activation (which is involved in central sensitisation) in people with OA in areas of referred pain in response to punctate stimuli^[41].

Although in this study we did not use the widely accepted National Joint Registry agreed Patient Reported Outcomes (PROMS) data^[42], 92% of the questions in the Oxford hip and knee score (OXHS and OXKS, respectively) questionnaires are accounted for by the questionnaire used in this study, as was 83% of the content in the EQ-5D questionnaire. The questionnaire measured used in this study therefore reflects a large majority of the material covered in the PROMS. On the other hand we have examined other factors that are not usually included as part of post TJR PROMS, such as comorbidities, use of analgesic medication and pre-surgery X-ray severity all of which contribute to patient self-reported satisfaction in our data. To our knowledge this is one of the few studies to date which has looked at pain assessment integrated with comorbidities and use of medication.

Some of the factors identified as contributing to satisfaction could be addressed pre-surgery or considered when assessing outcomes post-surgery. The presence of comorbid conditions appears also to have a considerable effect on patient satisfaction, and this information may be used to manage patient expectations pre-surgery.

In conclusion, the PDQ appears to be particularly useful in capturing factors that contribute to post-TJR outcomes and may be considered as an important post-surgical assessment. These results also highlight the importance of understanding the mechanisms behind NP symptoms post-TJR, as it is a significant factor

contributing to post-TJR satisfaction and, importantly, affects a considerable proportion of individuals post-TJR.

COMMENTS

Background

Total joint replacement is a very common type of surgery. Understanding the determinants of patient satisfaction is necessary to address the increasing need for this type of surgery with population aging.

Research frontiers

The authors investigated for the first time the relationship between pre-operative radiographic severity and neuropathic pain symptoms and satisfaction post total joint replacement.

Innovations and breakthroughs

The authors show that neuropathic pain symptoms are the most important contributor to post-total joint replacement satisfaction. Other contributors are smoking and low pre-operative radiographic severity.

Applications

The prediction models used in this work can be applied to patients undergoing total joint replacement surgery for osteoarthritis.

Terminology

Neuropathic pain symptoms, caused by changes or damage to the nervous system. Pre-operative radiographic severity, refers to the extent of large joint (hip or knee) damage detected in X-rays prior to surgery.

Peer-review

This manuscript aims to evaluate factors predict satisfaction post total joint replacement. It is a very serious paper dealing with the results of joints replacement. A well written paper and well organized study.

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Retrospective Cohort Study

Soft tissue swelling incidence using demineralized bone matrix in the outpatient setting

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Author contributions: All authors contributed with drafting writing and final revision of manuscript; Pencil FJR performed statistical analysis; Valdivia JM provided independent assessment of pre and post op radiographs; Chin KR performed supervision and important critical revision.

Institutional review board statement: IRB approval was granted for patients involved in study from George Washington University as part of a cohort of patients who had anterior cervical surgery.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We did not seek or receive any funding from the National Institutes of Health (NIH), Wellcome Trust, Howard Hughes Medical Institute (HHMI), or others for this work. Chin KR is a shareholder in and receives other benefits from SpineFrontier Inc.; none of the other authors (Pencil FJR, Valdivia JM and Seale JA) have any potential conflicts of interest to declare for this work.

Data sharing statement: This dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open-access home for the dataset.

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Abstract**AIM**

To assess use of demineralized bone matrix (DBM) use in anterior cervical discectomy and fusion (ACDF) in outpatient setting.

METHODS

One hundred and forty-five patients with prospectively collected data undergoing single and two level ACDF with DBM packed within and anterior to polyetheretherketone (PEEK) cages. Two groups created, Group 1 (75) outpatients and control Group 2 (70) hospital patients. Prevertebral soft tissue swelling (PVSTS) was measured anterior to C2 and C6 on plain lateral cervical radiographs preoperatively and one week postoperatively and fusion assessed at two years.

RESULTS

There was no intergroup significance between preoperative and postoperative visual analogue scales (VAS)

and neck disability index (NDI) scores between Group 1 and 2. Mean preoperative PVSTS in Group 1 was 4.7 ± 0.2 mm at C2 level and 11.1 ± 0.5 at C6 level compared to Group 2 mean PVSTS of 4.5 ± 0.5 mm and 12.8 ± 0.5 , $P = 0.172$ and 0.127 respectively. There was no radiographic or clinical evidence of adverse reaction noted. In Group 1 mean postoperative PVSTS was 5.5 ± 0.4 mm at C2 and 14.9 ± 0.6 mm at C6 compared to Group 2 mean PVSTS was 4.9 ± 0.3 mm at C2 and 14.8 ± 0.5 mm at C6, $P = 0.212$ and 0.946 respectively. No significant increase in prevertebral soft tissue space at C2 and C6 level demonstrated.

CONCLUSION

ACDF with adjunct DBM packed PEEK cages showed a statistical significant intragroup improvement in VAS neck pain scores and NDI scores ($P = 0.001$). There were no reported serious patient complications; post-operative radiographs demonstrated no significant difference in prevertebral space. We conclude that ACDF with DBM-packed PEEK cages can be safely done in an ASC with satisfactory outcomes.

Key words: Ambulatory surgery center; Anterior cervical discectomy and fusion; Demineralized bone matrix; Less Exposure Surgery; Packed polyetheretherketone cages

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Core tip: This manuscript scientifically assesses prevertebral swelling with the use of demineralized bone matrix (DBM) anterior to cervical cage. The use of clinical and radiographic outcomes demonstrates the safety of DBM in the outpatient setting. There are no studies showing safety or outcomes of DBM anterior to the cage and directly exposed to the pre vertebral soft tissues therefore we wanted to document this study.

Chin KR, Pencle FJR, Seale JA, Valdivia JM. Soft tissue swelling incidence using demineralized bone matrix in the outpatient setting. *World J Orthop* 2017; 8(10): 770-776 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i10/770.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i10.770>

INTRODUCTION

Instrumented anterior cervical discectomy and fusion (ACDF) introduced in 1952^[1] has remained the gold standard in the treatment of cervical spondylosis. Complications ranging from relatively minor and transient dysphagia, hoarseness, post-operative neck pain and wound infection to potentially catastrophic hematoma and airway compromise, vertebral artery and neurologic injury as well as esophageal perforation^[2] have reduced over the years. This can be attributed to better technology and less exposure surgery techniques.

The outcome of ACDF is based on adequate decompression and osseous radiographic fusion^[3,4]. Autogenous bone grafts have demonstrated high fusion rates however; the immediate and long-term morbidity associated with iliac crest harvest is well recognized^[5-7]. The use of demineralized bone matrix (DBM) to aid in fusion has been demonstrated to be safe and effective^[8-10]. A review conducted by Aghdashi *et al*^[9], DBM has similar outcome to autogenous bone graft^[11]. Studies also revealed good outcomes compared to recombinant bone morphogenic proteins (rh-BMP)^[12]. Rh-BMP has been shown to cause life threatening airway edema and compromise^[13-15].

Several studies over recent years have looked at the feasibility of ACDF being done on an outpatient basis with promising results and low complication rates^[2,16-18]. Additionally, there are studies which have found that it is clinically safe to use DBM during ACDF within cages in a hospital setting^[4,11,19]. A study by Suk *et al*^[20] demonstrated peak onset of prevertebral soft tissue swelling (PVSTS) at 3 d post op. There were no studies assessing prevertebral soft tissue swelling and DBM in the outpatient setting found. The authors aim to demonstrate the safety of DBM in the outpatient setting.

MATERIALS AND METHODS

This was a non-randomized, single-center, prospective study of a total of 145 patients. We reviewed the charts retrospectively of 75 consecutive patients who single and two-level instrumented ACDF in the ASC (Outpatient ACDF), in which polyetheretherketone (PEEK) cages (Arena-C[®], SpineFrontier Inc. Malden, MA, United States) with DBM (DBM pure[®], SpineFrontier Inc., Malden, MA, United States) packed within and anterior to the cage and assigned them to Group 1. Fusion was reinforced with an anterior cervical plate (Inset[®], SpineFrontier Inc. Malden, MA, United States). Our control group, Group 2 included 70 patients who had single and two levels ACDF in the hospital setting (Inpatient ACDF), all implants and DBM was from the same company and design. IRB approval was granted for patients involved in study as part of a cohort of patients who had anterior cervical surgery.

Operations were performed by a single surgeon, who was experienced in performing procedures in academic and private hospitals, prior to commencing in an outpatient setting. Patients were only considered for surgery after failed conservative management for at least six weeks. Indications for surgery included but not limited to patients with cervical degenerative disc degeneration (DDD) and herniated nucleus pulposus. Decision on type of surgery was based on severity of pathology. Exclusion criteria for surgery included acute severe trauma, fractures, malignancy, infection, unstable chronic medical illnesses, prior anterior cervical fusions and BMI > 42^[21-23]. All patients were assessed preoperatively and narcotics were recommended to be discontinued



Figure 1 Preoperative radiograph showing retropharyngeal/prevertebral soft tissue at the level of C2 vertebral body and at the level of C6 vertebral body.

in patients with chronic use^[24]. Patients with chronic but stable medical conditions, including hypertension, diabetes mellitus, asthma, hypercholesterolemia and heart disease were medically cleared by their family practitioner and/or cardiologist where applicable. All preoperative radiographs were reviewed by the chief surgeon, as well as two additional researchers, to rule out pre-existing abnormal widening of the prevertebral soft tissue space. This was standardized by ensuring that the prevertebral soft tissue space (PVSTS) at the level of C2 was less than 50% of the C2 vertebral body and at the level of C6 measurements were approximately less than 22 mm or the prevertebral measurement should not be greater than the width of the vertebral body of C6^[25] (Figure 1). Post-operative radiographs were assessed at one week, 3 mo and at the end of follow up. Prevertebral soft tissue space (PVSTS) was compared between pre-op and 1 wk post-op films^[20,26,27].

Surgical technique

Signed consent was obtained for the procedure and under general anesthesia; patients were prepped and draped under sterile conditions. Surgical exposure of the desired vertebral level was achieved through a midline anterior cervical incision. Following discectomy, the posterior longitudinal ligament was retained *in situ*^[28] and the appropriately sized PEEK cage was inserted. DBM was packed within and anterior to the cage prior to an anterior cervical plate (ACP) being placed (Figure 2). The smallest sized ACP was placed, hemostasis confirmed and a Penrose drain was placed in all patients for wound drainage for 24 h to prevent postoperative hematoma development at home.

Discharge and follow up

Outpatients were discharged within hours of completing surgery after being deemed oriented and neurologically intact by the anesthesiologist and operating surgeon^[22,23]. Outpatient postoperative instructions were discussed with patients and caregivers with written copies provided. An assigned member of the outpatient team was responsible

for educating patients prior to consent on the risks and benefits of outpatient ACDF, as well as potential complications such as transient to persistent dysphagia, postoperative hematoma, infection and soft tissue edema with possible airway compromise. A team member called patients postoperatively on the night of surgery as well as the following morning to ensure a normal and comfortable postoperative recovery period, as well as to identify any evolving complications, which may require hospital admission. In the event of a complication, a prearranged agreement with a nearby local hospital was established before surgery. Patient reported outcomes included visual analogue scales (VAS) for neck pain, neck disability index (NDI) score and Nurick grade for those with myelopathy. Clinical outcomes were assessed based on the presence of soft tissue swelling and airway compromise. Postoperative potential DBM-related side effects were assessed clinically in all patients by palpating for soft tissue edema or swelling along the medial aspect of the sternodeidomastoid muscle. Postoperative radiological assessment was conducted with the use of anteroposterior (AP) and lateral plain radiographs looking for soft tissue emphysema, airway narrowing, tracheal deviation and PVSTS measurement in the first week postoperatively^[25-27]. Evidence of interbody fusion was assessed by radiographs at the patient's final follow up. Follow up visits occurred within the first week, one month, three months, six months, twelve months and at final two year follow up. Additional postoperative complications were also recorded.

Statistical analysis

Statistical analysis was performed using SPSS v22 (IBM corporation, New York, United States). An independent sample student *T*-test was used to compare groups for continuous data and χ^2 used for categorical data. Continuous data comparisons were expressed as means with standard error. Tests were considered significant if $P < 0.05$.

RESULTS

Comparing group 1 (75 patients outpatient ACDF) to group 2 (70 patients inpatient ACDF) no statistical differences in age, BMI and gender were found between groups, $P = 0.591$, 0.484 and 0.631 respectively. Demographics and initial diagnosis are illustrated in Table 1.

There was no significance between preoperative VAS and NDI scores between Group 1 and 2, $P = 0.75$, $P = 0.289$ respectively as shown in Table 2. After two years follow up intragroup significant improvement was demonstrated in both groups for VAS and NDI scores demonstrated in Table 2. Statistical comparison of postoperative outcomes between Group 1 and 2 shows no statistical difference in VAS and NDI scores $P = 0.62$, $P = 0.34$ respectively (Table 2). The surgical operative time in Group 1 was 92 ± 15 min as compared to Group 2 which was 140 ± 3 min. This difference of 48 min did



Figure 2 Photograph showing demineralized bone matrix packed within cage after insertion into disc space and anterior cervical discectomy and fusion plate.

Table 1 Cohort demographics with chief complaint

Variable	ACDF + DBM outpatient	ACDF + DBM inpatient	P value
Sample size (<i>n</i>)	75	70	
Age (yr)	53 ± 1.0	53.4 ± 1.6	0.591
BMI (kg/m ²)	27.9 ± 0.8	25.4 ± 1.0	0.484
Male	33	34	0.631
Female	42	36	
Diagnosis			
Herniated disc	28	23	
Degenerative disc disease	26	24	
Spondylosis (chronic pain)	7	12	
Myelopathy	3	4	
Radiculopathy	11	7	

ACDF: Anterior cervical discectomy and fusion; DBM: Demineralized bone matrix; BMI: Body mass index.

Table 2 Showing preoperative and postoperative visual analogue scales and neck disability index scores

	Preoperative VAS	Postoperative VAS	Intragroup P value	Preoperative NDI	Postoperative NDI	Intragroup P value
Group 1	7.4 ± 0.2	4.0 ± 0.2	0.001	46.9 ± 1.9	26.1 ± 1.2	0.001
Group 2	8.9 ± 1.5	5.3 ± 0.3	0.03	46.2 ± 2.6	33.4 ± 2.4	0.002
Intergroup P value	0.75	0.62		0.289	0.34	

VAS: Visual analogue scales; NDI: Neck disability index.

achieve statistical significance, $P = 0.001$. Estimated blood loss of 42 ± 6 mL in group 1 compared to 77 ± 9 mL in Group 2 showed no intergroup significance, $P = 0.131$.

Preoperative dimensions of airway diameter were all within normal limits^[29]. No intergroup significance demonstrated (Table 3) preoperatively at C2 and C6, $P = 0.172$ and 0.127 respectively. None of our patients complained of difficulty breathing within the first 24 h postoperatively. There was no radiographic^[30] or clinical evidence of adverse reaction in the patients who had ACDF to DBM (airway edema or neck swelling) within the first week postoperatively, Figure 3. Postoperative PVSTS dimension increased in both groups; however this was not a significant intragroup increase or intergroup difference as shown in Table 3. Additionally, all our patients achieved solid bony fusion^[31] as evidenced

by clinical and radiological (confirmed by report from independent radiologist) by the final follow up visit.

Three patients (4%) in Group 1 diagnosed with myelopathy without radiculopathy had a preoperative Nurick grade of 2, 1 and 1 respectively, which improved to 1 and 0 for the first two patients and remained unchanged for the third patient by the final follow up visit.

During the study period from 2011-2014, no major complications were reported in our series and there were no unplanned postoperative admissions for pain, nausea or any other complaints, all complaints are listed in Table 4. The main postoperative complaint of postoperative dysphagia was defined as any discomfort or difficulty with swallowing which was not historically present prior to surgery^[32]. The severity was assessed using the Bazaz-Yoo dysphagia severity scale

Table 3 Showing preoperative and postoperative prevertebral soft tissue swelling at C2 and C6 vertebrae

	C2 preop PVSTS (mm)	C2 postop PVSTS (mm)	C2 intragroup P value	C6 preop PVSTS (mm)	C6 postop PVSTS (mm)	C6 intragroup P value
Group 1	4.7 ± 0.2	5.5 ± 0.4	0.08	11.1 ± 0.5	14.9 ± 0.6	0.285
Group 2	4.5 ± 0.5	4.9 ± 0.3	0.107	12.8 ± 0.5	14.8 ± 0.5	0.873
Intergroup P value	0.172	0.212		0.127	0.946	

PVSTS: Prevertebral soft tissue swelling.

Table 4 Demonstrating complications after surgery in each group

Complication	Outpatient	Inpatient
Dysphagia	4	5
Visited ER (not admitted)	3	0
Pain not relieved by TTH medications	2	0
Dressing completely soaked	1	0
Intractable pain	0	1

TTH: To take home.

of mild, moderate and severe, over the initial 3 mo postoperative period^[33].

DISCUSSION

The authors aimed to demonstrate the safety of the use of DBM within and anterior to an ACDF PEEK cage in the outpatient setting. This study shows significant improvement in postoperative outcomes in both groups; however no intergroup significance was noted. Analysis of postoperative PVSTS demonstrated no clinical or statistically significant intragroup increase as well as no significant difference between groups.

The literature has copious studies endorsing ACDF as the gold standard treatment for failed conservative management of numerous cervical pathologies^[34-37]. More recently, patients and spine surgeons are turning their attention toward the potential benefits of ACDF in an ambulatory surgery center, based on promising results of preliminary reports^[2,16,17,38]. While the feasibility and safety of outpatient ACDF has been established for up to three cervical levels^[39], there is a lack of consensus regarding the safety of DBM in the anterior cervical spine as an adjunct to fusion. Studies have looked at the effectiveness, safety of its use in a hospital setting^[4,11,19] as well as normal prevertebral soft tissue swelling post ACDF^[30]; however, the paucity of data on the clinical outcomes of DBM use during ACDF in an ASC, prompted the authors to report the results of a single-center local experience.

In this series there were no adverse graft related complications noted. There was no clinical or radiologic evidence of edema one week post-operative and therefore no further evaluation for this finding performed beyond this point. The creation of DBM involves a process of allograft bone acid extraction^[40] which exposes type I collagen, growth factors and BMPs. Although lacking

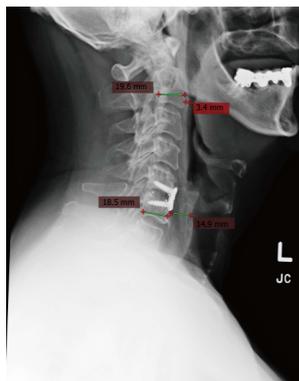


Figure 3 Plain lateral radiograph of the cervical spine, taken one week postoperatively, which shows the normal dimensions of the prevertebral space being less than 50% of the vertebral body at C2 and less than the body width of C6 respectively.

in structural integrity, DBM contains osteoconductive agents, which render it a viable alternative biologic agent for bony fusion. This study has demonstrated the effective use of DBM within and anterior to PEEK cages therefore, the authors conclude that the exposed BMPs within DBM is not significant in concentration to cause a clinical or radiographic response.

The adherence to our local, standardized outpatient criteria^[21-23], comprehensive patient education and postoperative protocol were instrumental in providing self-assurance to both patients and the surgeon when proceeding with this operation^[4,11,19]. Included in all preoperative counseling and consent sessions, were the potential risks for postoperative dysphagia, airway irritation and soft tissue swelling. Additional comfort was added by calling our patients the night of, and the morning after surgery in order to act in a timely manner should any complications occur, requiring immediate admission to hospital, which is always within 30 min of the patients' location.

As the literature expands on the safety and effectiveness of anterior cervical fusions in ambulatory surgery centers, this paper reinforces the conclusion that it is safe, with excellent patient satisfaction. The authors do acknowledge the limitations of this study: Its retrospective nature and the lack of CT scan to assess post-op soft tissue swelling. However, despite these limitations, we are confident that adherence to our strict patient selection criteria, preoperative education, consistent operating team, and systematic postoperative protocol can safely produce excellent outcomes. Our findings show that the

use of DBM within and anterior to cervical PEEK cages in the outpatient setting is safe with similar outcomes in the inpatient setting.

ACDF with adjunct DBM packed PEEK cages showed a statistical significant intragroup improvement in VAS neck pain scores and NDI scores. There were no reported serious patient complications; post-operative radiographs demonstrated no statistically significant difference in prevertebral space. We conclude that ACDF with DBM-packed PEEK cages can be safely done in an ASC with satisfactory outcomes.

COMMENTS

Background

Demineralized bone matrix (DBM) has been demonstrated to be safe in the hospital setting; however concerns may be heightened with use anterior to the cage in the outpatient setting. The authors hypothesize that clinical outcomes and safety should be similar or improved in the outpatient setting.

Research frontiers

Outpatient spine surgery continues to evolve with the introduction of minimally invasive and less exposure surgery. This study adds to the body of knowledge for outpatient surgery.

Innovations and breakthroughs

Based on literature no other study has assessed clinically DBM being placed anterior to the cage as well as within the cages looking specifically at soft tissue swelling.

Applications

This study demonstrates the safety of DBM being used anterior to polyetheretherketone interbody cage with no additional complications.

Terminology

Standard terminology used throughout text.

Peer-review

It is a well written paper.

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Retrospective Study

**Total joint replacement in inhibitor-positive haemophilia:
Long-term outcome analysis in fifteen patients**

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Abstract**AIM**

To collect data from joint replacement in inhibitor patients, evaluate haemostatic and patient outcomes, and analyse the costs.

METHODS

We report our 21-year, single-centre cumulative experience of 15 joint arthroplasties in six inhibitor patients.

RESULTS

Two low responder inhibitor patients were in the early days treated with FVIII, whereas bypassing agents were used in the rest of the high responder patients. The primary haemostatic outcome was good in 8/15, fair in 4/15 and poor in 3/15 operations. The overall patient outcome, including joint health and patient satisfaction, was good in 10/15, fair 4/15 and poor in 1/15. No deep infections were observed. Cost analysis was most beneficial in low responders and in two immune-tolerized, high responder patients. In all cases, factor replacement comprised the main treatment costs.

CONCLUSION

Our experience supports the initial use of bypassing agents as well as preoperative immune-tolerance induction when possible. Despite the challenges of haemostasis and severe joint disease, total joint arthroplasty can reach a good outcome, even in inhibitor patients. The risk for deep infection might be smaller than previously reported. Individual planning, intense multidisciplinary teamwork

and execution of operations should be centralised in a professional unit.

Key words: Haemophilia; Joint replacement; Inhibitor; Cost analysis; Arthroplasty

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Core tip: There are only few reports including joint arthroplasties on inhibitor-positive haemophilia patients. Generally the focus is mainly on immediate haemostatic outcome leaving the long-term orthopaedic results unreported. Our study brings out the importance of long-term and overall outcome when performing elective life-quality surgery. Management of inhibitor patients is especially challenging regarding not only the operative treatment but also the costs. As the health economic analysis of the topic is lacking, we provide new data. According to our cost analysis, preoperative immune-tolerance induction for high responder patients will bring cost- and outcome benefit both in surgery and preventing postoperative bleeds.

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INTRODUCTION

Total joint arthroplasty covered with coagulation factor replacement therapy is the treatment of choice in severe haemophilic arthropathy when conservative treatment has failed. The failure to stabilize the joint disease is usually due to the late initiation of secondary prophylaxis with replacement therapy. Patients may develop inhibitors to their factor replacement therapy due to the foreign protein and have thus often missed the prophylactic replacement therapy and surgical treatment because of the fear of bleeds and the high costs of the treatment. In the literature, the inhibitor prevalence is around 10% among the adult patient population, mainly affected by the earlier treatment and availability of immune-tolerance induction (ITI) therapy^[1-3].

The appropriate replacement therapy depends on the patient's individualized response, which is not always similar - nor predictable - at each haemostatic challenge or management strategy. The introduction of bypassing agents has enabled total joint replacements also for high responder inhibitor patients^[4]. However, the use of these products is costly.

The reports on joint arthroplasties in inhibitor patients are mainly case-based, and established standards of the management of these operations are scanty^[5-7]. At Orton Orthopaedic Hospital of Invalid Foundation, centralised

operative treatment of haemophilic joint disease has been carried out already since the 1970s. The haematological and laboratory support has been available by Red Cross Transfusion Central from 1957, and from 2002 also by the Helsinki University Hospital Coagulation Disorders unit. The first total hip replacement (THR) for a haemophilia patient in Finland was performed in 1982, and the first knee replacement (TKR) in 1984. The first TKR on a patient with recognized inhibitors was performed in 1991. We report our cumulative experience of 21 years of joint arthroplasties in six haemophilia inhibitor patients.

MATERIALS AND METHODS

From 1991 to 2012, six haemophilia patients with inhibitors (two low; inhibitor titre < or equal to 5 BU/mL) and four high responders; inhibitor titre > 5 IU/mL) were operated on (Tables 1 and 2). The 15 surgical procedures consisted of seven primary TKRs (in two patients, bilateral), one unicondylar knee arthroplasty, one glenohumeral replacement, two ankle arthroplasties, one THR and three knee revision arthroplasties.

Two patients were low responders (inhibitor titre < 5 BU/mL). Four patients who had a history of high inhibitor titre (> 5 BU/mL) were classified as high responders, but the titre immediately prior to surgery was < 5 BU/mL. Two high-titre inhibitor patients underwent successful ITI as a part of the ObsITI protocol at a later stage (from 2010 onwards) of the follow-up. Five patients (83%) had a history of hepatitis C. One patient also was antibody-positive for hepatitis B. None of the patients was HIV positive.

To manage surgery during the early 1990s, the historical peak inhibitor titre, whether low or high (< or > 5 BU/mL), dictated the strategy. Traditionally, immediately preoperatively in the absence of FVIII inhibitory antibodies (*i.e.*, confirmed normal recovery and half-life of FVIII), either recombinant or plasma-derived FVIII is infused intravenously to secure haemostasis by reaching normal FVIII levels (usually 80%-100%). In contrast, the presence of inhibitors neutralise FVIII, and for the surgery FVIII bypassing agents, either activated prothrombin complex concentrate (aPCC, FeibaR) or recombinant activated Factor VII (rFVIIa, NovoSeven), are the current effective options to maintain surgical haemostasis of blood. The specific agent is chosen according to the individual bleeding phenotype, history and patient weight. Initially, either cryoprecipitate or a plasma-derived FVIII (pdFVIII) was used in all low responders and initially in high responders having a preoperative low inhibitor titre, with the objective to switch to a bypassing agent once the inhibitor titre inclined. Low responders (Patients A and B) were initially treated with their standard replacement therapy: Cryoprecipitate (AHF-20[®], $n = 1/8$) or coagulation factor VIII (pdFVIII, Amofil[®], $n = 7/8$). For the high responder patients (C-F), the treatment was either activated prothrombin complex concentrate (aPCC, FEIBA[®]) or

Table 1 Main surgical operations in patients (A and B) with the low historical inhibitor titre (< 5 BU/mL)

Patient and operations (model)	Haemophilia therapy	Primary haemostatic outcome	Surgical outcome
A			
TKR (cruciate retaining)	Cryo (AHF-20) → pdFVIII	Good	Good
TKR (cruciate retaining)	pdFVIII	Good	Good
Ankle arthroplasty	pdFVIII	Good	Good
Ankle arthroplasty	pdFVIII	Good	Good
Knee revision arthroplasty (reconstructive)	rFVIII	Fair	Good
Knee revision arthroplasty (reconstructive)	rFVIII	Good	Good
B			
Knee hemiarthroplasty (unicondylar)	pdFVIII	Good	Poor
Revision arthroplasty (cruciate retaining)	pdFVIII → rFVIIa	Fair	Good

In A, six operations and in B, two operations were performed. TKR: Total knee replacement; pdFVIII: Plasma-derived factor VIII; rFVIII: Recombinant FVIII.

Table 2 Main surgical operations in the patients (C-F) with the high historical inhibitor titre

Patient and operations (model)	Replacement therapy	Primary haemostatic outcome	Surgical outcome ROM/pain
C			
TKR bilateral (hinge + posterior stabilised)	pdFVIII → aPCC	Poor	Fair
THR (uncemented)	rFVIII	Good	Good
D			
TKR bilateral (reconstructive)	aPCC → rFVIIa	Fair	Fair
E			
TKR (posterior stabilized)	aPCC → rFVIIa	Poor	Good
F			
Glenohumeral hemiarthroplasty	rFVIII	Good	Good

ROM: Range of motion; TKR: Total knee replacement; THR: Total hip replacement; aPCC: Activated prothrombinase complex concentrate.

recombinant activated factor VIIa (rFVIIa, NovoSeven®). In one case, the treatment was started with pdFVIII, but changed to aPCC when the inhibitor titre arose.

The routine blood coagulation tests were monitored daily during the FVIII replacement period to capture FVIII: C clotting activity or during bypassing therapy to capture the possible development of disseminated intravascular coagulation (DIC), anaemia or thrombocytopenia. Cefuroxime was used as standard antibiotic prophylaxis (or clindamycin, in case of allergy).

After TKR, continuous passive motion (CPM) treatment was started at the 2nd-7th postoperative day. After THR, immediate full body weight bearing was allowed, if the blood and haemostatic status supported the decision. After ankle arthroplasties, half-weight bearing with walker orthosis was recommended for 6-8 wk. After glenohumeral arthroplasty, the upper arm was immobilized in an arm sling for 4 wk and only passive mobilization for 6 wk was allowed.

Primary haemostatic outcome was considered good if the postoperative bleeding did not differ from the normal arthroplasty, fair if there were additional bleeds and poor if there were massive or repetitive additional bleeds that were difficult to manage.

The statistical analysis was carried out using the SPSS 20.0, Lead Technologies, Inc. statistical software system. For analysis, a paired-samples *T*-test was used. In this study, a *P*-value < 0.05 (two-sided probability)

was considered significant.

RESULTS

Low responders (A and B). Two low inhibitor titre patients underwent several operations, the details of which are captured in Table 1.

In Patient A, TKR was carried out under cryoprecipitate coverage. At three days, the treatment had to be changed to pdFVIII when the FVIII: C response started to decline. The haemostatic outcome was good.

Three years later, a second primary TKR with pdFVIII replacement therapy was performed. The inhibitor titre remained low, and the haemostatic and surgical outcomes were good. Two years later, the patient experienced recurrent knee bleeds at the recent TKR site. Three arthroscopical synovectomies were performed under pdFVIII replacement, while any vascular anomaly was excluded by popliteal angiography^[8,9]. After each synovectomy, the bleeding tendency decreased temporarily for a few months. Finally, the bleeds ceased with Holmium isotope radiosynoviorthesis. Additionally, two total ankle arthroplasties were performed successfully under pdFVIII coverage with good haemostatic and primary outcomes.

Later, the patient underwent revision knee arthroplasties due to aseptic loosening of the components. Both arthroplasties were performed using rFVIII. After



Figure 1 Unicondylar knee replacement and revision arthroplasty.

the first operation, the patient experienced a knee bleed at 8 d while on continuous replacement therapy, which was treated with higher dosing of rFVIII. There was a temporary rise in the FVIII antibody, but the final outcome was good. The second knee operation resulted in good haemostatic and overall outcome.

Patient B had experienced only occasional spontaneous bleeding episodes. Before the primary operation, he was devoid of inhibitor history. He suffered from posttraumatic medial knee arthrosis, and unicondylar knee replacement was performed with a good haemostatic outcome using pdFVIII. However, the patient needed revision arthroplasty 9 mo after the primary operation. Next, the replacement therapy was started with pdFVIII, and at 12 d postoperatively, the inhibitor titre raised the replacement therapy was switched to rFVIIa with good haemostatic outcome (Figure 1).

In conclusion, the two low responder inhibitor patients were managed successfully with FVIII concentrate, while the inhibitor titre remained low. Individually and according to the type of surgery, the FVIII was switched to bypassing agents when the inhibitor titre rose. One postoperative bleed in association with 8 operations occurred without long-term consequences.

High-responders, patients C-F

The surgical details of Patients C-F are presented in Table 2. In Patient C with bilateral primary knee arthroplasty, the preoperative inhibitor titre was < 5 BU/mL, and the operation was carried out without complications using pdFVIII. At five days when the inhibitor titre rose, however, the patient experienced bilateral knee bleeds and aPCC was started. The dose (up to 200-250 U/kg) had to be increased for several days due to a fair haemostatic response. DIC or deep venous thrombosis did not develop. After 5.5 years, the patient underwent a successful ITI therapy with rFVIII, and a primary THR could be performed with rFVIII 6 mo later with good haemostatic and surgical outcome. The recovery and half-life of rFVIII were appropriate, and the inhibitor did not reoccur throughout the early and later follow-up.

Patient D had bilateral TKR with aPCC as replacement therapy. At 8 d the patient experienced a severe knee

bleed, which ceased with rFVIIa [two doses of 5 mg (90 μ g/kg *iv*) at 2 h interval]. Next, aPCC was re-administered (at 200 IU/kg) but the patient bled with regard to the operated knee twice, at days 11 and 14. After the third bleed, the replacement therapy was carried out with rFVIIa for four days and thereafter with sequential aPCC and rFVIIa for two weeks.

Patient E underwent TKR with aPCC as replacement therapy pre- and perioperatively. At two days, he suddenly bled a lot (800 mL/30 min) with regard to his operated knee. A bolus of 12 mg of rFVIIa (220 μ g/kg) stopped the bleed immediately. The replacement therapy was continued with rFVIIa (6 mg every 2 h) for several days, and the haemostatic outcome was finally optimal.

Patient F had a history of high inhibitor titre and successful ITI with rFVIII one year preoperatively. He underwent glenohumeral hemiarthroplasty with good haemostatic outcome and without an increase of the inhibitor titre during the follow-up.

Overall, in 5 operations out of 12, the patients experienced major bleeds at 2-8 d postoperatively. Albeit this initial haemostatic response was either fair or even poor in two patients, the joint outcome was good. One patient had bilateral knee operation initially managed with pdFVIII, during which there was the reactivation of the inhibitor and both-sided bleeds occurred. He had the poor haemostatic response. However, the complication was controlled by switching the therapy to bypassing agents. A single bypassing therapy did not necessarily manage to control haemostasis, but the switch between aPCC and rFVIIa or their sequential use finally secured the haemostatic outcome.

Primary arthroplasties

The mean follow-up for patients with primary TKR (eight arthroplasties) was 7.3 years (0.3-20.3, SD 7.6). The median age of the patients at the time of the operation was 48.4 years (35.4-66.1, SD 10.9). The median hospital stay was 19.6 d (10-25, SD 6.1). The range of motion (ROM) improved from mean 81.9° flexion to 96.9° (SD 17.1 and 11.9, $P = 0.07$) and from mean 21.3° extension deficiency to 7.5° (SD 12.7 and 8.4, $P = 0.09$). One high

responder patient (Patient D) with severe knee flexion contracture with bilateral knee arthroplasty had a patellar fracture. It was observed at the two-month control and treated conservatively with orthosis. No deep infections were observed.

The two ankle arthroplasties were performed without complications to the same low responder Patient A. The patient had severe haemophilic arthropathy without significant deformation or bone loss in both ankles, and the preoperative walking distance had diminished below 500 m. Preoperative ROM in both ankles was from neutral position to 20° plantar flexion and primary outcome was from 5° dorsiflexion to 30° of plantar flexion, respectively. In 6.1 and 7.0 years follow-up 0°-20° ROM in plantar flexion of both ankles was observed. The patient could stand on his toes, walking ability was improved to 2 km and both ankles were pain-free. Radiologically, the components were in good position without signs of loosening or other complications.

The total hip arthroplasty for the high responder Patient C with a preoperative successful ITI was performed with an excellent haemostatic and primary outcome. At the 2-mo follow-up, the patient had a pain-free joint and ROM 0°-90° extension-flexion, 20° rotation and 40° abduction. The radiographic control showed a good position of the prosthesis.

The high responder Patient F with glenohumeral hemiarthroplasty had also undergone recent preoperative ITI. The patient had a painful haemophilic arthropathy with restricted ROM (abduction 45°, flexion 60° and outer rotation -10°), severe prolonged pain problems and an addiction to opiates. The surgery succeeded well under rFVIII coverage. The pain significantly diminished, and at the 7-mo follow-up, ROM substantially improved (abduction 80°/110° using scapulae, flexion 90°/130° using scapulae and outer rotation 45°) with pain-free peripheral movements. The X-rays showed a good position of the prosthesis.

Revision arthroplasties

Two revision knee arthroplasties using reconstructive prostheses for Patient A were performed at 17.7 and 15.7 years after primary operations because of loosening of the components. The hospital stay was 16 and 11 d, and CPM treatment was started three and five days after the operation, respectively. The postoperative mobility was 0°-100° and 0°-110° at 2.1 years and 1.8 years follow-up. After the first operation there was an initial bleed, but the joint outcome was good. The second operation and primary rehabilitation were successful with both good haemostatic and primary outcome. Five months postoperatively, a bacterial prepatellar bursitis was treated with peroral antibiotics. No deep infection was detected and the patient recovered well.

The third knee revision arthroplasty was performed at 9 mo after a primary operation for Patient B because of loosening of the components. The patient had suffered from posttraumatic medial knee arthrosis, and the

joint problem was considered primarily posttraumatic rather than haemophilic arthropathy. For these reasons, unicondylar knee replacement was performed. The loosening was thought to result from mechanical factors, but the compromised haemostasis by haemophilia may also play a role. Neither bacteria nor the signs of infection were detected. In spite of the fair haemostatic outcome, the joint outcome was good with 0°-110° ROM and freedom from pain at the 3.5-year follow-up. Radiologically, the components were in good position, and the walking ability had improved from 100 m to over one kilometre.

Cost analysis

Since 2005 in Orton Orthopaedic Hospital, 11 major orthopaedic procedures (13 arthroplasties) on inhibitor patients were performed (Table 3). Among the high responder patients when aPCC and/or rFVIIa were needed, the total costs varied between 350900-500400 Euros. In these cases, the replacement therapy covered the great majority, *i.e.*, 87%-94%, of the total costs, even though two of the three operations were bilateral. Of the two low responders and in two cases among high responder patients after ITI, the replacement therapy costs were lower, being 59%-81% of the total costs. The total costs of these operations were also clearly lower compared to the high responders with an active inhibitor: About 1/5 - 1/3, *i.e.*, 47200-103200 Euros, in the low responders and about 1/10, *i.e.*, 43300-49800 Euros, in the two high responders having undergone ITI.

High responder patients with postoperative inhibitor formation had also a longer hospital stay (15-24 d) compared with the low responder patients (8-18 d) or the high responders with preoperative ITI (8-9 d). However, two of the three operations in high responder patients were also bilateral.

DISCUSSION

According to the guidelines of World Federation of Haemophilia^[10], joint replacement surgery for haemophilia patients requires multidisciplinary teamwork. Despite the demanding surgery, good results among haemophilia patients with inhibitors have been previously reported^[5-7,11-16]. However, there are only a few reports including joint arthroplasties on inhibitor patients^[7,11,12,16-19] with scant follow-up data. As this is a rare patient group, randomised controlled trials are not - and are not likely - to become available.

In our report, the primary haemostatic outcome was good in half of the patients and poor in 20% of the high responder patients, and improved only with switching between the bypassing agents. However, the primary surgical outcome turned out fairly well, even in those patients who initially had a poor haemostatic outcome. Along prolonged rehabilitation, postoperative bleeding complications increase costs and reduce the patient's

Table 3 Cost analysis of arthroplasties on inhibitor patients since 2005

Resp	Operation	Component	TOT eur	HT ² eur	HT (%) ³	Product [®]	Hospital stay(d)	
Low	Knee revision arthroplasty	Unilateral	Reconstructive	103200	75700	73	Kogenate Bayer	18
Low	Knee revision arthroplasty	Unilateral	Reconstructive	95400	66900	70	Kogenate Bayer	11
Low	Ankle arthroplasty	Unilateral	Primary ankle	47200	35600	75	Kogenate Bayer	10
Low	Ankle arthroplasty	Unilateral	Primary ankle	60200	48800	81	Kogenate Bayer	12
Low	Knee hemiarthroplasty	Unilateral	Unicondylar	51500	41600	81	Amofil	9
Low	Knee revision arthroplasty	Unilateral	Cruciate retaining	50200	36300	72	Amofil	8
High	Knee arthroplasty	Bilateral	Ps ⁴ + hinge	350900	305500	87	Amofil FEIBA	24
High	Hip arthroplasty	Unilateral	Primary uncemented	43300	27800	64	ReFacto AF ¹	8
High	Knee arthroplasty	Bilateral	Reconstructive	500400	445100	89	FEIBA NovoSeven	24
High	Knee arthroplasty	Unilateral	Ps ⁴	409900	386100	94	FEIBA NovoSeven	15
High	Glenohumeral arthroplasty	Unilateral	Primary glenohumeral	49800	29300	59	ReFacto AF ¹	9

¹Successful preoperative ITI; ²HT haemophilia therapy (costs of replacement therapy); ³Procentual costs of replacement therapy; ⁴Ps posterior stabilized; Resp: Inhibitor responder (low = historical inhibitor titre < 5 BU/mL, high = historical inhibitor titre > 6 BU/mL).

quality of life by increasing pain and disability. Every effort should focus on the avoidance of postoperative bleeds. Point of care monitoring with thromboelastography or a calibrated automated thrombogram may help in treatment decisions as the therapy unexpectedly may fail^[20]. The therapy should be started preferentially with the bypassing agents, and the team should work intimately together with bedside visits to secure the haemostasis when the patient is to be mobilized. According to our experience, the use of cold to reduce swelling and pain may not be optimal, as cooling in the knee may impair the early haemostatic response. Finally, the tailored use of tranexamic acid, not only with rFVIIa but also with aPCC, may turn beneficial^[21-23].

Radiosynovectomy has been shown to be an effective treatment in chronic haemophilic synovitis, diminishing pain and bleeding occurrence^[24-26]. One of our patients had joint bleeds after TKR with only a temporary help from arthroscopical synovectomies. Even angiography was performed to exclude vascular anomalies, which have been reported in the form of pseudoaneurysms and their rupture after joint surgery or even natively^[8]. Radiosynoviorthesis with Holmium isotope finally ended the bleeding episodes. The case is similar to Papavasiliou's report^[27] of successful radiosynovectomy after TKR, although that patient was not reported to have inhibitors. In our experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty.

The risk of infection (early- and late-onset) is known to be greater in haemophilia patients undergoing arthroplasty compared with the non-haemophilia population^[21,28]. In our report there was one prepatellar bursitis, but deep infections were absent. However, the follow-up times were partly short.

In one case, a unicondylar knee replacement was performed to a patient devoid of previous inhibitor history. The patient suffered from posttraumatic medial arthrosis and the primary hemostatic outcome was good.

However, a rapid revision (9 mo postoperatively) was performed because of aseptic loosening of components. The loosening was thought to result from mechanical factors, but the compromised haemostasis by haemophilia may also play a role. In our experience, we do not recommend unicondylar arthroplasty to a patient with haemophilia.

Surgery for patients with inhibitors is expensive and highly demanding. In our report, in 3/8 primary TKRs, revision-type (constrained or reconstructive) prostheses were used because of severe bone defects and soft tissue degeneration. According to our cost analysis, the operation itself including the components, surveillance, medication and hospital stay was less significant, whereas the major cost comprised of the haemostatic replacement therapy. This was especially evident among the high responder patients and when bypassing agents were needed, thus constituting ca. 90% of total costs. Instead, in high responder cases that had undergone preoperative ITI, the cost of replacement therapy was similar to the low responder patients' cases and those of regular haemophilia management. The hospital stay was prolonged for the high responder patients, albeit two of the three operations were bilateral arthroplasties. In our opinion, preoperative ITI for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds^[29-31]. The disadvantages of ITI are its partial success rates and time constraints, under conditions where there is an urgent need for surgery.

When determining the optimal timing for arthroplasty one must consider the grade of arthrosis, the patient's age, the supposed survival of the chosen prosthesis, as well as the risk of complications. Also, working ability, the status of other joints, osteoporosis and the estimated overall prognosis are to be taken into account. For optimal prognosis, the operation should be performed before permanent joint contractures. From the haematological point of view, the patient

characteristics, plan for replacement therapy for surgery and rehabilitation must be meticulously evaluated preoperatively. An appropriate rehabilitation program prior to and after surgery takes into account other joints and their functionality during recovery in order not to induce other joint problems. In the surgery of haemophilia patients, especially with inhibitors, the comprehensive medical team has to observe the patient for early haemostatic symptoms and signs. Therefore, it is essential that these operations are centralized in a professional unit with the availability of skilled surgeons and haematologists having access to the bypassing agents and optimal laboratory tools.

COMMENTS

Background

Total joint arthroplasty covered with coagulation factor replacement is the treatment of choice in severe haemophilic arthropathy. Inhibitor patients are especially challenging regarding not only the operation and haemostasis management but also the costs since the treatment can be very expensive. The aim was to collect data from joint replacement in inhibitor patients, evaluate haemostatic and patient outcomes, and analyse the costs.

Research frontiers

Despite the demanding surgery, good results among haemophilia patients with inhibitors have been previously reported. However, there are only a few reports including joint arthroplasties on inhibitor patients with scant follow-up data.

Innovations and breakthroughs

In this report, the primary haemostatic outcome was good in half of the patients and poor in 20% of the high responder patients, and improved only with switching between the bypassing agents. However, the primary surgical outcome turned out fairly well, even in those patients who initially had a poor haemostatic outcome. In the authors' opinion, preoperative immune-tolerance induction (ITI) for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds. Also, in the authors' experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty.

Applications

In the authors' opinion, preoperative ITI for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds. Also, in the authors' experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty. Surgery of haemophilia patients should be centralized in a professional unit with the availability of skilled surgeons and haematologists having access to the bypassing agents and optimal laboratory tools.

Terminology

ITI: With ITI therapy, factor concentrate is given regularly over a period of time until the body is trained to recognize the treatment product without reacting to it.

Peer-review

The manuscript is written well.

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Observational Study

Digital blinding of radiographs to mask allocation in a randomized control trial

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Abstract**AIM**

To demonstrate the effectiveness of a digital radiographic altering technique in concealing treatment allocation to blind outcome assessment of distal femur fracture fixation.

METHODS

Digital postoperative anteroposterior and lateral radiographs from a sample of 33 randomly-selected patients with extra-articular distal femur fractures treated by surgical fixation at a Level 1 trauma center were included. Using commercially available digital altering software, we devised a technique to blind the radiographs by overlaying black boxes over the implant hardware while preserving an exposed fracture site for assessment of fracture healing. Three fellowship-trained surgeons evaluated a set of blinded radiographs twice and a control set of unblinded radiographs once. Each set of radiographs were reviewed independently and in a randomly-assigned order. The degrees of agreement and disagreement among evaluators in identifying implant type while reviewing both blinded and unblinded radiographs were assessed using the Bang Blinding Index and James Blinding Index. The degree of agreement in fracture union was assessed using kappa statistics.

RESULTS

The assessment of blinded radiographs with both the Bang Blinding Index (BBI) and James Blinding Index (JBI) demonstrated a low degree of evaluator success at identifying implant type (Mean BBI, far cortical locking: -0.03, SD: 0.04; Mean BBI, standard screw: 0, SD: 0; JBI: 0.98, SD: 0), suggesting near perfect blinding. The assessment of unblinded radiographs with both blinding indices demonstrated a high degree of evaluator success at identifying implant type (Mean BBI, far cortical locking: 0.89, SD: 0.19; Mean BBI, standard screw: 0.87, SD: 0.04; JBI: 0.26, SD: 0.12), as expected. There was moderate agreement with regard to assessment of fracture union among the evaluators in both the blinded (Kappa: 0.38, 95%CI: 0.25-0.52) and unblinded (Kappa: 0.35, 95%CI: 0.25-0.45) arms of the study. There was no statistically significant difference in fracture union agreement between the blinded and unblinded groups.

CONCLUSION

The digital blinding technique successfully masked the surgeons to the type of implant used for surgical treatment of distal femur fractures but did not interfere with the surgeons' ability to reliably evaluate radiographic healing at the fracture site.

Key words: Methods; Randomized controlled trials; Patient outcome assessment; Fracture healing; Femoral fractures

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Core tip: The purpose of this study was to demonstrate the effectiveness of a digital blinding protocol to conceal treatment allocation and permit blinded assessment of radiographic healing of various distal femur fractures. Digital postoperative radiographs from a randomly-selected sample were blinded using digital altering software and evaluated by three fellowship-trained surgeons. This study demonstrates the success with which an uncomplicated and reproducible technique can blind radiographs of distal femur fractures. The blinding protocol successfully masked the surgeons to the type of fixation devices implanted but did not interfere with reliable evaluation of radiographic union.

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INTRODUCTION

Locking plates with standard locking screws are currently used as the gold standard of treatment to stabilize displaced extra-articular distal femur fractures. These plate and screw constructs provide excellent strength

to withstand early joint motion and rehabilitation. However, emerging evidence suggests that the rigidity of these constructs may cause complications such as delayed union, nonunion, implant failure, late loss of alignment, and subsequent need for an additional surgical procedure^[1-7]. In response to the increasing clinical concern that plates with standard locking screws are too stiff, "far cortical locking" (FCL) screw technology has been introduced to permit controlled micro-motion within a locked construct, which in theory leads to earlier and more predictable healing^[8,9]. While initial reports in animal studies and small retrospective clinical series have examined the efficacy of FCL screw technology in treating femur fractures, with more uniform callus formation^[6,9], prospective clinical trials comparing standard locking and FCL technologies are necessary to guide treatment recommendations.

The comparison of standard locking screws vs FCL screws is currently being conducted in a multi-center randomized control trial (RCT). One of the challenges of surgical RCT's is blinding to reduce bias, since surgeons cannot be blinded to treatment allocation. However, blinding independent outcome assessors can be an effective way to reduce bias^[10]. The purpose of this study is to demonstrate the effectiveness of a digital blinding protocol to conceal treatment allocation and permit blinded assessment of radiographic healing of distal femur fractures treated with standard locking screws and FCL screws.

MATERIALS AND METHODS

Blinding

Digital postoperative anteroposterior and lateral radiographs from a sample of 33 randomly-selected patients with extra-articular distal femur fractures (OTA 33-A) were included. All patients were treated with a pre-contoured distal femur plate. Twelve subjects had been treated with standard locking screws, while the other 21 had been managed with FCL screws. Radiographs from the 6 wk, 12 wk, and 24 wk postoperative follow-up visits were acquired for each patient. Week 6 images were not always available, and when this was the case, week 2 postoperative images were substituted. All available radiographs from each patient were of adequate quality for use in the study.

Using commercially available digital altering software (Acorn 1.5.5, Flying Meat, Inc., Everett, WA, United States), we devised a technique to blind the radiographs by overlaying black boxes over the hardware while preserving an exposed fracture site for assessment of healing. The radiographs of standard locking screw constructs contained an average of 6 shaft screws, while those of FCL screw constructs contained an average of 4. To deal with this discrepancy, we standardized each radiograph by placing a minimum of 6 blinding boxes on the shaft portion of the distal femur (Figure 1). A single investigator (L.S.) digitally modified the entire series of images. This investigator had minimal experience with



Figure 1 Examples of radiographs before (top) and after (bottom) blinding. Images were taken at 12- (left) and 24-wk (right) post-operation.

digital photo alteration and no previous experience with the digital altering software.

Study design

Three attending physicians with fellowship training in orthopaedic traumatology evaluated the images. All of the evaluators had experience operating with both types of locking screws and interpreting postoperative radiographs. All were aware of, and one was directly involved with, the development of the blinding protocol.

The 33 patients were each assigned a subject number, and random number generating software was used to order the radiographs corresponding to each patient into two PowerPoint (Microsoft, Redmond, WA) presentations, one with unblinded images and the other with blinded images. Each PowerPoint slide contained orthogonal views of four radiographs corresponding to each patient. One set of anteroposterior and lateral views from the time point of healing assessment—either the 12-wk or 24-wk postoperative follow-up visit—and another set of views from a previous time point was used for comparison. Specifically, week 24 images were paired with week 12 images, and week 12 images were paired with week 6 images.

The blinded set of radiographs was assessed twice and the unblinded control once. The evaluations were performed independently and in a randomly-assigned order. A minimum of 2 wk elapsed between evaluations.

For each PowerPoint slide (unblinded and blinded radiographs), the surgeons assessed: (1) the type of

hardware used (standard locking screws, FCL screws, or unsure); and (2) status of bony union (healed, not healed, or unsure). Although radiographic fracture healing is subjective and without a clear gold standard^[11], in this study radiographic healing was defined as evidence of minimum bridging of 2 cortices. For the blinded images, the evaluators were also asked whether or not the blinding interfered with his or her ability to assess fracture healing (yes, no). If the blinding did interfere, the evaluators were asked to specify which area of the image was problematic (proximal, distal, or both).

Statistical analysis

Statistical analysis was performed using Stata 10.0 (Stata Corp LP, College Station, TX) to calculate the Bang Blinding Index^[12,13] and the James Blinding Index^[14]. The Bang Blinding Index is commonly used to measure the degree of agreement between evaluators beyond the degree expected by chance. Scores range from -1 to 1, with 1 representing a complete lack of blinding, 0 representing perfect blinding, and -1 representing opposite guessing, which may be related to unblinding^[12]. The James Blinding Index measures the degree of disagreement between evaluators. Scores range from 0 to 1, with 0 representing a complete lack of blinding, 0.5 representing completely random blinding, and 1 representing perfect blinding^[15].

The kappa statistic is related to the James Blinding Index and was calculated to measure the degree of fracture union agreement between evaluators. The kappa statistic was interpreted using the methods of Landis and Koch, commonly used for interpreting inter-evaluator agreement for qualitative or categorical outcome measures^[16].

RESULTS

Evaluation of blinding

The assessment of blinded radiographs with both the Bang Blinding Index and James Blinding Index demonstrated a low degree of evaluator success at identifying implant type, suggesting near perfect blinding (Table 1). The mean Bang Blinding Index was 0 ± 0 for the images with standard locking screws and -0.03 ± 0.04 for those with FCL screws. The mean James Blinding Index was 0.98 ± 0 .

The assessment of unblinded radiographs with both indices demonstrated a high degree of evaluator success at identifying implant type (Table 2), as expected. The mean Bang Blinding Index was 0.92 ± 0.87 for the images with standard locking screws and 0.89 ± 0.19 for those with FCL screws. The mean James Blinding Index was 0.26 ± 0.12 .

Evaluation of fracture healing

There was moderate agreement with regard to assessment of fracture healing among the evaluators in

Table 1 Blinding assessment with blinded radiographs

	BBI-FCL screw	BBI-standard screws	James Blinding Index
Observer 1	0	0	0.99
Observer 2	0	0	0.99
Observer 3	-0.08	0	0.98
Mean	-0.03	0	0.98
SD	0.04	0	0

BBI: Bang Blinding Index; FCL: Far cortical locking; SD: Standard deviation.

Table 2 Blinding assessment with unblinded radiographs

	BBI-FCL screw	BBI-standard screws	James blinding index
Observer 1	1	0.85	0.32
Observer 2	1	0.85	0.32
Observer 3	0.67	0.92	0.12
Mean	0.89	0.87	0.26
SD	0.19	0.04	0.12

BBI: Bang Blinding Index; FCL: Far cortical locking; SD: Standard deviation.

both the blinded and unblinded arms of the study (Table 3). There was no difference in agreement between the blinded and unblinded groups.

DISCUSSION

This study demonstrates the success with which an uncomplicated and reproducible technique can blind radiographs of distal femur fractures. The blinding protocol successfully masked the surgeons to the type of locking screws implanted in the distal femur. Statistical analysis with the Bang Blinding Index and James Index scores confirmed the success of the blinding protocol: The interval estimates were all close to 0 and 1, respectively, representing near perfect blinding. The blinding protocol did not interfere with the surgeons' ability to evaluate radiographic healing at the fracture site. There was no difference in agreement for assessment of fracture union between the blinded and unblinded radiographs. Furthermore, moderate agreement of fracture healing using radiographs is consistent with previously published literature^[17].

The protocol used to blind the type of hardware placed in the distal femur is based upon the previously published work by Karanickolas *et al.*^[18]. Karanickolas *et al.*^[18] identified three different methods of digitally concealing radiographic hardware in the femoral neck: The "blackout" technique involves the placement of an opaque polygon over the hardware, the "subtraction" technique involves digitally copying bone from another region and passing it over the hardware, and the "overlay" technique involves digitally copying one implant and passing it over a radiograph consisting of the other implant. Although all three techniques successfully

Table 3 Agreement scores for the assessment of fracture healing

Type of review	Kappa	95%CI
Blinded	0.376	0.253-0.515
Unblinded	0.353	0.252-0.453

blinded evaluators to the type of hardware implanted, the "blackout" technique resulted in the most difficulty in identifying hardware and required the least amount of time per radiograph. Although our study differs in the anatomic location of implanted hardware, focusing on the distal femur, our digital blinding protocol is similar to their most easily reproducible and effective method, the "blackout" technique.

Our results must be interpreted within the limitations of the study design. The number of fractures included in this study was limited, with radiographs from only 33 subjects being assessed. Furthermore, the quality and profile of the radiographs were not uniformly standardized, potentially affecting the radiographic assessment. Finally, we blinded the distal articular portion of the plate to mask subtle differences in the plate design of the various manufacturers. This may have impeded some assessments of fracture healing; however, this will not be necessary in the current RCT because all enrolled patients will receive the same locking plate.

Our study design has a number of strengths, including the separation of a randomized order of independent images into two PowerPoint presentation modules (unblinded and blinded) for individual surgeon assessment a minimum of 2 wk apart. All radiographs were evaluated for distal femur fracture union by the overall impression of trauma surgeons, which has been reported to be a moderately reliable method of assessing the quality of radiographic healing of femur fractures^[19]. Additionally, our blinding protocol was successfully utilized without negative consequence on fracture healing assessment. A gathering of results and thorough statistical analysis was performed independently to test the criteria for effective blinding, further limiting detection bias. The James and Bang Blinding Indices were both used to limit the effect of "correct guessing"^[5-7]. Finally, our blinding method is effective, efficient, and easily reproducible for future study designs.

Distal femur fractures are commonly treated by plate and screw constructs, but comparative efficacy research in this field is difficult to perform due to the practical limitation of blinding outcome assessments. This study provides not only a simple blinding technique for outcome evaluation but also a method to assess the success of blinding, both of which increase the validity of future trials which compare standard locking screws and FCL screws in the treatment of distal femur fractures. These techniques may be applied to investigations in other fields of orthopaedic surgery which involve evaluation of radiographs containing opaque implants.

COMMENTS

Background

Surgical fixation of distal femur fractures with locking plates and far cortical locking screw (FCL) technology may cause controlled, micro-motion at the fracture site to allow more reliable and uniform callus formation for predictable healing. However, no comprehensive studies comparing the effectiveness of FCL technology to standard locking screws in the treatment of distal femur fractures exist. The aim of this study was to devise and analyze a digital radiographic altering technique to conceal treatment allocation and blind outcome assessment of distal femur fracture fixation. This would allow unbiased comparison of distal femur fixation methods.

Research frontiers

Locking screws are necessary for surgical fixation of displaced extra-articular distal femur fractures. Standard locking or FCL screws may be used. However, there are few studies which directly compare, without bias, standard locking and FCL screws in effectively healing distal femur fractures.

Innovations and breakthroughs

The authors created and analyzed a digital blinding technique to objectively assess radiographic union of distal femur fractures treated with two types on plate-and-screw constructs. Statistical analysis with the Bang Blinding Index and James Index scores confirmed the success of the blinding protocol. There was no statistically significant difference in agreement for assessment of fracture union between the blinded and unblinded radiographs.

Applications

The results of this study suggest that a simple digital radiographic blinding technique may be a reliable method for objective, unbiased outcome evaluation in trials comparing the efficacy of standard locking screws and FCL screws in the treatment of distal femur fractures. These techniques may be applied to investigations in other fields of orthopaedic surgery which involve evaluation of radiographs containing opaque implants.

Terminology

Digitally altering radiographs with black boxes overlaying hardware, while preserving an exposed fracture site, is a technique to blind outcome assessors in evaluating distal femur fracture fixation.

Peer-review

This is an interesting study on the use of a digital protocol to blind outcome assessors in evaluating radiographic union of bone fractures after surgical fixation.

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Observational Study

Restoration of the joint geometry and outcome after stemless TESS shoulder arthroplasty

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Abstract**AIM**

To evaluate the joint geometry and the clinical outcome of stemless, anatomical shoulder arthroplasty with the TESS system.

METHODS

Twenty-one shoulders with a mean follow-up 18 of months were included. On scaled digital radiographs the pre-morbid center of rotation (CoR) was assessed and compared to the CoR of the prosthesis by using the MediCAD® software. Additionally, the pre- and post-operative geometry of the CoR was assessed in relation to the glenoid, the acromion as well as to the proximal humerus. Radiological changes, such as radiolucencies, were also assessed. Clinical outcome was assessed with the Constant and DASH score.

RESULTS

Both, the Constant and DASH scores improved signifi-

cantly from 11% to 75% and from 70 to 30 points, $P < 0.01$ respectively. There were no significant differences regarding age, etiology, cemented or metal-backed glenoids, *etc.* ($P > 0.05$). The pre- and postoperative humeral offset, the lateral glenohumeral offset, the height of the CoR, the acromiohumeral distance as well as neck-shaft angle showed no significant changes ($P > 0.05$). The mean deviation of the CoR of the prosthesis from the anatomic center was 1.0 ± 2.8 mm. Three cases showed a medial deviation of more than 3 mm. These deviations of 5.1, 5.7 and 7.6 mm and were caused by an inaccurate humeral neck cut. These 3 patients showed a relatively poor outcome scoring.

CONCLUSION

TESS arthroplasty allows an anatomical joint reconstruction with a very good outcome. Outliers described in this study sensitize the surgeon for an accurate humeral neck cut.

Key words: Anatomical shoulder arthroplasty; Stemless; Omarthrosis; Total shoulder replacement; Joint geometry

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Core tip: By using bony landmarks that are not altered by osteoarthritic changes, the premorbid center of rotation (CoR) was assessed in comparison to the postoperative one after TESS arthroplasty. Furthermore, joint geometry changes were assessed in relation to the glenoid, the acromion and the proximal humerus. Our data demonstrate a precise restoration of the joint and a very good clinical outcome. This study also describes outliers with a clinically relevant medialized CoR. Being caused by a slightly inaccurate humeral neck cut, this study might sensitize us that this osteotomy is a crucial step to ensure a good clinical outcome.

von Engelhardt LV, Mancke M, Breil-Wirth A, Filler TJ, Jerosch J. Restoration of the joint geometry and outcome after stemless TESS shoulder arthroplasty. *World J Orthop* 2017; 8(10): 790-797 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i10/790.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i10.790>

INTRODUCTION

The traditional stemmed design of anatomical total shoulder arthroplasties is based on the principles of total hip replacement. Similarly to hip arthroplasty, stem-related complications, such as a bone loss secondary to stress shielding, humeral fractures, *etc.*, are not so infrequent^[1-4]. A further difficulty of a stemmed shoulder arthroplasty is that the restoration of the individual anatomy with its offset and center of rotation (CoR) is not always reached even with newer modular designs^[5,6]. Another aspect is the revision surgery, where severe difficulties may arise during and after

stem revision. A recent report describes complications such as a canal perforation, bone destructions and humerus fractures in around 50% of the cases^[7]. Thus, avoiding stem-related complications, improved options to gain an anatomic reconstruction of the proximal humerus and preserving the bone stock for easier revisions are practical reasons why stemless designs have been introduced as an alternative to traditional designs. However, both patients and surgeons have high expectations regarding activity levels and return to sports following shoulder replacement surgery^[8]. In regard to these data, the ongoing development of shoulder arthroplasty is a logical consequence.

The Total Evolutive Shoulder System (TESS, Biomet-Zimmer, Warsaw, IN, United States) uses different sizes of an impaction-implanted 6-armed corolla for a peripheral metaphyseal anchoring close to the cortical bone. This method of fixation is different to those with a much more central anchoring within the metaphysis, *e.g.*, the threaded central cage of the Arthrex Eclipse (Arthrex, Karlsfeld, Germany) or the Simpliciti system with a nucleus and 3 fins for central impaction (Wright Medical, formerly Tornier, Montbonnot, France)^[9]. The principle of a peripheral metaphyseal anchoring might influence the reconstruction of the individual anatomy of the proximal humerus. The purpose of this study was to evaluate the restoration of the joint geometry as well as the clinical and radiographic outcome of the TESS system for anatomical shoulder arthroplasty.

MATERIALS AND METHODS

This study has been approved by the Ethical Committee of the University of Duesseldorf (Study No. 4426). All patients were operated at the Department of Orthopedics, Trauma Surgery and Sports Medicine of the Johanna-Etienne Hospital Neuss. Patients included in this study had an anatomical shoulder arthroplasty with the TESS system (TESS, Biomet-Zimmer, Warsaw, IN, United States). Pre-operative planning of the prosthesis components was performed in all cases on scaled anteroposterior digital radiographs using the MedicaCAD[®] software. After a deltopectoral approach, the elevation of the subscapularis tendon and the dislocation of the humeral head, the rotator cuff insertions, the humeral head and the anatomical neck were visualized. The cutting guide was held parallel to the anatomical neck and the inclination, retroversion and the height of the cut were adjusted by using these landmarks. After the saw cut, the size of the corolla broach was measured using the humeral sizing templates. Then the glenoid was prepared. A cemented all-polyethylene component or a metal-backed glenoid which allows a conversion to a reversed version were available. After broaching and impaction of the corolla into the metaphysis, different trial heads with a diameter of 41, 43, 45, 48, 50 and 52 mm with or without an offset were available. The subscapularis tendon was reattached to its origin by using transosseus Ethibond sutures. A biceps tenodesis was performed in patients with slender

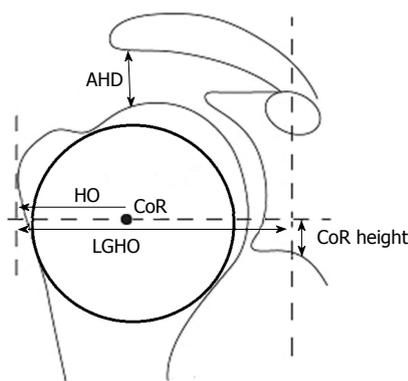


Figure 1 Assessment of the pre- and postoperative joint geometry. The best-fit circle with the premorbid center of rotation (CoR) is generated with bony landmarks which are not altered by osteoarthritic deformities: The lateral major tubercle border, the medial calcar at the inflection point and the medial edge of the greater tuberosity at the medial supraspinatus insertion. Further parameters were the acromiohumeral distance (AHD), the humeral offset (HO) as the distance between the CoR and the lateral major tubercle border, the lateral glenohumeral offset (LGHO) as the distance between the coracoid and the lateral major tubercle border, and the height of the center of rotation (height CoR) as the distance to the inferior glenoid.

overarms. Physiotherapy with restricted external rotation was started directly after the operation. Besides the exclusion of patients with rotator cuff tears or a defect arthropathy, there were no further exclusion criteria for the implantation of an anatomical TESS prosthesis. All patients received a non-stemmed version. The decision whether to use a stemmed or non-stemmed design was made intraoperatively depending on the metaphyseal bone quality. One patient with a humeral head necrosis had an incorrect positioning of the humeral component leading to an extensively elevated humeral offset. In this patient, a revision to a stemmed version was performed immediately. This case was considered a surgical failure. Another patient suffered a fall with a traumatic rotator cuff tear before the follow-up appointment. Both patients were excluded from this study. Finally, 21 shoulders in 19 patients (m/f = 10/9) with anatomic TESS shoulder prostheses were evaluated regarding their clinical and radiological outcome. The mean follow-up was 18 ± 9 mo. The average age at surgery was 66 years (range 32-79 years). In 10 cases, the dominant side was involved. 15 shoulders received a total arthroplasty with a metal-backed glenoid, four a cemented PE glenoid and three received a hemiarthroplasty. Indications were an osteoarthritis ($n = 19$) and a humeral head necrosis ($n = 2$). One necrosis was caused by a thalassaemia and one was posttraumatic after plate fixation of a proximal humeral fracture.

As recommended by Booker *et al.*^[10], the clinical outcome of the patients was assessed with the combination of two outcome scoring tools. The Disabilities of the Arm, Shoulder, Hand (DASH) score was used as a patient self-assessment measurement tool and the constant score (CS) as a clinically-based outcome measuring.

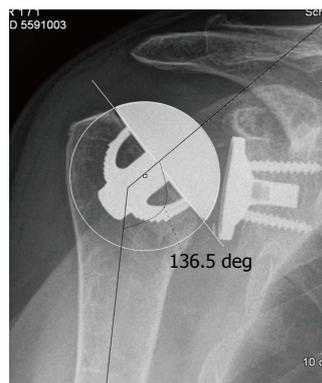


Figure 2 The postoperative center of rotation of the prosthesis shows no deviation compared to the native one. The neck shaft angle is defined as the medial angle between the shaft axis and a perpendicular line to the preoperative anatomic neck or the base of the humeral head component.

A standardized anterior-posterior- and an axillary view were performed preoperatively and at the follow-up appointment. Preoperative X-rays were scaled by using a 25 mm diameter ball marker. Postoperative X-rays were scaled using the size of the glenosphere. Measurements were performed with the Mediacad[®] software. The premorbid CoR was assessed with the best-fit circle method generated with three bony landmarks which are not altered by the osteoarthritic articular surface (Figures 1 and 2): The lateral cortex of the greater tuberosity, the medial calcar at the inflection point where the calcar meets the articular surface, and the medial edge of the greater tuberosity at the medial supraspinatus insertion^[11]. This way, the deviation of the CoR of the implanted humeral head can be assessed in comparison to the native anatomic one. As described by Alolabio *et al.*^[12], a deviation of more than 3 mm was considered as being clinically significant. A medial deviation compared to the premorbid CoR was defined as an overstuffing (Figure 3), whereas a lateral deviation was defined as an understuffing (Figure 4). To further assess the geometry of the pre- and postoperative CoR in relation to the glenoid, the acromion as well as to the proximal humerus, further parameters were measured as described by Thomas *et al.*^[13] (Figure 1). Because some preoperative X-rays showed a poor positioning quality, four cases had to be excluded from the assessment of these pre- to postoperative geometry changes. The following differences of the pre- and postoperative values were calculated: The acromiohumeral distance (AHD) is defined as the shortest distance between the humerus and the acromion, the humeral offset (HO) as the distance between the CoR and the lateral border of the greater tuberosity, the lateral glenohumeral offset (LGHO) as the distance between the basis of the coracoid and the lateral border of the greater tuberosity and the height of the CoR regarding to the inferior border of the glenoid (CoR height)^[13]. Pre- to post-operative neck shaft angles, defined as the medial angle between the shaft axis and a perpendicular line to the anatomic neck, were also

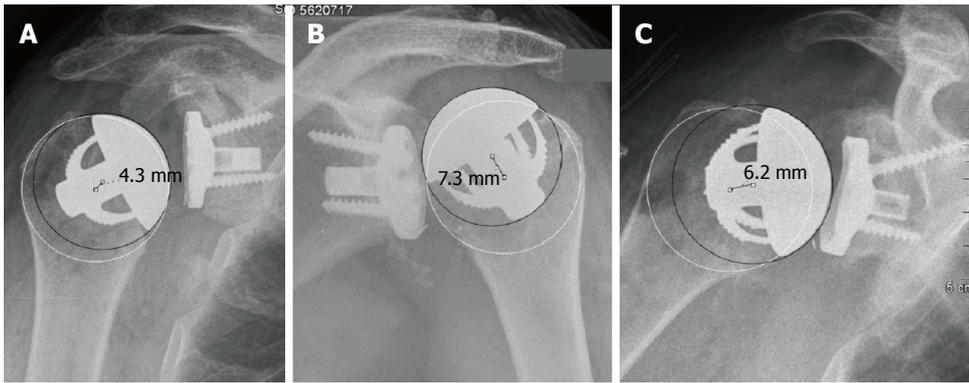


Figure 3 In three cases, a medial deviation of 4.3 (A), 7.3 (B) and 6.2 (C) mm was caused by an inaccurate humeral neck cut with a resection level which was too high in all cases. These findings were defined as an overstuffing: These patients showed a relatively poor outcome scoring.



Figure 4 The center of rotation of the prosthesis was 3.7 mm lateral to the anatomical one and caused by a slightly too small humeral head size. This patient showed a relatively high postoperative constant score.

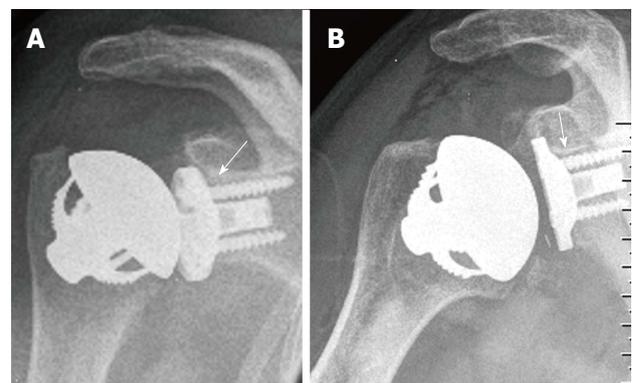


Figure 5 In two cases small radiolucent lines of a maximal thickness of 2 mm were noticed at the upper screw and behind the superior third of the baseplate (white arrows).

measured (Figure 2).

Statistical analysis

Statistical analysis were performed with SPSS Statistics software 22.0 (SPSS Inc., Chicago, Illinois, United States). The Wilcoxon test was used for the comparison between the pre- and postoperative data of the clinical scores, the Mann-Whitney-*U* test to compare the clinical scores between two different groups of the population and the Kruskal-Wallis test to compare the clinical scores between several groups. The parametric Students *t*-test was used to compare pre- and post-operative geometrical measurements. The level of significance was set to $\alpha < 0.05$. A statistical review was conducted by a biomedical statistician.

RESULTS

Functional outcome

The relative CS and DASH score improved significantly from a median of $11\% \pm 19\%$ to $75\% \pm 26\%$ and from 70 ± 22 points to 30 ± 19 points, $P < 0.01$, respectively. In the symptoms section of the DASH score, the patients improved from 24 ± 7 points to 12 ± 5 points ($P < 0.01$). In the function section, the

score improved from 82 ± 19 points to 53 ± 18 points. There were no significant differences regarding age, sex, etiology groups, side of surgery, cemented or metal back glenoids treatment with a hemi- or total arthroplasty ($P > 0.05$).

Radiological results

With the best-fit circle method, the mean deviation of the CoR of the prosthesis from the anatomic CoR was 1.0 ± 2.8 mm. Of the 21 cases, four (19%) exhibited a deviation of more than 3 mm. Three cases (14%) showed an overstuffing with a medial deviation of 4.9, 6.2 and 7.6 mm. These patients showed a relatively poor outcome with a CS of 39, 41 and 51 points. The reasons for these deviations were a too high resection level (Figure 3A and C) and an inaccurate inclination of the humeral neck cut (Figure 3B). In the fourth case, the CoR of the humeral component was 3.7 mm lateral to the anatomical CoR. This deviation with an understuffing was caused by a slight undersizing of the humeral head (Figure 4). This patient showed a relatively high postoperative CS of 77 points.

The geometry of the CoR in relation to the glenoid, the acromion as well as to the proximal humerus, described by the AHD, HO, LGHO, the CoR height and the neck-shaft

Table 1 Pre- to post-operative geometrical joint parameters

	Mean	Median	SD	Minimum	Maximum
Pre-OP neck shaft angle	135.4°	135.3°	3.0°	131.6°	139.7°
Post-OP neck shaft angle	136.6°	133.8°	9.4°	119.3°	158.9°
Pre-OP AHD (mm)	6	6.5	3.1	2	13
Post-OP AHD (mm)	9.6	7	6.8	2	25
Pre-OP HO (mm)	25.3	25	2.8	22	32
Post-OP HO (mm)	25.2	25.5	4.2	18	36
Pre-OP LGHO (mm)	63.9	63	6	52	74
Post-OP LGHO (mm)	60.9	62.5	6.5	49	74
Pre-OP CoR height (mm)	17.2	17	6.3	8	28
Post-OP CoR height (mm)	17.7	17.5	6.5	5	29

All changes depicted were statistically not significant ($P > 0.05$). CoR: Center of rotation; AHD: Acromiohumeral distance; LGHO: Lateral glenohumeral offset.

angle, showed only slight differences between the pre- and post-operative measurements. By using the Students *t*-test all these minor changes of the geometry presented in Table 1 were not significant ($P > 0.05$).

Small radiolucent lines were seen in two of 15 cases with a metal-backed glenoid (13%) (Figure 5). In both cases it was above the superior part of the upper screw and behind the superior third of the baseplate. Both radiolucencies measured a maximal thickness of 2 mm. Further signs of a loosening were not noticed. At the last follow-up, both patients were pain-free and showed a CS of 75 and 52 points. At the cemented all-polyethylene glenoid radiolucent lines and/or osteolyses were not noticed. Radiolucent lines were also not detected around the 21 humeral components.

Complications

We observed three (14%) complications. One patient with a posttraumatic humeral head necrosis developed a frozen shoulder which was treated with an arthroscopic capsular release. The CS at the last follow-up was 48 points. One patient showed a partial brachial plexus lesion. He underwent an intensive rehabilitation. At the follow-up appointment, he recovered partially but still showed a CS of only 15 points. One of the patients with an overstuffed positioning of the humeral component (Figure 3B) suffered a cuff failure three months after the last follow-up appointment nine months postoperatively. This patient showed a CS of only 51 points. A revision to a reversed prosthesis was performed.

DISCUSSION

In this study, we had to document three complications which lead to an overall complication rate of 14%. Looking closer, one partial brachial plexus lesion was treated with an intensive rehabilitation, one shoulder arthrofibrosis was treated with an arthroscopic capsular release and one cuff failure needed a revision to a reversed prosthesis. In recent review articles, the overall

complication rate lies between 4.2% and 15.2%^[14,15]. In the literature, an arthrofibrosis after shoulder arthroplasty is rarely documented^[15,16], whereas a rotator cuff failure is reported with incidences between 1.3% and 14%^[17-19] and a *plexus* lesion with incidences up to 15%^[20,21]. Taken together, our complication rate is high and lies in the upper range compared to the literature. In our opinion, these results are poor and interfere with the outcome scorings. This should be highlighted at the beginning of this discussion.

The humeral head varies individually in its retroversion, inclination as well as its medial and posterior offset^[22,23]. Therefore, first and second generation stemmed arthroplasties did not meet the requirements to reach an exact restoration of the anatomy^[22]. Even if newer modular stemmed designs have improved the adaptation to the individual anatomy, an exact anatomic match is not always achieved^[5,6]. In a finite element analysis, Büchler and Farron^[24] demonstrated the importance of an anatomically reconstructed humeral head to avoid an eccentric glenoid loading. In a study on patients with dissatisfaction after shoulder arthroplasty, main findings were substantially malpositioned components with or without loosened glenoids, stiffness and instabilities^[25]. These clinical and biomechanical studies demonstrate the importance of an exact reconstruction of the joint geometry to achieve a good clinical outcome.

The impacted corolla of the TESS prosthesis provides a peripheral metaphyseal anchoring^[9]. This relatively stable fixation close to the cortical bone might explain why findings indicating a loosening were not noticed. This is in accordance to previous studies where no radiolucent lines were noticed around the corolla of the TESS implant^[26,27]. On the other hand, the peripheral metaphyseal anchoring with different sizes might influence the reconstruction of the joint geometry. Our hypothesis was that the stemless TESS system provides a reliable reconstruction of the individual anatomy with a good clinical outcome. In our series, the relative CS and DASH scores improved significantly with results that are in a similar range to previous reports on the anatomic TESS prosthesis^[26-28]. Youderian *et al.*^[11] demonstrated that the pre-morbid CoR can be accurately predicted by a circle fitted from preserved nonarticular bony landmarks. We used this best-fit circle to measure the deviation of the center of the prosthesis to the pre-morbid CoR. Previous studies demonstrated that a malpositioning of 3 to 4 mm can affect the clinical outcome^[5,12,29-31]. According to Alolabi *et al.*^[12] and Kadum *et al.*^[31], we defined a deviation of 3 mm as clinically relevant. In our series, 81% showed no deviation or a deviation of less than 3 mm. Another study also used the best-fit circle method to assess the restoration of the CoR with different anatomical prosthesis types. This study demonstrated no deviation or a deviation of less than 3 mm with lower rates lying between 34.9% and 68.8%. The mean deviation between the pre-morbid CoR and the center of the prosthesis measured between 2.5 and 3.8 mm which is two to four times higher compared to our study^[12]. However, even if

our results are relatively good, we have to notice that we were not able to demonstrate a 100% rate of an exact restoration of the CoR. Thus, four patients (19%) showed a deviation of more than 3 mm. We hypothesized that a significant deviation might lead to a relatively poor clinical outcome. One patient showed an understuffing with a lateral deviation of the implant CoR which was caused by a relatively small humeral component. Showing a relatively high CS of 77 points, this deviation did not lead to a poor clinical outcome. Three patients showed an overstuffing caused by an inaccurate resection level for the humeral neck cut. With 51, 39 and 41 points, these patients showed a relatively poor CS. Because the inaccurate humeral neck cut lead to a clinically relevant overstuffing, these cases have to be characterized as avoidable failures during surgery. Besides a poor clinical outcome, one of these three patients suffered a cuff failure after the last follow-up, requiring a revision to a reversed arthroplasty. Showing an incidence of 11%, a recent systematic review suggests that these cuff tears following total shoulder arthroplasty may be more common than previously thought^[19]. Maybe these data should sensitize the surgeon to be aware of an exact identification of anatomical landmarks for a correct humeral neck cut. Besides a digital scaled preoperative planning, the use of the best-fit circle method might support the surgeon's ability to find the right resection level and to choose the correct head size. In some cases, osteophytes as bony landmarks might be helpful to mark the correct resection level and angle during surgery. In some cases, an intraoperative fluoroscopy, where the best-fit circle method can be used again, might provide an increased security to achieve an exact humeral head position and size. Especially in cases with advanced deformities or in cases where the achievement of an optimal soft tissue balancing of the implant is not completely satisfactory, such additional intraoperative X-rays might be helpful.

The pre- and post-operative AHD, HO, LGHO and the CoR height were measured as described by Thomas *et al.*^[13]. Table 1 depicts that these measurements, including the pre- and postoperative neck shaft angles, showed only minimal changes. Thus, the geometry of the CoR in relation to the glenoid, the proximal humerus and the acromion does not seem to be altered. Regarding these data, the TESS system allows a reliable restoration of the individual joint geometry. This might explain the relatively good clinical outcome of the TESS prosthesis described in our series as well as in previous studies with follow-up times ranging from 6 to 45 mo^[26-28,32-34].

At the cemented all-polyethylene glenoid components, radiolucent lines were not noticed. This is similar to previous studies on pegged designs, where radiolucent lines were not detected^[35,36]. At the metal-backed glenoids, small radiolucent lines were seen in two cases (2/15, 13%) behind the superior third of the baseplate and above the upper screw (Figure 5). Further signs of a loosening were not noticed. In previous studies with newer metal-backed glenoids,

radiolucencies were also noticed in 7%^[37], 10%^[38,39] and 23%^[40] of the cases. The TESS system has a central convex section in both the polyethylene and the metal-backed component. Compared to those with a flat-backed glenoid, this design showed lower distraction forces in biomechanical testings^[41] as well as a lower presence and progression of radiolucencies^[40]. Moreover, the metal-backed glenoid baseplate of the TESS system has a double coating with porous titanium and hydroxyapatite. Besides the design characteristics, these material features have also been shown not to be as critical as those with older flat shaped, uncoated metal-backed glenoid components^[40,42,43]. These features of the TESS system might explain why radiolucencies were noticed in our series in only two cases of metal-backed components and in none of the cases with a polyethylene glenoid component.

We acknowledge that our study has several limitations. There was no randomized control group treated with a conventional stemmed prosthesis to compare our results. Further limitations of this study are the short mean follow-up of 18 mo and the small number of 21 shoulders being evaluated. The study presented here was a necessary first step in exploring our first experiences with the TESS system, which seems to provide reasonable advantages. Therefore, the outcome scorings and the assessment of complications should be regarded cautiously. Larger studies with longer follow-up intervals are needed to assess the sustainability of the clinical outcome as well as long-term changes of the joint geometry. For this reason we recently applied for ethical approval of a long term study on the TESS prosthesis.

In conclusion, the stemless shoulder arthroplasty using the TESS system allows a reliable reconstruction of the individual anatomy with an excellent clinical outcome. On the other hand, we noticed three cases with a slight but clinically relevant overstuffing reconstruction of the CoR caused by an inaccurate humeral neck cut. This should increase our awareness. An optimized bone cut is a crucial step to ensure a good clinical outcome during surgery.

COMMENTS

Background

An exact reconstruction of the individual anatomy of the shoulder joint is vital to reach a good clinical outcome of anatomical shoulder replacement. The restoration of the joint geometry as well as the clinical and radiographic outcome of stemless, peripheral metaphyseal anchored shoulder arthroplasty by using the TESS system is evaluated.

Research frontiers

Besides modular prosthesis designs, current developments in shoulder arthroplasty include smaller, bone sparing components. Research is needed to interpret advantages, pitfalls and the clinical efficacy.

Innovations and breakthroughs

Stemless TESS shoulder arthroplasty allows an exact reconstruction of the pre-morbid center of rotation (CoR). Additional parameters, such as the relation between the pre- and postoperative CoR and the glenoid, the acromion as

well as the proximal humerus are reconstructed. Thus, the data demonstrate a precise restoration of the joint geometry with a good clinical outcome. A loosening of the metaphyseal anchoring was not detected. Similarly to previous studies, this article also demonstrates that even a slightly inaccurate humeral neck cut can cause a clinically relevant medialized CoR.

Application

Surgical precision work and a highly modular prosthesis system with variable sizes is needed to ensure a good clinical outcome. The use of the best-fit circle method during the preoperative planning might be helpful to find the right resection level and to choose the correct head size. During surgery, an exact identification of anatomical landmarks is vital to find the correct level and angle for the humeral neck cut. In some cases, intraoperative fluoroscopy might be an additional support.

Terminology

TESS: Total Evolutive Shoulder System; DASH score: Disabilities of the Arm, Shoulder and Hand score; CS: Constant score; CoR: Center of rotation; AHD: Acromiohumeral distance; HO: Humeral offset; LGHO: Lateral glenohumeral offset.

Peer-review

It is a well-written manuscript with information useful to the readers of the journal.

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Scaffolds based therapy for osteochondral lesions of the talus: A systematic review

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Abstract

AIM

To clarify the effectiveness of scaffold-based therapy for osteochondral lesions of the talus (OLT).

METHODS

A systematic search of MEDLINE and EMBASE databases was performed during August 2016 and updated in January 2017. Included studies were evaluated with regard to the level of evidence (LOE) and quality of evidence (QOE) using the Modified Coleman Methodology Score. Variable reporting outcome data, clinical outcomes, and the percentage of patients who returned to sport at previous level were also evaluated.

RESULTS

Twenty-eight studies for a total of 897 ankles were included; 96% were either LOE III or IV. Studies were designated as either of poor or fair quality. There were 30 treatment groups reporting six different scaffold repair techniques: 13 matrix-induced autologous chondrocyte transplantation (MACT), nine bone marrow derived cell transplantation (BMDCT), four autologous matrix-induced chondrogenesis (AMIC), and four studies of other techniques. The categories of general demographics (93%) and patient-reported outcome data (85%) were well reported. Study design (73%), imaging data (73%), clinical variables (49%), and patient history (30%) were also included. The weighted mean American Orthopaedic Foot and Ankle Society (AOFAS) score at final follow-up was: 86.7 in MACT, 88.2 in BMDCT, and 82.3 in AMIC. Eight studies reported that a weighted mean of 68.3% of

patients returned to a previous level of sport activity.

CONCLUSION

Scaffold-based therapy for OLT may produce favorable clinical outcomes, but low LOE, poor QOE, and variability of the data have confounded the effectiveness of this treatment.

Key words: Scaffold; Ankle; Talar osteochondral lesion; Systematic review; Cartilage

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Core tip: This systematic review demonstrated that scaffold-based therapy for lesions of the talus (OLT) may produce favorable clinical outcomes. However, 96% of included studies were classified into the category of poor level of evidence and no papers were of good methodological quality. Therefore, careful attention should be paid when evaluating scaffold-based therapy for OLT. In addition, large variability and underreporting of clinical data between studies made it difficult to reliably compare the results. Further well-designed studies are necessary to determine the effectiveness of scaffold-based therapy for OLT, especially when compared to the available traditional treatments.

Shimozono Y, Yasui Y, Ross AW, Miyamoto W, Kennedy JG. Scaffolds based therapy for osteochondral lesions of the talus: A systematic review. *World J Orthop* 2017; 8(10): 798-808 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i10/798.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i10.798>

INTRODUCTION

Numerous surgical treatment strategies for osteochondral lesions of the talus (OLT) have been proposed, but a universally ideal treatment has yet to be established^[1,2]. The operative treatment for OLT can be divided into two broad categories: Reparative and replacement procedures. Reparative procedures aim to regenerate tissue with biomechanical properties similar to normal hyaline cartilage. Bone marrow stimulation (BMS) is the most common reparative procedure, which stimulates mesenchymal stem cell proliferation and promotes fibrous cartilage repair tissue at the defect site. However, the fibrous cartilage repair tissue has different biological and mechanical properties compared to native hyaline cartilage and is likely to degenerate over time^[3]. Autologous chondrocyte implantation (ACI) is another reparative procedure that attempts to regenerate damaged cartilage with more hyaline-like repair tissue, but this procedure has the disadvantage of the need for a two-staged intervention, which increases both cost and the potential for morbidity^[4].

Recently, tissue-engineering approaches using various

types of bioavailable scaffolds has emerged with greater potential for cellular differentiation and maturation. The templates are typically seeded with elements selected to improve the quality of reparative cartilage and include stem cells and growth factors. Matrix-induced autologous chondrocyte transplantation (MACT) is a second-generation ACI technique, which uses a type I / III bilayer collagen membrane seeded with cultured autologous chondrocytes. However, MACT also requires a two stage procedure^[5,6]. Autologous matrix-induced chondrogenesis (AMIC) is a one-step scaffold-based therapy that combines bone marrow stimulation (BMS) with the use of a porcine collagen I / III matrix scaffold^[7]. Bone marrow-derived cell transplantation (BMDCT) is also a one-step procedure and is a combination of concentrated bone marrow aspirate and scaffold material^[8].

Scaffold-based therapy for OLT offers alternative reparative procedures and is quickly becoming more popular as data supporting clinical efficacy increases^[9]. However, no consensus has been reached regarding the effectiveness of scaffold-based therapy on OLT to date.

The purpose of the current systematic review was to clarify the effectiveness of scaffold-based therapy for OLT based on available clinical evidence.

MATERIALS AND METHODS

Search strategy

Two independent reviewers performed a systematic review of the databases PubMed/MEDLINE and EMBASE in January 2017 based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[10].

The combination of search terms were: (cartilage OR cartilage injury OR cartilage damage OR cartilage repair OR cartilage defect OR osteochondral lesion OR osteochondral dissecans OR osteochondral defect OR osteochondral injury OR osteochondral fracture OR osteochondritis dissecans) AND (ankle OR talus OR tibia OR talocrural joint) AND (scaffold OR scaffold-based repair OR matrix-assisted chondrocyte implantation OR cartilage regeneration OR osteochondral repair). The reference list of all articles and relevant studies were also scanned for additional articles potentially not identified through our electronic search alone.

The inclusion and exclusion criteria are shown in the Table 1. No time limit was given to publication date.

The titles and abstracts were reviewed by applying the aforementioned criteria, and the full text of potentially relevant studies was then selected. Scaffold-based therapy for OLT was defined as operative treatment using any scaffolds for OLT.

Differences between reviewers were discussed until agreement was achieved, and the senior author was consulted in the event of persistent disagreement.

Assessment of level of evidence

Two independent investigators reviewed each study and the LOE was determined using previously published

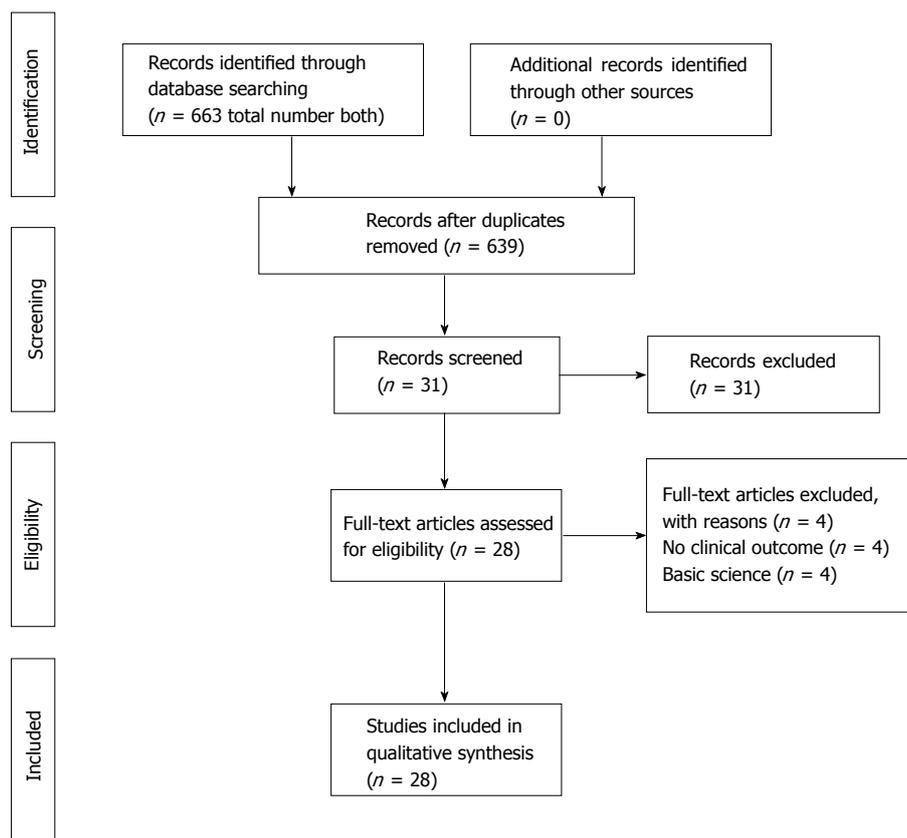


Figure 1 PRISMA flowchart outlining the systematic review.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Therapeutic clinical studies evaluating the effect of scaffolds for ankle cartilage repair All patients included had > 6-mo follow-up Published in a peer-reviewed journal Published in English Full-text version available
Exclusion criteria	Review articles Case reports Technique articles Cadaveric studies Animal studies <i>In vivo</i> studies

criteria^[11].

Assessment of methodological quality of evidence

Two independent investigators evaluated the methodological quality of evidence (QOE) of the included studies using the Modified Coleman Methodology Score (MCMS) (Table 2)^[12,13]. Instances of discrepancy were resolved by consensus and if any disagreement persisted, a senior author was consulted and a consensus was reached. Excellent studies were considered those that scored 85 to 100 points; good studies scored 70 to 84 points; fair studies scored 55 to 69 points, and poor studies scored less than 55 points^[14].

Data extraction and analysis

Two reviewers independently extracted data from each study and assessed variable reporting of outcome data using parameters of previously published criteria^[15]. In addition, clinical outcomes and the percentage of patients who returned to sport at previous level were evaluated.

Statistical analysis

All statistical analysis was performed using a commercially available statistical software package (SAS 9.3; SAS Institute, Inc., Cary, NC, United States). Descriptive statistics were calculated for each study and parameters analyzed. For each variable, the number and percentage of studies that reported the variable was calculated. Variables were reported as weighted average ± weighted standard deviation where applicable.

RESULTS

After full text review, 28 clinical studies for a total of 897 ankles were identified for inclusion in the current study (Figure 1)^[4-8,16-38]. The weighted mean follow-up was 37.7 (range 6-87) mo, with only three studies reporting a follow-up time of greater than five years^[20,22,24].

Of the 28 clinical studies, there were 30 treatment groups, including six different scaffold-based therapies: 13 MACT^[5,6,16-26], nine BMDCT^[4,8,26-31], four AMIC^[7,32-34], two cartilage extracellular matrix^[35,36], one autologous

Table 2 Modified Coleman Methodology Score

		Score
Part A: Only 1 score to be given for each section		
Number of study patients	> 60	10
	41-60	7
	20-40	4
	< 20, not stated	0
Mean follow-up (mo)	> 24	5
	12-24	2
	< 12, not stated or unclear	0
Number of different surgical procedures included in each reported outcome	1	10
	> 1, but > 90% of patients undergoing the 1 procedure	7
	Not stated, unclear, or < 90% of subjects undergoing the 1 procedure	0
Type of study	Randomized controlled trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
Diagnostic certainty (MRI)	In all	5
	In > 80%	3
	In < 80%	0
Description of surgical procedure given	Adequate (technique stated and necessary details of that type of procedure provided)	5
	Fair (technique only stated without elaboration)	3
	Inadequate, not stated, or unclear	0
Description of postoperative rehabilitation	Well described (ROM, WB, and sport)	10
	Not adequately described (2 items between ROM, WB, and sport)	5
	Protocol not reported	0
Part B: Scores may be given for each option in each of the 3 sections if applicable		
Outcome criteria	Outcome measures clearly defined	2
	Timing of outcome assessment clearly stated (<i>e.g.</i> , at best outcome after surgery or follow-up)	2
	Objective, subjective, and imaging criteria	6
	2 items between objective, subjective, and imaging criteria	4
	Objective, subjective, or radiological criteria	2
Procedure for assessing outcomes	Patients recruited (results not taken from surgeons' files)	5
	Investigator independent of surgeon	4
	Written assessment	3
	Completion of assessment by patients themselves with minimal investigator assistance	3
Description of patient selection process	Selection criteria reported and unbiased	5
	Recruitment rate reported	
	> 80%	5
	< 80%	3
	Eligible patients not included in study satisfactorily accounted for or 100% recruitment	5

collagen-induced chondrogenesis (ACIC)^[37], and one cell free scaffold therapy^[38]. All included studies of scaffold-based therapy were summarized in Table 3. Patient demographics and clinical characteristics of each procedure are shown in Table 4.

LOE

There was one (3.6%) study of LOE II^[30], three studies (10.7%) of LOE III^[4,24,26], and 24 studies (85.7%) of LOE

IV^[5-8,16-23,25,27-29,31-38] (Table 5) according to established criteria^[11]. No study of LOE I was reported. The further data of LOE in each procedure group was shown in Table 5.

QOE

The weighted mean MCMS of the overall population of studies was 49.3 ± 10.0 out of a possible 100 points. There were seven studies (25%) of fair

Table 3 Studies of two-step and one-step procedures for ankle scaffold-based repair

Procedure	Product	Scientific publication	Type of study	LOE	No. of patients	Lesion size (cm ²)	Follow-up (mo)	Results
Two-step MACT	MACI	Schneider <i>et al</i> ^[6] , 2009	Case series	IV	20	2.3	21	Significant improvement in functional score Pain improved in 70% of patients
		Giza <i>et al</i> ^[5] , 2010	Case series	IV	10	1.3	24	Significant clinical improvement at 1 yr and maintained at 2 yr
		Aurich <i>et al</i> ^[16] , 2011	Case series	IV	18	-	25	Significant improvement in all clinical scores 64% were excellent or good Age and symptoms duration were correlated with results
		Dixon <i>et al</i> ^[17] , 2011	Case series	IV	25	1.3	44	72% improved symptoms 78% patients over 40 yr reported restricted recreational activity
		Lee <i>et al</i> ^[18] , 2013	Case series	IV	38	1.9	24	Functional outcomes improved significantly at 2 yr 68% were excellent or good outcome 75% ICRS grade I or II in 2 nd look arthroscopy at 1 yr
	Hyalograft C	Johnson <i>et al</i> ^[19] , 2013	Case series	IV	18	1.9	82	Functional outcomes improved at final follow-up
		Giannini <i>et al</i> ^[20] , 2014	Case series	IV	46	1.6	87	Significant clinical improvement at 1 yr and maintained at 3 yr; 3 failures
		Giannini <i>et al</i> ^[21] , 2008	Case series	IV	46	1.6	36	Significant clinical improvement at 1 yr and 3 yr Results correlated with age and previous surgery Hyaline-like cartilage regeneration in histological evaluation
		Battaglia <i>et al</i> ^[22] , 2011	Case series	IV	20	2.7	60	Significant clinical improvement T2 mapping MRI showed 69% of lesion are covered with repair tissue
		Nehrer <i>et al</i> ^[23] , 2011	Case series	IV	13	-	47	Significant clinical improvement in all cases
Two-step BMDCT	Spontostan Powder HYAFF-11	Domayer <i>et al</i> ^[24] , 2012	Comparative study	III	18	1.2	65	Significant clinical improvement but no significant difference compared to MFX group No difference between MFX and MACT on T2 maps
		Apprich <i>et al</i> ^[25] , 2012	Case series	IV	10	1.2	48	Significant clinical improvement No differences in functional outcome and MOCART score between MFX and MACT
	Spontostan Powder HYAFF-11	Giannini <i>et al</i> ^[8] , 2009	Case series	IV	48 (25 HA membrane, 23 collagen powder)	2.1	29	Significant clinical improvement at 1 yr maintained at 2 yr Similar results with two scaffolds Correlation between clinical outcome and lesion size
		Giannini <i>et al</i> ^[26] , 2010	Comparative study	III	25 BMDCT 46 two-step MACT	2.2 1.6	39 57	Significant clinical improvement at 1 yr and further improvement at 3 yr 76% complete intergration with surrounding cartilage on MRI Hyaline-like cartilage tissue on histological evaluation
		Battaglia <i>et al</i> ^[27] , 2011	Case series	IV	20	1.5	24	85% excellent or good clinical results at 2 yr 78% of lesion are covered with repair tissue comparable to hyaline cartilage
Spontostan Powder HYAFF-11	Giannini <i>et al</i> ^[28] , 2013	Case series	IV	49	2.1	29	Significant clinical improvement at 1 yr with subsequent significant decrease at 2 and 3 yr 78% of repaired tissue similar to hyaline cartilage on T2 maps	
Spongostan Powder	Buda <i>et al</i> ^[29] , 2014	Case series	IV	64	5.3	53	Clinical results peaked at 2 yr, declining gradually at follow-up of 6 yr	

	Biopad	Cadossi <i>et al</i> ^[30] , 2014	Comparative study	III	15 BMDCT 15 BMDCT with PEMF	2 1.9	12 12	Significant clinical improvement in both groups
	HYAFF-11	Buda <i>et al</i> ^[4] , 2015	Case series	IV	40	1.8	48	Significant clinical improvement Higher presence of hyaline-like cartilage in BMDCT than ACI on MRI T2 mapping
	HYAFF-11 Spongostan Powder	Vannini <i>et al</i> ^[31] , 2017	Case series	IV	140	2	26	Significant clinical improvement at 2 yr maintained at 4 yr Return to sports at preinjury level; 32.1% at 12 mo, 72.8% at 48 mo
AMIC	Unclear	Wiewiorski <i>et al</i> ^[7] , 2013	Case series	IV	23	-	23	Significant clinical improvement
	Chondro-Gide	Valderrabano <i>et al</i> ^[32] , 2013	Case series	IV	26	-	31	Significant clinical improvement Normal signal intensity of repair tissue was seen in 15% on MRI
	Chondro-Gide	Kubosch <i>et al</i> ^[33] , 2016	Case series	IV	17	2.4	39	Significant clinical improvement MOCART score correlated with AOFAS score
	Chondro-Gide	Wiewiorski <i>et al</i> ^[34] , 2016	Case series	IV	60	-	47	Calcaneal osteotomy was performed in 63% of patients Low rate for return to sports; postoperative sports activity levels remain stable when compared with preoperative levels
Cartilage ECM	BioCartilage	Desai S ^[35] , 2016	Case series	IV	9	1.3	12	78% excellent, 22% good clinical outcomes
		Clanton <i>et al</i> ^[36] , 2014	Case series	IV	7	-	8	Significant clinical improvement
ACIC	Cartifill	Volpi P <i>et al</i> ^[37] , 2014	Case series	IV	5	3.1	6	Significant clinical improvement at 6 mo
Cell-free scaffold	MaioRegen®	Christensen <i>et al</i> ^[38] , 2015	Case series	IV	4	-	30	No clinical scores improvement No improvement in MOCART score and 3 patients had 0%-10% bone formation in defect at 1 yr on CT

Table 4 Patient demographics and clinical characteristics

	Procedure						
	Total	MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Treatment groups, <i>n</i>	30	13	9	4	2	1	1
Ankles, <i>n</i>	897	330	416	126	16	5	4
Sex, male/female/unknown, <i>n</i>	501/322/72	174/111/45	238/153/22	79/47/0	7/9/0	3/2/0	-
Age, yr, weighted mean (range)	30.9 (19-61)	30.1	30.2	34.9	42.7	25.6	-
Duration of symptoms, mo, weighted mean (range)	34.3 (6-216)	34.5	36.5	23	-	-	-
Lesion size, mm ² , weighted mean (range)	215 (116-527)	171	248	240	130	-	-
Follow-up, mo, weighted mean (range)	37.7 (6-87)	45.8	32.7	38.2	10.4	6	30

Table 5 Level and quality of evidence of included studies *n* (%)

	Total Studies	Procedure groups					
		MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Level of evidence							
1	0	0	0	0	0	0	0
2	1 (3.6)	0	2 (22.2)	0	0	0	0
3	3 (10.7)	2 (15.4)	2 (22.2)	0	0	0	0
4	24 (85.7)	11 (84.6)	5 (55.6)	4 (100)	2 (100)	1 (100)	1 (100)
Quality of evidence							
Excellent (MCMS ≥ 85)	0	0	0	0	0	0	0
Good (MCMS 70-84)	0	0	0	0	0	0	0
Fair (MCMS 55-69)	7 (25.0)	3 (23.1)	4 (44.4)	0	0	0	0
Poor (MCMS < 55)	21 (75.0)	10 (76.9)	5 (55.6)	4 (100)	2 (100)	1 (100)	1 (100)

quality^[8,18,20,21,30,31,38] and the remainder (75%) were of poor quality^[4-7,16,17,19,22-29,32-37] (Table 5). Further QOE

Table 6 Data reported (in percentage)

	Total	Procedure					
		MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
Procedure groups, <i>n</i>	30	13	9	4	2	1	1
Demographic information	93	92	94	100	100	100	0
Sex	90	85	89	100	100	100	0
Mean age + range	97	100	100	100	100	100	0
Patient history	30	35	31	44	13	0	0
Body mass index	33	31	33	50	50	0	0
Mean duration of symptoms	23	38	22	25	0	0	0
Previous traumatic experience(s)	33	38	44	50	0	0	0
Activities of daily living/athletic participation	30	31	22	50	0	0	0
Study design	73	71	78	72	56	63	38
Type of study	50	23	56	25	0	0	100
Number of patients	97	100	100	100	100	100	0
Percentage of patients in follow-up	97	100	100	100	100	100	0
Consecutive patients	23	23	22	50	0	0	0
Follow-up time + range/standard deviation	100	100	100	100	100	100	100
Method of lesion size measurement	43	54	44	50	0	0	0
Lesion classification system utilized	77	77	100	50	50	100	0
Surgical approach used to access lesion	97	92	100	100	100	100	100
Clinical variables	49	53	50	58	33	33	33
Lesion size	93	100	100	75	50	100	100
Lesion location	77	77	100	75	50	0	0
Presence of cyst	13	23	0	25	50	0	0
Associated pathology	13	23	0	25	0	0	0
Concomitant procedures	20	15	22	50	0	0	0
Description of rehabilitation	80	77	78	100	50	100	100
Imaging data	73	81	83	75	50	0	100
Imaging used to identify lesion	80	92	89	75	50	0	100
Imaging used at follow-up	67	69	78	75	50	0	100
Patient-reported outcomes	85	85	100	88	0	100	100
Pain, function, and activity scale, pre-operative	80	77	100	75	0	100	100
Pain, function, and activity scale, at follow-up	90	92	100	100	0	100	100

data is shown in Table 5.

Variable reporting of outcome data

The defined data that were reported in the studies included in this review are listed and the each data according to procedure group is shown in Table 6. General demographic information including age and gender were reported in 93% of the studies. While the study design, imaging data, and patient-reported outcomes were well-reported variables with 73%, 73% and 85% respectively, patient history was the least reported variable of all with 30% of the data being reported. Clinical variables were reported in only 49% of studies.

Clinical outcomes were evaluated using a number of different scoring systems for scaffolds-based therapy for OLT (Table 7). The American Orthopaedic Foot and Ankle Society (AOFAS) score was the most frequently utilized in 25 studies of the included [4-8,16-18,20-34,37,38]. Of the 25 studies that used AOFAS, 22 studies investigated both pre- and post-operative scores [4-8,16,18,20-23,25-32,34,37,38].

Twelve of 13 MACT groups reported pre and post-operative AOFAS scores and of the 310 patients who underwent MACT [5,6,16-18,20-26], the mean AOFAS score improved from 59.1 to 86.7 at a mean follow-up of 47.9 mo. Of the 416 patients from the nine BMDCT groups [4,8,26-31], the mean AOFAS score improved from

61.1 to 88.2 at a mean of 32.7 mo of follow-up. Of the 126 patients from the four AMIC groups [7,32-34], the mean AOFAS score improved from 50.7 to 82.3 at a mean follow-up of 38.2 mo. Of the two cartilage ECM studies included, one publication reported outcomes at less than one year follow-up [36], and the other one did not describe clinical outcomes [35]. There was only one publication reporting ACIC data but clinical evaluation was insufficient due to a follow-up of only six mo [37]. In the cell-free scaffold group, only one study was published, which showed no clinical improvement in AOFAS score at a mean 30 mo (from 48.7 to 52.7) follow-up. However, these results only included four studies [38].

In this systematic review, 12 procedure groups reported sequential clinical outcomes at two or more post-operative time points [4,5,8,18,20,21,26,28-31]. Four groups, which were all BMDCT studies, found temporal improvement in AOFAS scores over the first 2-3 years of post-operative follow-up with a mean decrease in AOFAS score of 87.1 reported at a mean 41.8 mo follow-up [4,28,29,31]. In contrast, eight groups, including four MACT and four BMDCT groups, demonstrated that there were no deteriorations during a weighted mean 38-mo follow-up [5,8,18,20,21,26,30].

Return to sport activity at previous level

Overall, eight studies (MACT: One study, AMIC: Two

Table 7 Clinical outcome scores utilized in included studies *n* (%)

Score	Studies, total	Procedure group					
		MACT	BMDCT	AMIC	Cartilage ECM	ACIC	Cell-free scaffold
AOFAS	25 (89)	12 (92)	9 (100)	4 (100)	0 (0)	1 (100)	1 (100)
VAS	7 (25)	1 (8)	2 (22)	4 (100)	0 (0)	1 (100)	0 (0)
Tegner activity score	3 (11)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	1 (100)
SF-36	2 (7)	1 (8)	2 (22)	0 (0)	0 (0)	0 (0)	0 (0)
FFI	2 (7)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)
FADI	1 (4)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)
HSS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LEAS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AHS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AAOS	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ARS	1 (4)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)
Halasi score	1 (4)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Mazur ankle score	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cincinnati score	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AAOS: American Academy of Orthopaedic Surgeons; AHS: Ankle-Hindfoot Score; AOFAS: American Orthopaedic Foot and Ankle Society; ARS: Activity Rating Scale; FADI: Foot and Ankle Disability Index; FFI: Foot Function Index; HSS: Hannover Scoring System; LEAS: University of California Lower Extremity Activity Scale; SF-36: Short Form-36 Health Survey; VAS: Visual analog scale.

studies, BMDCT: five studies) reported that a mean 68.3% of patients receiving scaffold-based therapy with mean lesion size of 250 mm² returned to previous sport activity at previous level^[4,8,21,28,29,31,32,34]. Of the MACT procedures, Giannini *et al.*^[21] showed that 20 of 29 patients (69%) returned to sport at previous levels. In patients treated with AMIC procedures, Valderrabano *et al.*^[32] reported only nine of 20 patients (45%) returned to previous sport activity level, and Wiewiorski *et al.*^[34] also showed no significant difference when comparing preoperative and postoperative activity scores (ARS, Tegner). BMDCT was the most reported in five studies, and of these studies, 74.5% of patients were able to resume sports at preinjury level, with a range of 69% to 78%^[4,8,28,29,31].

DISCUSSION

The results from this systematic review demonstrate that recommendations for scaffold-based therapy based solely on evidence is not yet conclusive. In the current evaluation, 96% of included studies in which scaffold-based therapy was performed for the treatment of OLT were classified into the category of poor LOE. In addition, of 28 included articles, no papers were of good or better methodological quality. According to the principles of evidence-based medicine^[39], a high level of clinical evidence and good methodological quality are fundamentally warranted to treat patients because low LOE and QOE studies are more likely to show overestimated outcomes compared to higher LOE and QOE studies^[40,41]. Careful attention therefore should be paid when evaluating outcomes following the studies of scaffold-based therapy for OLT.

The results from the current systematic review demonstrate large variability and underreporting of clinical data between studies reflecting and inability to compare the

results across studies. These inconsistencies and general underreporting of data make it difficult to pool data, which furthermore makes it difficult to draw conclusions about effectiveness of the use of scaffold in the treatment for OLT. As Hannon *et al.*^[15] described, adequate reporting of data in the studies of the treatment for OLT should be required to perform high quality studies, and investigators should be encouraged to implement data collection both before and after surgery according to recommended list described by Hannon *et al.*^[15] in this review, the categories of imaging data were reported in 73% of included studies. Compared with reporting of outcome data on microfracture for OLT in the systematic review by Hannon *et al.*^[15], imaging data was reported in only 39% among the studies. However, this review showed a higher percentage of reporting of imaging data (73%). Nevertheless, only 67% of studies used MRI for patient follow-up evaluation, although MRI evaluation for scaffold-based treatment of OLT is crucial because the aim of the use of scaffolds and is generally believed to promote the subchondral bone and cartilage repair. In addition, the categories of clinical variables and patient history were reported only with 49% and 30% respectively. As these data including BMI, lesion location, presence of cyst, associated pathology, and concomitant procedures can have significant effect on patient outcome, what is alarming is that appropriate information is not enough taken in the current studies.

Lesion size has been widely accepted as the most commonly used predictor of clinical outcomes after BMS for OLT^[42,43]. Choi *et al.*^[42] demonstrated that BMS should be indicated for lesions less than 150 mm² and lesions greater than this value resulted in poor outcomes. More recently, Ramponi *et al.*^[13] suggested that BMS could be best reserved for lesion size of less than 107.4 mm² rather than 150 mm². In the current review, however, the mean lesion size treated with scaffolds was 215 mm², which is much larger than traditional indication

size for BMS or the most current new indication size of 107 mm²^[13]. This suggests that the use of scaffolds may further improve the potential of reparative techniques. However, further well-designed studies are necessary to determine the effectiveness of scaffold-based therapy on OLT because of low LOE and QOE and the large variability in the data.

Despite of high frequency of OLT in the athletic population, little is reported regarding return to sport following surgical treatment of OLT in this population. In the current review, weighted mean 68.3% of patients receiving scaffold therapy with weighted mean 250 mm² of lesion size returned to previous sport activity at previous level in eight studies. There are no studies investigating the effectiveness of BMS alone for athletic populations who have large lesion as described above, but Choi *et al.*^[42] reported clinical failure rate in patients with lesion area ≥ 150 mm² was 80%. Furthermore, Chuckpaiwong *et al.*^[43] reported a 97% of failure rate in 32 patients with a lesion area ≥ 150 mm². This suggests that the use of scaffolds may provide better outcomes than BMS alone for larger lesions but high quality studies are warranted. On the other hand, in replacement procedures, including autologous osteochondral transplantation, which is generally indicated for larger lesions, several studies reported that more than 90% of patients returned to play sport at previous levels^[44,45]. Although there is inconsistency in indications for the treatment strategy, the rate of return to sport following scaffold-based therapy appears to be relatively lower than AOT procedures. The highest rate of return to sport after scaffold-based therapy was only 78.0% in athletes treated with BMDCT^[31]. However, there was variability of sport type, postoperative rehabilitation protocol, and time to return to sport, which makes it difficult to assess these results appropriately.

Our review found that there were 12 different scoring systems used to assess clinical outcomes, with AOFAS score being the most commonly used (89%). However, there remains no validated scoring system for the clinical follow-up for the treatment of OLT^[13]. Moreover, four BMDCT groups have shown that clinical outcomes deteriorate after peaking at 2-3 year post-operatively^[4,28,29,31], whereas four MACT and four BMDCT groups have no deterioration during follow-up^[5,8,18,20,21,26,30]. A potential reason for these lags in clinical outcome data may be the invalid clinical evaluation methods after OLT surgery in addition to the use of the different kinds of scaffolds. A novel validated scoring system for the clinical follow-up of the treatment for OLT are currently warranted.

The appropriate treatment for OLT is still controversial. While the ideal procedure would regenerate a tissue with biomechanical properties similar to normal hyaline cartilage, reparative techniques can offer the replacement of the articular cartilage with a hyaline-like repair tissue. Scaffolds have been introduced to improve the requirements of the cartilage regeneration process, as ACI, the first generation approach for cartilage treatment, has evident biological and surgical limitations^[46]. In fact, the use of scaffolds has overcome

the drawbacks and simplified the procedure. However, any available substitute materials have not yet matched the properties of the normal cartilage, and there is no consensus about the superior effectiveness of these procedures over the other procedures, including replacement procedures. While the scaffold-based treatment has shown promising clinical results in numerous studies of case series, the current systematic review showed low LOE and poor methodological quality of the use of scaffolds for OLT. Further long-term comparative studies are warranted to investigate the potential of a bioengineered approach compared to other treatments. Furthermore, the definitive indications for this technique, including lesion size and character of the lesion, still remains controversial^[13].

This systematic review has several inherent limitations and/or potential biases. The criterion was limited to MEDLINE, EMBASE and Cochrane Library Database articles published exclusively in English. The variables may not be all inclusive of data in each study, but they should be a representative summary of the most commonly used data. Another inherent concern was the overlapping of cohorts or subgroups of several cohorts studies in longitudinal follow-up studies. Finally, the data extraction was not performed blindly, but was performed by two independent reviewers and later confirmed by the lead author.

In conclusion, this systematic review demonstrated that the scaffold-based therapy for the treatment of OLT may produce favorable clinical outcomes, but low level of evidence, poor quality of evidence, and the variability of the data have confounded the effectiveness of scaffold-based therapy for OLT. Further, well-designed studies, are necessary to determine the effectiveness of the use of scaffold for the treatment of OLT, especially when compared to available traditional treatments.

COMMENTS

Background

Recently scaffold-based therapy for osteochondral lesions of the talus (OLT) has become more popular as an alternative reparative procedure. However, no consensus has been reached regarding the effectiveness of scaffold-based therapy in the treatment of OLT to date. In this study, the effectiveness of scaffold-based therapy was systematically reviewed based on available clinical evidence.

Research frontiers

Scaffolds have been introduced to improve the requirements of the cartilage regeneration process, as autologous chondrocyte implantation (ACI), the first generation approach for cartilage treatment, has evident biological and surgical limitations. Recently, the use of scaffolds has overcome the drawbacks and simplified the procedure.

Innovations and breakthroughs

The scaffold-based treatment has shown promising clinical results in numerous studies of case series and the use of scaffolds may further improve the potential of reparative techniques. Retrieved manuscripts were reviewed by the authors, and the data were extracted.

Applications

This systematic review suggests that the scaffold-based therapy for the

treatment of OLT may produce favorable clinical outcomes, but low level of evidence, poor quality of evidence, and the variability of the data have confounded the effectiveness of scaffold-based therapy for OLT.

Terminology

Matrix-induced autologous chondrocyte transplantation is a second-generation ACI technique, which uses a type I/III bilayer collagen membrane seeded with cultured autologous chondrocytes. Autologous matrix-induced chondrogenesis is a one-step scaffold-based therapy that combines bone marrow stimulation with the use of a porcine collagen I/III matrix scaffold. Bone marrow-derived cell transplantation is also a one-step procedure and is a combination of concentrated bone marrow aspirate and scaffold material.

Peer-review

The paper adequately concludes what is already suspected in that variable quality, small studies with limited outcome data serve to confuse the authors' knowledge. It's a useful review.

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Managing extremely distal periprosthetic femoral supracondylar fractures of total knee replacements - a new PHILOS-ophy

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Institutional review board statement: The case report was exempt from the Institutional Review Board standard at Altnagelvin Area Hospital in Londonderry, Northern Ireland.

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Abstract

We report two cases where a proximal humeral locking plate was used for the fixation of an extremely distal, type III peri-prosthetic femoral fractures in relation to a total knee replacement (TKR). In each case there was concern regarding the fixation that could be achieved using the available anatomic distal femoral plates due to the size and bone quality of distal fragment. The design of the Proximal Humeral Internal Locking System (PHILOS) allows nine 3.5-mm locking screws to be placed over a small area in multiple directions. This allowed a greater number of fixation points to be achieved in the distal fragment. Clinical and radiological short-term follow-up (6-12 mo) has been satisfactory in both cases with no complications. We suggest the use of this implant for extremely distal femoral fractures arising in relation to the femoral component of a TKR.

Key words: Distal; Femoral; Periprosthetic; Fracture; PHILOS; Open reduction and internal fixation

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Core tip: When dealing with periprosthetic fractures around a total knee replacement it is essential to consider the fracture site and configuration to allow selection of an implant that provides optimal fixation. When managing extremely distal femoral fractures a non-anatomic locking plate, such as Proximal Humeral Internal Locking System, may provide an option for fixation other than the available site-specific plates.

Donnelly KJ, Tucker A, Ruiz A, Thompson NW. Managing extremely distal periprosthetic femoral supracondylar fractures of total knee replacements - a new PHILOS-ophy. *World J Orthop* 2017; 8(10): 809-813 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i10/809.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i10.809>

INTRODUCTION

Supracondylar periprosthetic femoral fractures around total knee replacement (TKR) are uncommon injuries with a reported prevalence in the literature of between 0.3% and 2.5%^[1]. It is expected that these injuries will become more common as the population ages and an increasing number of TKRs are performed. Non-operative treatment of these fractures results in poorer outcomes and hence is reserved for minimally displaced fractures in low demand patients with significant comorbidities^[2,3].

A variety of operative treatment options exist, including retrograde femoral nailing, open reduction and internal fixation and revision arthroplasty. Perhaps the most challenging fracture patterns are the extremely distal peri-prosthetic femoral fractures. In these cases internal fixation or revision arthroplasty may be required as retrograde nailing may not be possible due to implant design or the inability to insert a locking screw in the distal fragment. Outcomes in treating these extreme distal fractures using femoral locking plates have been comparable with more proximal fractures treated in the same way^[4]. One potential problem with anatomically designed distal femoral locking plates is the location and orientation of the screws, which may not allow adequate fixation in the distal fragment in these extremely distal peri-prosthetic femoral fractures.

Locking plates have been used successfully in proximal humeral fractures. The Proximal Humeral Internal Locking System (PHILOS) (DePuy Synthes, Switzerland) allows placement of 9 multi-directional locking screws over a small area. We discuss the use of the PHILOS in two elderly patients with very distal periprosthetic supracondylar fractures with satisfactory outcomes at short-term follow-up.

CASE REPORTS

Patient A

An 85-year-old female presented following a fall at home with pain and deformity around her left knee. She had undergone a left TKR four years previously. An ipsilateral long-stem revision total hip replacement was also noted. There was no other significant past medical history. She lived in sheltered accommodation and was independently mobile with the use of a single walking stick. Radiographs of her left femur revealed a very distal peri-prosthetic femoral fracture (Figure 1A).

Patient B

An 85-year-old female presented with pain and deformity around her left knee following a fall at home. She had undergone bilateral TKR's 19 years previously. Significant medical comorbidities were noted which included atrial fibrillation and previous transient ischaemic attack, anticoagulation with warfarin, hypothyroid disease and polymyalgia rheumatica. She lived at home alone, with input from her family twice daily. She was independently mobile with the use of a rollator. Radiographs of her left femur revealed a very distal periprosthetic femoral fracture (Figure 2A).

Operative techniques

Both senior authors reviewed each case and the injury radiographs. Pre-operative planning and templating was performed using the Northern Ireland Picture Archive and Communication System (Sectra AB, Sweden) (Figure 1B and Figure 2B). For both cases, surgery was performed under spinal anaesthesia and femoral nerve block. A single dose of 2 g IV Flucloxacillin and 160 mg IV Gentamicin were administered at induction of anaesthesia. A tourniquet was not used in either case. A direct lateral approach to the distal femur was performed in both cases. The fracture patterns extended very distally in each case and also narrow femoral shafts were noted. Taking these factors into consideration, a 6-hole PHILOS plate was used allowing optimal locking screw placement in the distal fragment and placement of the plate on the lateral aspect of the femur. Locking screws were placed in the distal fragment in both patients. To avoid a stress riser in Patient A the plate overlapped the distal aspect of the hip replacement stem by at least two cortical diameters. Three non-locking screws were inserted below the tip of the stem and two cables passed at the area of overlap (Dall-Miles, Stryker, Switzerland). Patient B had five diaphyseal screws inserted.

Both patients had uneventful peri-operative periods and were discharged day 8 post-operatively to rehabilitation units for on-going physiotherapy and social care. Immobilisation was achieved using a locked cast brace and both patients were kept non-weightbearing for six weeks followed by a period of partial weight bearing with the brace unlocked. At 3 mo both patients were allowed to mobilise bearing full-weight on the injured side albeit with the use of a walking aid.

Outcomes

Patient A: At 6 mo follow-up, the patient was fully weight bearing with the use of one crutch, with a range of movement of 10-70 degrees. Radiographs demonstrated bridging callus on both the AP and lateral views (Figure 1D). At 19 mo, the range of movement had improved to 5-95 degrees and remained independently mobile. Radiographs confirmed radiological union (Figure 1E).

Patient B: At 5 mo follow-up position has been main-

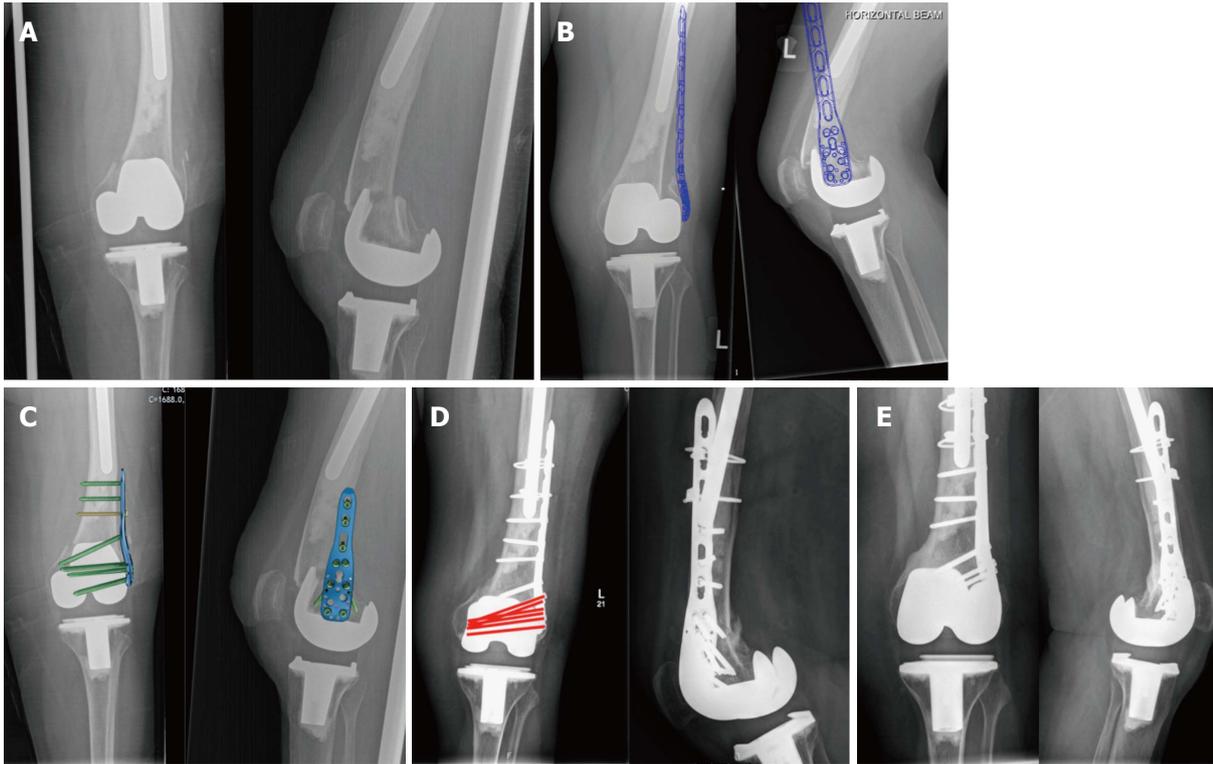


Figure 1 Radiograph series of patient A. A: Anteroposterior and lateral injury radiographs; B: Templated anteroposterior radiograph showing proposed position of implant; C: Anteroposterior and lateral radiographs with PHILoS plate image superimposed to show orientation of screws; D: Post-operative radiographs at 6 mo with orientation of screws behind the femoral component shown in red; E: Anteroposterior and lateral radiographs at 19 mo post-op.

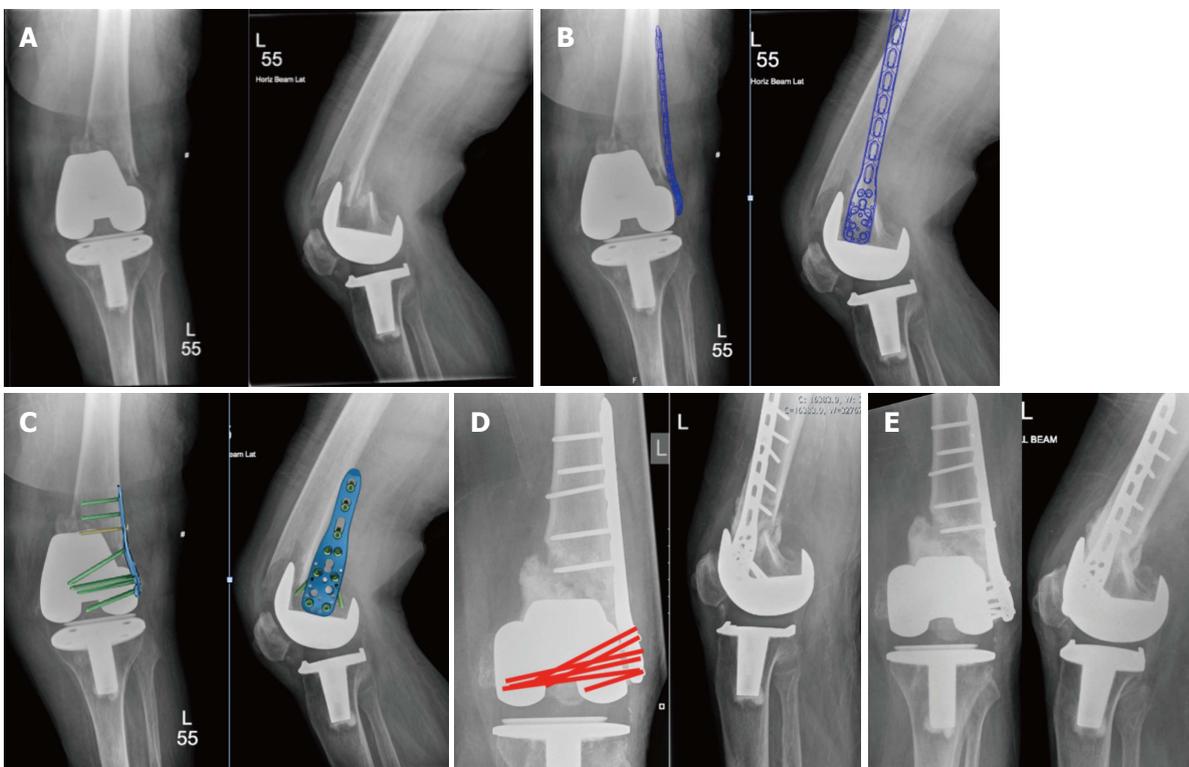


Figure 2 Radiograph series of patient B. A: Anteroposterior and lateral injury radiographs; B: Templated anteroposterior radiograph showing proposed position of implant; C: Anteroposterior and lateral radiographs with PHILoS plate image superimposed to show orientation of screws; D: Post-operative radiographs at 5 mo with orientation of screws behind the femoral component shown in red; E: Anteroposterior and lateral radiographs at 16 mo post-op.

tained. Callus is present posteriorly (Figure 2D). Range of movement 10-90 degrees. Has started progressive weightbearing. At 16 mo, range of movement was 5-90 degrees and the patient mobilised independently with the assistance of a walking frame. Radiographs confirmed radiological union (Figure 2E).

DISCUSSION

Fractures within 15 cm of the joint line or 5 cm of the proximal end of the femoral component of a TKR are considered peri-prosthetic femoral fractures. These fractures often occur in the setting of osteoporotic bone with rheumatoid arthritis, chronic steroid use and neurological disorders being established risk factors^[1].

Su *et al.*^[1] suggested a classification system for these injuries based on fracture site and the available surgical options. Type I fractures are proximal to the femoral component. Type II fractures originate at the proximal aspect of the femoral component. These types were considered amenable to retrograde femoral nailing or fixation with a fixed angle device. In Type III fractures all parts of the fracture line is distal to the anterior flange of the femoral component. Revision arthroplasty is one possible treatment, especially in the presence of a loose femoral component. Fixation may also be possible if the distal fragment allows placement of screws. Each of the patients we have discussed had Type III fracture patterns.

A review performed by Ristevski *et al.*^[3] found favourable results with the use of retrograde intramedullary nailing and locked plating over conservatively managed fractures and those treated with conventional plating. However, in many cases the choice of fixation technique is influenced by factors such as the presence of a box in the femoral component to facilitate retrograde nailing^[5], distal extent of the fracture, availability of existing bone stock and fix of the components. Good results have been reported with the use of site-specific locking plates^[6-8], such as the Less Invasive Stabilization System (DePuy Synthes, Switzerland).

Biomechanically, locking plates create a fixed-angle single-beam construct^[9]. This provides relative stability, allowing for secondary bone healing. Their use has been shown to possess superior resistance to rotational strain over both static and dynamically locked intramedullary nails -3.8° for locking plates, vs 14.2° and 15.7° for static and dynamic locking respectively^[10]. Locking plate systems allow for even stress distribution along the implant length, and the plates function to convert shear forces into compressive forces at the screw bone interface^[11].

The PHILOS has been used successfully in proximal humeral fractures where similar problems with osteoporotic bone and small fracture fragments can exist^[12]. Again, it has been shown to resist torsional and bending forces more so than intramedullary nailing under cyclical loading, which is comparative to normal *in vivo* physiological functionality^[13,14]. Periprosthetic fracture resulting

in primary implant failure is rare complication, with rates quoted at 0.7%. The mechanical benefits of a PHILOS locking plate in managing this injury pattern make it an attractive implant option where longevity is required^[15]. However, the PHILOS has not been studied for its use in lower limb fracture management.

A study by Stein *et al.*^[16] demonstrated that at any age, women have smaller femora, with less cortical bone and higher bone stresses than men. The PHILOS is narrower than many of the specific distal femoral locking plates and therefore may be a more appropriate fit for smaller females, such as the cases discussed. The major benefit we found of using the PHILOS was the design of the plate, which allowed the placement of a maximum of nine polyaxial divergent screws over a small area. This allowed us to maximise our fixation in the distal fragment.

In conclusion, we have shown that a PHILOS can be considered as a viable treatment option for very distal Type III fracture patterns with good short-term results in low demand patients. Each case highlights the need for careful consideration of the fracture configuration to allow the treating surgeon to select an appropriate means of fixation.

COMMENTS

Case characteristics

Two cases of 85-year-old females who both presented with pain and deformity of their lower limb following a fall at home.

Clinical diagnosis

Pain and deformity about the knee was apparent, with localised swelling and the inability to weight bear. Midline anterior scars in keeping with a previous knee arthroplasty were evident.

Differential diagnosis

Periprosthetic fractures involving the distal femur or proximal tibia, fracture of femoral diaphysis.

Laboratory diagnosis

All laboratory tests were within normal limits.

Imaging diagnosis

A periprosthetic fracture about the femoral component of a total knee arthroplasty was evident on plain film radiographs. No additional 3D imaging (*i.e.*, computed tomography) was required.

Pathological diagnosis

A very distal periprosthetic femoral fracture.

Treatment

Open reduction and internal fixation of the fracture using a PHILOS locking plate, using the ability to place polyaxial locking screws into the small distal fragment, thereby maximising construct stability.

Related reports

Periprosthetic femoral fracture about a total knee arthroplasty are rare, and several methods for managing these are reported in the literature. This case is unique in that the distal fragment was too small to allow for a lateral LISS femoral plate, nor did the implants allow for a retrograde intramedullary device

to be used.

Term explanation

PHILOS is an acronym for Proximal Humeral Internal Locking Osteo-Synthesis, and describes the locking screw nature of the internal implant.

Experiences and lessons

The use of the PHILOS for this particular fracture configuration is novel. The authors have managed to use this in a rare, and challenging circumstance, with success both in terms of radiological union and restoration of mobility and function. Careful pre-operative planning, knowledge of available implants and appreciation of fracture configuration is crucial in managing the very distal femoral periprosthetic fracture about a total knee arthroplasty.

Peer-review

This is a nice paper. The idea for using PHILOS plate is very unique. This manuscript presents a novel technique for the management of periprosthetic supracondylar femoral fractures which deserves attention from the orthopaedic community in order to be fairly judged.

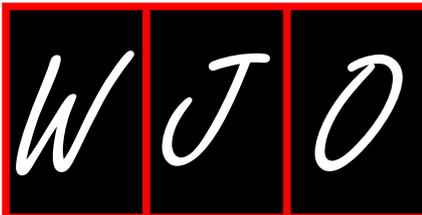
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Retraction note to: Strategy for prevention of hip fractures in patients with Parkinson's disease

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Author contributions: Cui Q wrote this retraction note.

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RETRACTION NOTE

Retraction note to: Iwamoto J, Sato Y, Takeda T, Matsumoto H. Strategy for prevention of hip fractures in patients with Parkinson's disease. *World J Orthop* 2012; 3(9):137-141 PMID: 23173109 DOI: 10.5312/wjo.v3.i9.137. The online version of the original article can be found at <https://www.wjgnet.com/2218-5836/full/v3/i9/137.htm>.

This meta-analysis article^[1] has been retracted at the request of the Co-Editors-in-Chief, as a substantial portion of the primary studies on which the review was based [References 12, 14, 15] have subsequently been retracted.

The Editors-in-Chief recently received communications indicating that 3 of the 5 articles on which the study was based upon were retracted, raising concerns about the integrity of the meta-analysis and its findings. The Editorial Office has conducted an investigation and has contacted the authors concerning the allegation. The authors declare that at the time the article was written, none-except for Dr. Yoshihiro Sato were aware of the fact that the studies subject to the analysis had been fraudulently conducted. The authors have agreed to retract the article from the Journal.

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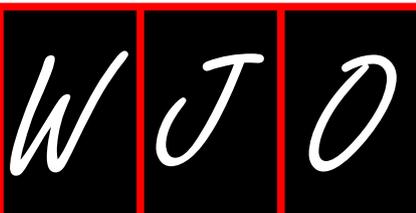
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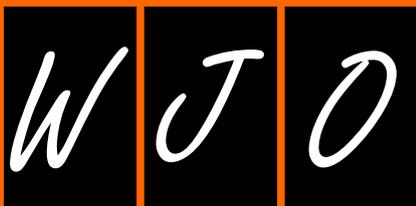
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Balance control during gait initiation: State-of-the-art and research perspectives

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Abstract

It is well known that balance control is affected by aging, neurological and orthopedic conditions. Poor balance control during gait and postural maintenance are associated with disability, falls and increased mortality. Gait initiation - the transient period between the quiet standing posture and steady state walking - is a functional task that is classically used in the literature to investigate how the central nervous system (CNS) controls balance during a whole-body movement involving change in the base of support dimensions and center of mass progression. Understanding how the CNS in able-bodied subjects exerts this control during such a challenging task is a prerequisite to identifying motor disorders in populations with specific impairments of the postural system. It may also provide clinicians with objective measures to assess the efficiency of rehabilitation programs and better target interventions according to individual impairments. The present review thus proposes a state-of-the-art analysis on: (1) the balance control mechanisms in play during gait initiation in able bodied subjects and in the case of some frail populations; and (2) the biomechanical parameters used in the literature to quantify dynamic stability during gait initiation. Balance control mechanisms reviewed in this article included anticipatory postural adjustments, stance leg stiffness, foot placement, lateral ankle strategy, swing foot strike pattern and vertical center of mass braking. Based on this review, the following viewpoints were put forward: (1) dynamic stability during

gait initiation may share a principle of homeostatic regulation similar to most physiological variables, where separate mechanisms need to be coordinated to ensure stabilization of vital variables, and consequently; and (2) rehabilitation interventions which focus on separate or isolated components of posture, balance, or gait may limit the effectiveness of current clinical practices.

Key words: Balance control; Anticipatory postural adjustments; Leg stiffness; Foot placement; Lateral ankle strategy; Foot strike pattern; Vertical center of mass braking; Dynamic stability; Gait initiation; Biomechanics

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Core tip: This review proposes a state-of-the-art on: (1) the balance control mechanisms in play during gait initiation in able bodied subjects and in the case of some frail populations; and (2) the biomechanical parameters used in the literature to quantify dynamic stability. The following viewpoints were put forward: (1) dynamic stability during gait initiation may share a principle of homeostatic regulation similar to most physiological variables, where separate mechanisms need to be coordinated to ensure stabilization of vital variables, and consequently; and (2) rehabilitation interventions which focus on separate or isolated components of posture, balance, or gait may limit the effectiveness of current clinical practices.

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INTRODUCTION

Gait initiation refers to the transient period between the quiet standing posture and steady state walking^[1-5]. It is a functional task that is classically used in the literature to investigate how the central nervous system (CNS) controls balance during a whole-body movement involving change in the base of support dimensions and center of mass progression. Gait initiation is known to be a highly challenging task for the balance control system. Gait initiation indeed requires the integration of multiple sensory information arising from somatosensory, vestibular and visual systems, along with the coordination of multiple skeletal muscles distributed over the whole body. As such, it may potentially expose populations with sensory or motor deficits or disorders to the risk of fall^[6-8]. Falls represent the second cause of mortality in the world, and one third of subjects over 65 years and 50% of those over 80 years living at home fall at least once a year^[9]. Although being a very important issue gait

analysis however received relatively little attention by orthopedic surgeons. This is particularly troublesome for understanding the pathogenesis of fractures, such as hip or wrist fractures, by those treating these highly frequent traumatic issues.

Understanding how the CNS in able-bodied subjects controls balance during such a challenging task is a prerequisite to identifying motor disorders in populations with specific impairments of the postural system or fear of falling, such as the elderly or patients with neurological/orthopedics conditions. It may also provide the clinicians with objective measures to assess the efficiency of rehabilitation programs and to better target interventions according to individual impairments. Hence, beside a basic interest *per se*, it is therefore important to identify the different balance control mechanisms available to participants that ensure stabilization during whole-body progression. It is also important to define adequate biomechanical measures of stability to evaluate the efficiency of these mechanisms. Recent studies in the biomechanical field bring novel insights on these two aspects and open new research avenues, some of which will be mentioned in the present paper.

The present review thus proposes a state-of-the-art on: (1) the balance control mechanisms in play during gait initiation in able bodied subjects and in the case of some frail populations; and (2) the biomechanical parameters used in the literature to quantify postural stability during gait initiation. Before considering these aspects, let us first recall why balance is challenged during gait initiation.

BALANCE IS DISTURBED DURING GAIT INITIATION

During quiet standing, stability requires that the vertical projection of the center of mass falls within the base of support^[10,11] (Figure 1). The center of mass corresponds to the point where the mass of the whole body is concentrated. It is the point of application of the gravity force vector. In the standing posture, the base of support refers to the area that includes every point of contact that the foot (or the feet) make(s) with the supporting surface. When one lifts the foot from the ground to step in the desired direction, balance is potentially challenged along the mediolateral direction because the base of support width in this direction is then drastically reduced. If the center of mass is not repositioned above the new base of support, a mediolateral gap between the center of mass and the center of pressure will be created. The center of pressure corresponds to the barycenter of the ground reaction forces. As a consequence of the mediolateral gap between the center of pressure and center of mass, the whole body will fall towards the swing leg side during the unipodal (or "execution") phase of gait initiation. The amplitude of this mediolateral fall can be estimated from the center of mass displacement

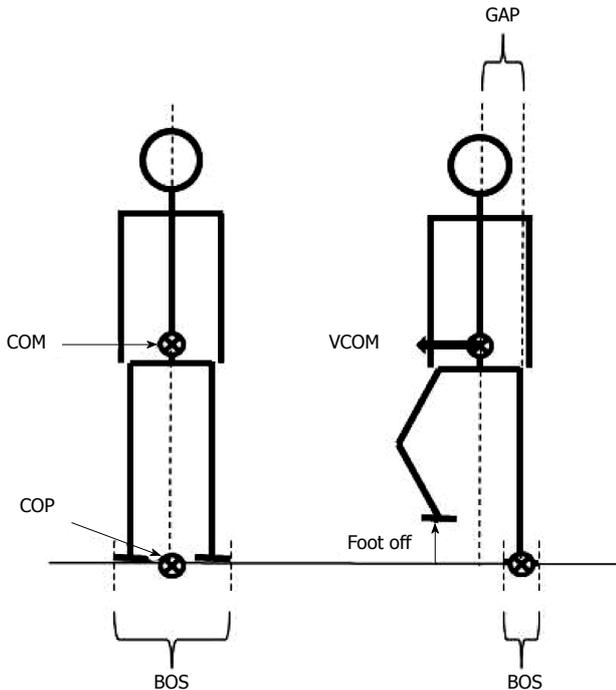


Figure 1 Representation of selected basic notions for balance analysis in biomechanics. Note that in the quiet standing posture (left figure), the vertical projection of the COM onto the ground falls on the COP. When the subject lifts the foot to step forward (right figure), the base of support size is drastically reduced. A gap between the COP and the COM may then occur, thus causing a disequilibrium towards the stance leg. COM: Center of mass; COP: Center of pressure; BOS: Base of support; VCOM: COM velocity.

and velocity at the time of swing foot contact, *i.e.*, the greater these two quantities, the larger the mediolateral fall^[12-15].

Although a recent modelling study reported that an attenuation of this mediolateral fall may theoretically occur during the execution phase of gait initiation *via* an action on the stance leg stiffness^[15] (cf. paragraph “stabilizing features of gait initiation”), this fall towards the swing leg side seems mainly to be braked by the swing foot landing. Swing foot landing indeed acts to provide an immediate enlargement of the base of support size so that the center of pressure may then be shifted laterally beyond the center of mass and thus create a counterbalancing torque oriented toward the stance leg side. Now, this lateral fall may be too significant to be braked by swing foot contact, *e.g.*, if the hip musculature of the swing leg becomes too weak to ensure this braking. This may be the case with aging or neurological/orthopedic conditions. In these cases, the center of mass may then be shifted laterally beyond the base of support with potential risk of the body falling onto the ground if appropriate actions are not undertaken.

It is noteworthy that such lateral falls are common in older adults and are associated with a 6-fold greater risk of hip fracture, compared with falls in other directions, *i.e.*, anterior and posterior falls (*e.g.*, Ref^[16-19]). Deficits in the capacity to overcome the mediolateral perturbation to balance due to gravity force is thus thought to be

of major importance in the aetiology of falls in frail populations^[20,21].

Beside mediolateral instability, it is well known that the collision of the swing foot with the ground generates a large peak vertical ground reaction force. The amplitude of this peak may reach approximately twice body weight during barefoot walking at maximal speed (approximately 2 m/s). This peak, and probably most important, the slope of the vertical ground reaction force rise following the swing foot contact, may potentially cause discomfort or pain to body joints with task repetition (*e.g.*, Ref^[22,23]). This perturbing effect is due to the transmission of the vibration from the swing foot to the whole body *via* bones and soft tissues. When walking with shoes at a normal speed (approximately 1.3 m/s) onto an unobstructed track, the amplitude of this vibration can easily be supported by any subject with either pathology or frailty. This may not be the case if participants have to clear a large obstacle (*e.g.*, Ref^[15,24]), which may then increase the fall duration of the center of mass and therefore the vertical peak impact force and the associated slope. This perturbing effect may also be exacerbated if participants initiate gait barefoot and on a hard surface, if they descend large stairs, or if they suffer from knee joint pain or knee hypomobility, *e.g.*, due to the use of an orthosis or to pathology.

Knee joint mobility (flexion) *post* swing foot contact is known to play an important role in damping these vertical ground reaction forces (*e.g.*, Ref^[25,26]). Mechanisms other than swing leg knee flexion are also developed in anticipation of swing foot contact. These mechanisms act in combination to attenuate these disturbing forces and thus avoid body collapse on the ground. As such, they also contribute to maintaining stability. These stabilizing mechanisms are described in the paragraph below.

To summarize, balance is disturbed during gait initiation because the act of lifting the swing foot from the ground induces a gap between the center of mass and the center of pressure. This gap is responsible for generating body disequilibrium and a fall towards the swing leg side. In addition, the collision of the swing foot with the ground generates a peak vertical ground reaction force which is transmitted from swing foot to the whole body *via* bones and soft tissues. These perturbations may be responsible of falls if not properly counterbalanced.

STABILIZING MECHANISMS INTO PLAY DURING GAIT INITIATION

Once the different sources of disturbance are identified, the question arises as to what the nature of the different mechanisms allowing able-bodied subjects to progress safely (*i.e.*, without falling) in the desired direction is.

Anticipatory postural adjustments

Gait initiation is classically divided in three successive

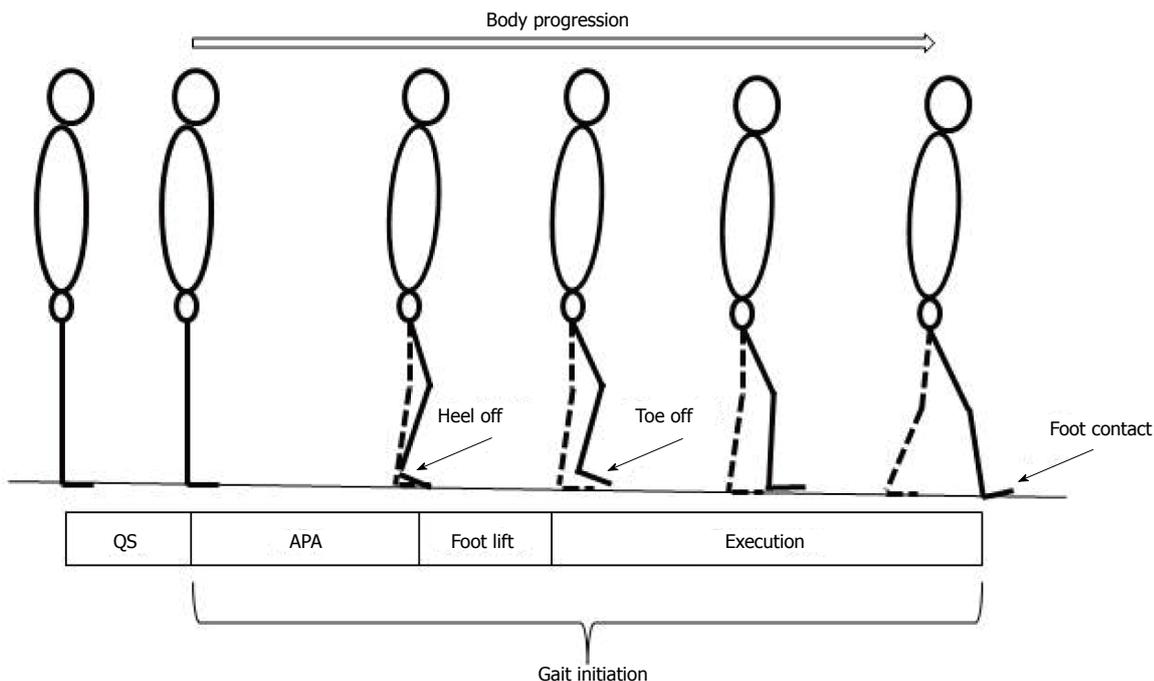


Figure 2 Stick representation of the different phases and temporal events of gait initiation. APA: Anticipatory postural adjustments.

phases: A postural phase which precedes the swing heel off (this phase corresponds to the so-called anticipatory postural adjustments, APAs, described in this paragraph), followed by the foot lift phase that ends at the time of swing toe clearance (the mass of the body is transferred to the stance leg during this phase), and an execution phase that ends at the time of swing foot contact with the supporting surface (Figures 2 and 3).

It is now well established that dynamical and electromyographical phenomena are developed during APAs. Their functional role depends on the axis considered. APAs along the anteroposterior axis are predictive of motor performance^[2,27] while APAs along the mediolateral axis are predictive of postural stability^[14,15,28-31].

Along the anteroposterior axis, APAs include a backward center of pressure shift which promotes the initial forward propulsive forces (prior to toe off) required to reach the intended motor performance, in terms of step length and progression velocity^[2,27]. The anticipatory backward center of pressure shift is due to bilateral inhibition of the ankle plantar-flexors activity followed by activation of ankle dorsi-flexors^[32,33].

Along the mediolateral axis, APAs include center of pressure shift toward the swing leg which promotes center of mass shift in the opposite direction, *i.e.*, towards the stance leg^[15,24,31] (Figure 3). These mediolateral APAs thus reduce the gap between the center of mass and the center of pressure at the foot off time. This gap reduction attenuates the mediolateral fall of the center of mass toward the swing leg during the execution phase due to gravity^[12,15,28,29] (*cf.* paragraph above).

The anticipatory mediolateral center of pressure

shift has been classically attributed to the loading of the swing leg associated with the activation of swing leg hip adductors^[1,11]. Recent studies further reported that, the stance knee and hip are slightly flexed during APAs^[31,34], which acts to unload the ipsilateral leg and therefore complement the action of swing hip abductors. EMG analysis revealed that the flexion of the stance knee is favored by bilateral soleus silencing and a greater ipsilateral tibialis anterior activity with respect to contralateral activity, while stance hip flexion was associated with activation of the stance rectus femoris. It is to note that, due to biomechanical constraints, initiating gait from a wider stance decreases the effectiveness of hip abductor activity and increases the reliance on stance knee flexion and *vice versa*^[31].

As a direct consequence of this muscle synergy, when mediolateral balance control is examined in patients suffering from motor problems during gait initiation, hip abduction, stance hip and knee flexion should be considered. Knee flexion control in the frontal plane during APAs could be inadequate in patients suffering from gait problems such as cerebral palsy, Parkinson's disease^[35-39], stroke, amputees^[40]. For instance, freezing of gait in Parkinsonian patients is associated with knee trembling^[41-45]. Jacobs *et al.*^[46] found that during gait initiation, knee trembling causes multiple APAs that are observable as a right-left leg loading-unloading cycles (*cf.* also^[47]). Interestingly, the alternating unloading and loading of the legs was accompanied by similar alternating activation and deactivation of right-left *tibialis anterior* (Figure 2 in Jacobs *et al.*^[46]). Therefore, knee trembling in Parkinsonian patients may be preventing them from correctly displacing their center of mass towards the stance leg and thus not allowing them to

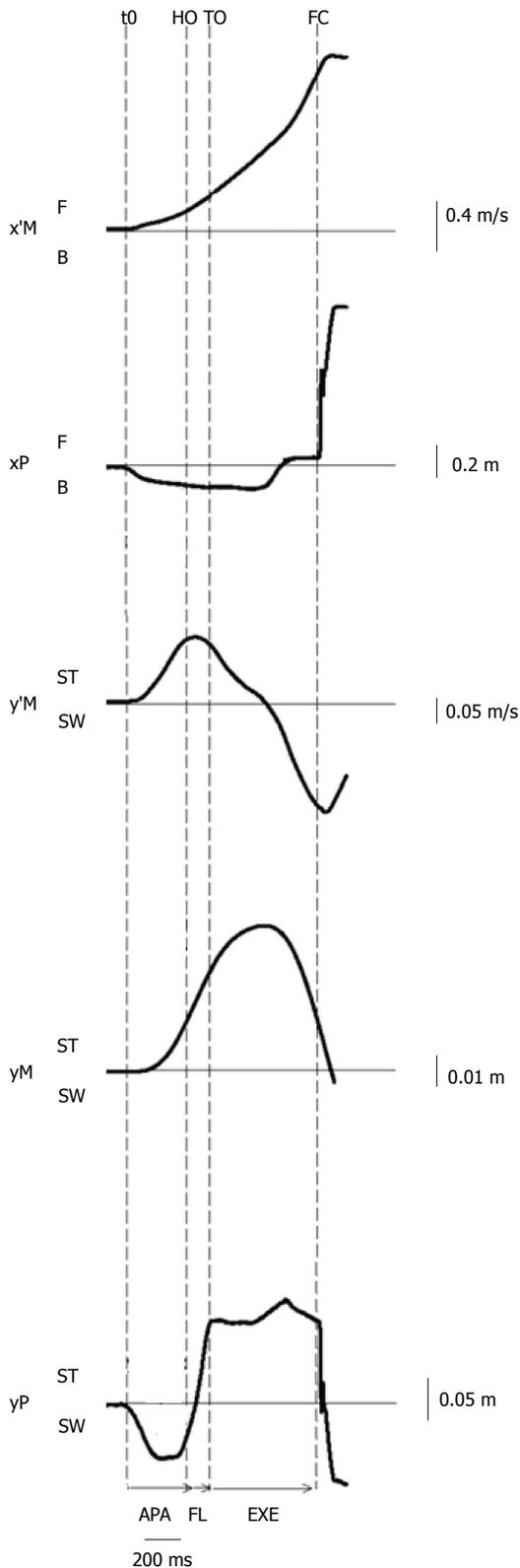


Figure 3 Example of biomechanical traces obtained for one representative subject initiating gait at a maximal velocity (one trial). Anteroposterior direction x'M: center of mass (COM) velocity; xP: Center of pressure (COP) displacement; F: Forward; B: Backward. Mediolateral direction y'M: Mediolateral COM velocity; yM: Mediolateral COM displacement; yP: Mediolateral COP displacement; ST: Stance limb; SW: Swing limb. Vertical dashed lines: t0 onset variation of biomechanical traces; HO: Swing heel off; FO: Swing foot off; FC: Swing foot contact. Horizontal arrows: APA: Anticipatory postural adjustments; FL: Foot lift; EXE: Execution phase.

initiate gait properly. Indeed, the smaller mediolateral center of pressure displacement during APAs and larger step width of the first step at gait initiation have been observed in Parkinson's disease^[37,38]. This could be in part associated to inappropriate knee flexion. Therefore, it has been proposed by Honeine *et al.*^[31] that correcting the knee flexion angle of the stance leg during APAs with a smart orthosis could be an effective solution to enhance gait initiation and possibly steady-state gait in such patients. Future studies should investigate this aspect.

To summarize, lifting the swing foot for stepping forward induces a potential lateral body imbalance. This imbalance is partly countered in advance before swing foot off, *i.e.*, during APA. This APA includes center of pressure shift towards the swing leg which act to move the center of mass towards the stance leg. This lateral postural dynamics is due to motor synergy involving swing hip adduction, combined with stance knee and stance hip flexion. Deficits in this motor synergy with aging or pathology may increase the risk of imbalance.

Stance leg stiffness

To investigate the link between mediolateral APAs and postural stability during the execution phase of gait initiation (from toe off to foot contact), a recent study^[15] modeled the human body as a single conic inverted pendulum which rotates about a fixed point (Figure 4).

This model was based on work carried out in earlier studies^[3,12,13,48]. During the execution phase, it was considered that the center of mass was falling laterally under the influence of two forces: The gravity force $P = mg$ (where m is the mass of the solid, and g is the gravitational acceleration) and an elastic restoring force T that reflects active muscular control of movement^[49,50], with $T = k|yM|$ (where k is the stiffness of the stance leg muscles during the execution phase^[11] and $|yM|$ is the absolute value of the mediolateral center of mass shift, which was systematically oriented towards the swing leg (positive values) during the execution phase. The initial position and velocity of the cone corresponds to the position and velocity of the subject's center of mass at toe off. The addition of a restoring force on the conic model was necessary in order to control the initial velocity at toe off. A visual analysis of Figure 2 illustrates the excellent fit between the experimental traces obtained during gait initiation and those obtained with the mechanical model. The best fit between experimental (dashed line) and theoretical (full line) data was obtained for stance leg stiffness in the frontal plane of about 1000 N/m. This corresponded to a restoring force of approximately $T = 50$ N, applied at the center of mass of the participant.

The results obtained in this latter study^[15] suggested that changing the stance leg stiffness during the execution phase of gait initiation has the potential to influence the amplitude of the mediolateral fall of the center of mass. Stance leg stiffness can theoretically be modified by changing the co-activation level of agonistic/

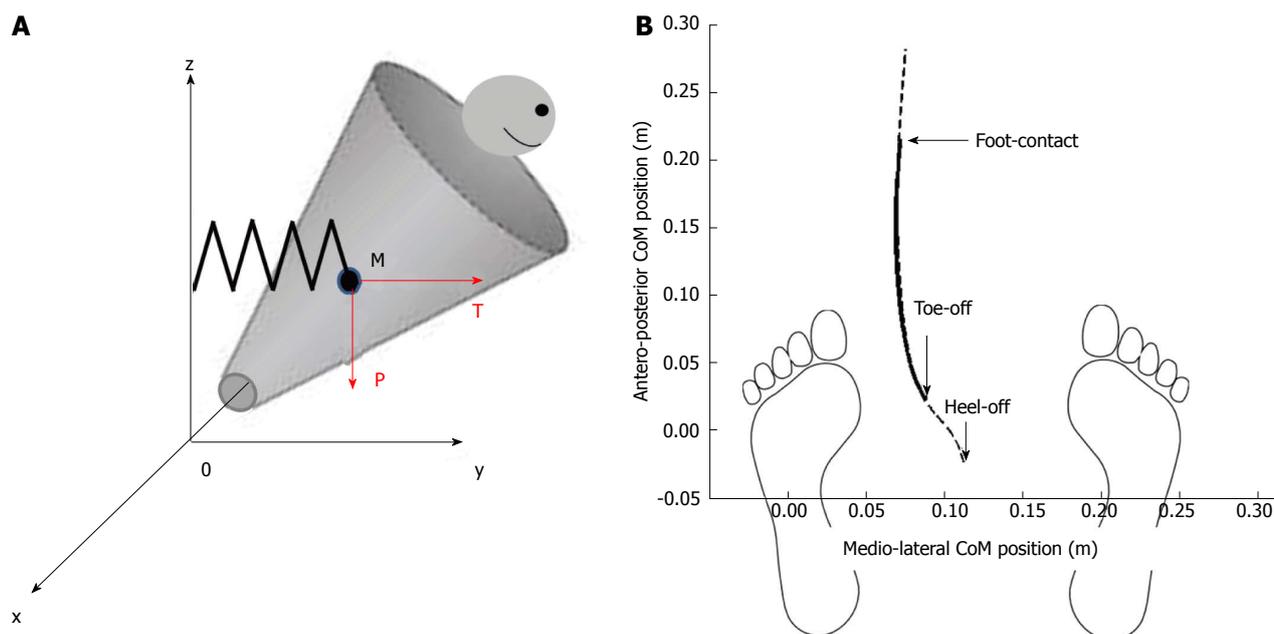


Figure 4 Mechanical model of the body during the execution phase of gait initiation. A: The mechanical model is represented as conic inverted pendulum which pivots around fixed point O. Body displacement presents five degrees of freedom. The center of mass M falls under the influence of the gravity force “P” and the elastic restoring force “T”; B: Anteroposterior vs mediolateral path of the center of gravity. Dash line represents experimental data during the whole trial and full line represents theoretical data during the execution phase of gait initiation. Note the excellent fitting between these two traces.

antagonistic pairs of muscles crossing the ankle, knee or hip joints. Whether the global mediolateral leg stiffness is equally sensitive to co-activation of the muscles groups crossing each of these joints remains to be investigated. Whether the CNS uses this theoretical leg stiffness tuning strategy in combination with mediolateral APAs in order to attenuate the fall of the center of mass during gait initiation, and whether the use of this strategy depends on the sensorimotor state of the postural system also remain unanswered.

Interestingly, an increase in leg stiffness is commonly found in many neurological patients such as patients with Parkinson’s disease, multiple sclerosis, stroke, *etc.* Based on this mechanical model, it can be speculated that part of the unstable state that is classically observed in these populations during gait initiation can be ascribed to an increase in stance leg stiffness. Besides, the use of medical devices such as leg orthoses, prostheses, plaster, *etc.* may also be expected to modify stance leg stiffness. On this aspect, Delafontaine *et al.*^[51] showed that wearing an orthosis over the ankle of the stance leg induced an increase in the mediolateral fall of the center of mass. In contrast, unpublished observations from our laboratory showed that wearing an orthosis over the knee of the stance leg did not induced any change in the mediolateral fall of the center of mass. These findings suggest that stance leg stiffness in the frontal plane may not be equally sensitive to ankle or knee stiffness. Future studies should investigate this aspect.

To summarize, stance leg stiffness during the execution phase of gait initiation may theoretically influence the mediolateral fall of the center of mass. It can thus be speculated that the increased leg stiffness in neurological

patients such as patients with Parkinson’s disease, multiple sclerosis, stroke, *etc.*, or in patients wearing a leg orthosis, may be responsible of part of their unstable state.

Foot placement and lateral ankle strategy

Although modulations of both the mediolateral APAs and the stance leg stiffness may influence the extent to which the center of mass falls toward the swing leg during step execution, it is known that these mechanisms do not fully stabilize the whole-body in the frontal plane during gait initiation^[3,12,14,15]. Yet, mediolateral stability must necessarily be restored in order to ensure safe forward progression. It is acknowledged that the primary mechanism employed to restore stability in the frontal plane following the swing foot off is the foot placement^[48,52,53]. As stated above, the action of repositioning the swing foot onto the ground allows to enlarge the base of support and opens the possibility of displacing laterally the center of pressure beyond the center of mass. In this way, it becomes possible to create a mediolateral gap between the center of mass and the center of pressure that will brake the lateral body fall and accelerate the center of mass in the direction of the stance leg (Figure 5).

Results from the literature reveal that the foot placement is actively regulated by the CNS to restore and control balance in the mediolateral direction^[54-57]. Foot placement would be mainly adjusted by the activity of the hip abductors of the swing limb in response to the mechanical state of the body, in terms of center of mass position and velocity^[58,59]. Interestingly, Caderby *et al.*^[60] have investigated the effect of the progression

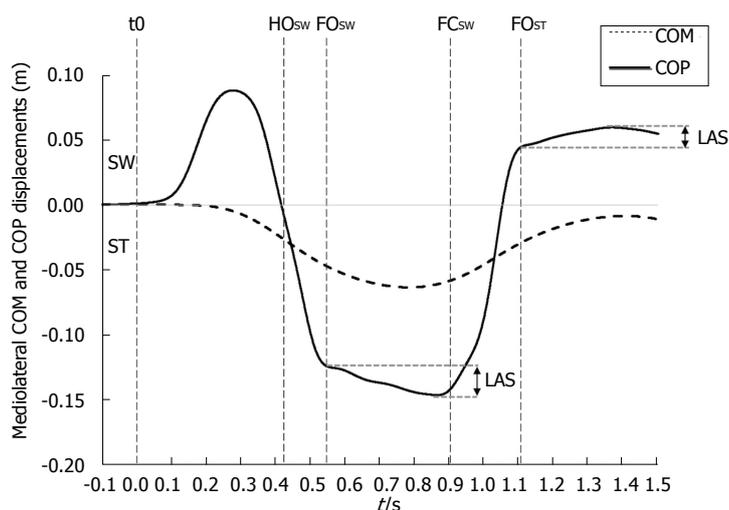


Figure 5 Typical time course of the center of mass and the center of pressure along the mediolateral direction during gait initiation. The traces were obtained for one subject initiating gait at self-selected speed (one trial). SW and ST indicate swing limb and stance limb, respectively. t_0 , HOSW, FOSW, FCSW, FOST: Onset variation of biomechanical traces, swing heel-off, swing foot off, swing foot contact, stance foot off, respectively. LAS indicates "lateral ankle strategy". The extent of the corrections achievable by this strategy may be appreciated by the difference between both the initial and the maximum lateral positions of the COP during the single support phase. COM: Center of mass; COP: Center of pressure.

velocity on the mediolateral stability control during gait initiation. These authors noted that when participants initiated gait at high speed, the lateral fall of the center of mass toward the swing limb during step execution was increased compared with gait initiation performed at low and normal speeds. Nevertheless, it was observed that the participants were able to compensate this higher mediolateral instability in the high speed condition by enlarging the step width (*i.e.*, the base of support) such that the mediolateral dynamic stability at the time of foot contact remained unchanged. These findings underlined that healthy young adults were able to finely tune the mediolateral foot placement such as to maintain an invariant mediolateral stability during gait initiation. Results obtained during steady state walking indicate that the accuracy of the foot placement may be altered in patients suffering from sensory and motor impairments. Specifically, it has been observed that above-knee amputees^[58] and patients with stroke^[61] exhibited a reduced ability to appropriately control foot placement, which may consequently contribute to a higher lateral instability.

It is worth noting that small errors in the foot placement may be corrected even after foot landing. Indeed, after the swing foot is positioned onto the ground, it remains possible to adjust the mediolateral position of the center of pressure located beneath this foot (Figure 5). This mechanism, called "lateral ankle strategy", would be mainly controlled by the ankle invertor/eversor muscles of the supporting foot^[58,62]. Although the extent of the corrections achievable by this mechanism is small, as it is limited by the width of the foot, it allows a fine-tuning of the torque induced by the mediolateral gap between the center of pressure and the center of mass that acts to brake the lateral fall of the body. During steady state walking, Hof *et al.*^[58]

have shown that the range of corrections attainable by this mechanism was reduced in above-knee amputees for their prosthetic leg (1-2 cm) compared with their sound leg (1.7-4.4 cm) and compared with healthy subjects (0.7-3 cm). These findings suggest that this mechanism could also be altered in people suffering from sensorimotor problems.

Reinmann *et al.*^[63] advanced that foot placement and lateral ankle strategy may be two independent mechanisms that are likely coupled and temporally coordinated. What the relative importance of each mechanism is in balance maintenance and how they are coordinated in normal subjects and in patients with postural disorders are questions that remain to be elucidated.

To summarize, lateral swing foot placement and lateral ankle strategy are two independent mechanisms that are likely coupled and temporally coordinated. These mechanisms may complement the mediolateral APAs and stance leg stiffness regulation to stabilize the whole-body in the frontal plane^[64-67].

Vertical center of mass braking

As stated above, during the execution phase of gait initiation, the backward center of pressure shift that is generated during APAs propels the center of mass away from the base of support^[27,68]. The distance between the center of mass and the center of pressure allows gravity to generate a disequilibrium torque which accelerates the center of gravity in both the anterior and downward directions^[11]. Consequently, the lowest center of mass position throughout gait initiation is measured at the instant of foot contact. Nonetheless, in healthy adults, the center of mass velocity reaches a maximum absolute value around mid-single stance and then is decreased (Figure 6). This center of mass

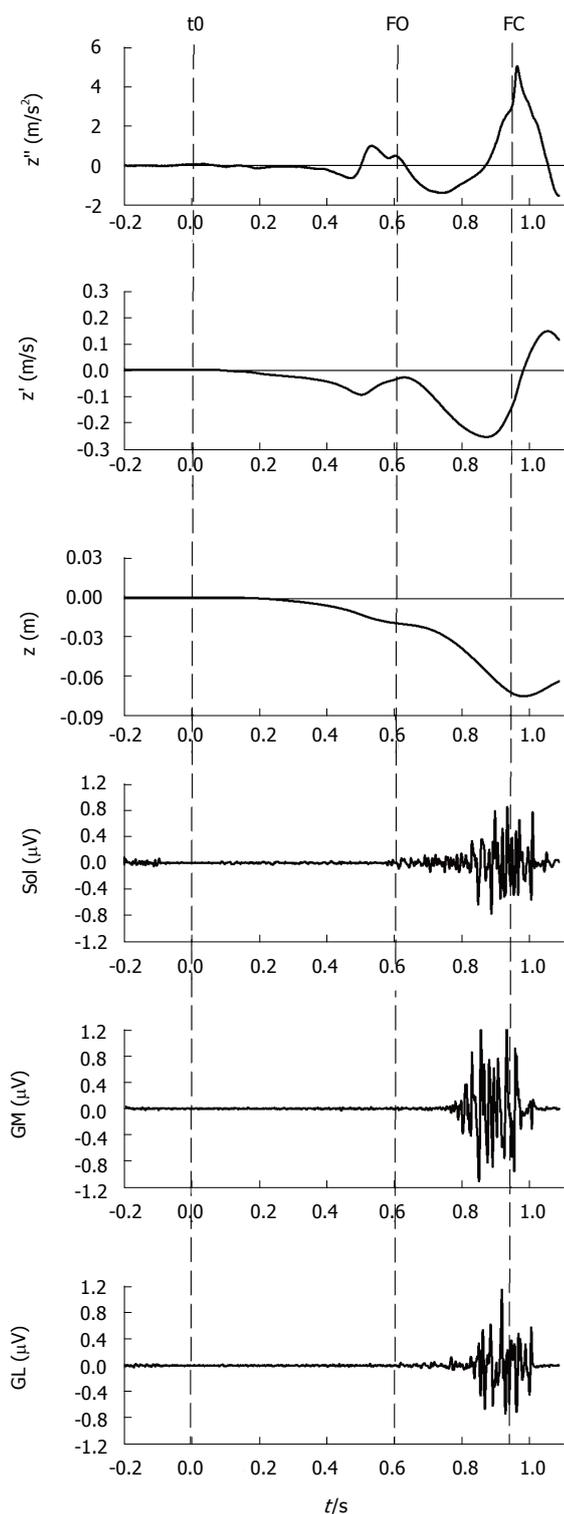


Figure 6 Vertical braking of center of mass during gait initiation. This figure shows, from top to bottom, the timelines of the COM vertical acceleration (z''), COM vertical velocity (z'), COM vertical position (z) as well as the electromyographical activity of stance leg triceps surae activity, *i.e.*, soleus (Sol), gastrocnemius medialis (GM) and gastrocnemius lateralis (GL) of a single recording during gait initiation. The dashed lines indicate the instants of initiation (t_0), foot off (FO) and foot contact (FC). As can be seen in the figure, step execution is accompanied by a downward (negative) COM acceleration. During mid-single stance, triceps surae activity counteracts gravity and brakes the vertical fall of COM. The braking action of COM is observable as a positive acceleration (top panel) which causes the vertical absolute velocity at foot contact to be lower than the peak absolute velocity measured in mid-single stance. COM: Center of mass.

vertical deceleration has been shown to result from the increase in *triceps surae* activity that occurs during the second half of the execution phase of gait initiation^[69].

By counteracting gravity, the triceps surae also plays a role in modulating the disequilibrium torque and setting velocity and duration of step execution as well as step length^[70]. On the one hand, it has been argued that the braking action limits the amplitude of the impact of the swinging leg with the ground at foot contact^[71,72]. On the other hand, Kuo^[73] reasoned that the vertical force produced during late single-stance decreases the work needed to raise the center of gravity in the ensuing double stance phase. Consistent with this hypothesis, Bregman *et al.*^[74] showed that the spring assistive ankle foot-orthosis decreases the energetic cost of hemiplegic patients by 10% during double support.

The active braking of the center of mass during step execution is not observed before the age of 4^[75]. This implies that active braking requires a process of neural learning^[76-78]. In addition, progressive supranuclear palsy^[72] and Parkinson patients^[79,80] as well as elderly people^[81] have all been found to have difficulties in decelerating the center of mass' downward velocity. The dysfunction in the braking action of center of mass has been linked to lesion or dysfunction of the network linking the primary motor cortex and the mesencephalic locomotor region which is involved in the control of gait and balance^[82]. Furthermore, induced ankle joint mobility on healthy individuals has also been shown to play a role in modulating the active braking of center of mass^[51,83]. In those studies, the modifications in the proprioceptive inputs, due to strapping the ankle joint or by wearing a rigid ankle foot orthosis, are likely the cause of the deterioration in vertical braking. While proprioception has been shown to play a role in modulating the APAs phase of gait^[84-86], more research is needed to understand how somatosensory inputs are integrated in order to generate the central commands responsible for the vertical braking action on center of mass.

To summarize, the center of mass' downward velocity is actively braked during step execution thanks to the activation of the triceps surae of the stance leg. Difficulties to perform this active vertical braking, as observed in patient with progressive supranuclear palsy and with Parkinson disease as well as in elderly people, may induce postural instability.

Swing foot strike pattern

During locomotion, it is known that the collision of the swing foot with the ground can occur in three ways (*e.g.*, Ref^[22,23]): A rear foot strike, in which the heel lands first; a mid-foot strike, in which the heel and ball of the foot land simultaneously; and a fore foot strike, in which the ball of the foot lands before the heel comes down. During running, the strike patterns vary within subjects and whether participants are shod or barefoot. Kinematic and kinetic analyses showed that even on hard surfaces, barefoot runners who fore-foot strike

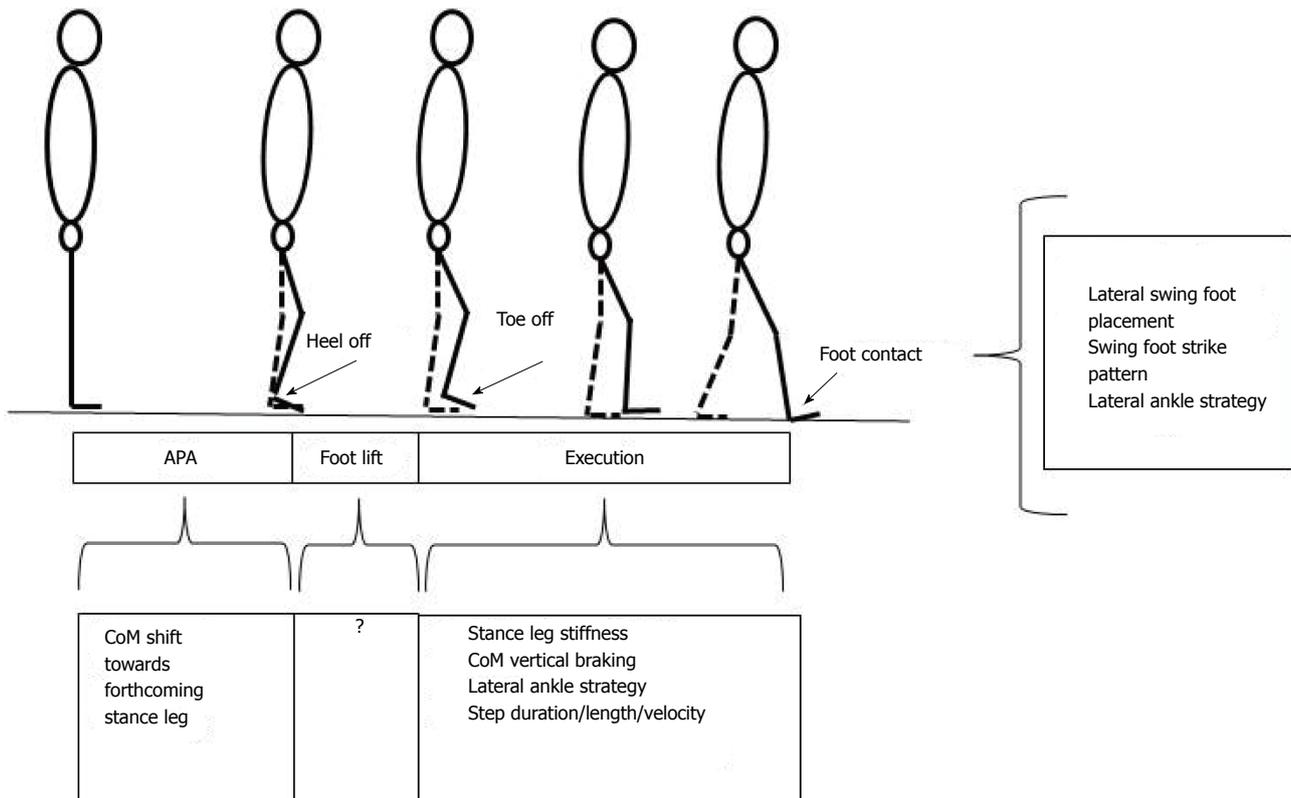


Figure 7 Synthesis of balance control mechanisms into play during gait initiation. The coordination between these different mechanisms remains to be elucidated.

generate smaller collision forces than shod rear-foot strikers^[23]. This difference results primarily from a more plantar-flexed foot at landing and more compliance during impact, decreasing the effective mass of the body that collides with the ground. To date, in most studies on gait initiation, participants initiate gait unshod on an unobstructed track and over the hard surface of a force plate. In these classical conditions, participants spontaneously use a rear foot strike whatever the progression velocity. Recent study^[15] however reported that when participants initiate gait at maximal velocity with the instruction to clear an obstacle, the percentage of fore-foot strike progressively increased with the obstacle distance, passing from 8% for obstacle at 10% of body height to 21% for obstacle at 30% of body height. Forefoot strike was also reported in young healthy adults during stairs descend^[64]. The question of how the CNS in young healthy adults vs frail subjects with high risk of fall coordinates their foot strike pattern with the strategy of active braking of the vertical center of mass fall (cf. paragraph above), remains to be explored in both walking and running. Impairment in the coordination between these two strategies of vertical ground reaction force damping may potentially increase the risk of injuries (e.g., tibial stress fractures^[65,66] and plantar fasciitis^[67]) and/or of body collapse on the ground. This research avenue is currently under investigation in our laboratory.

To summarize, the swing foot strike pattern used by

participants during locomotion (rear foot, mid-foot, or fore foot strike pattern) influences the damping of the ground impact force. Swing foot strike pattern may be combined with active vertical braking of the center of mass to attenuate the potentially damaging effects of the collision forces generated at the time of foot contact.

The different balance control mechanisms at play during gait initiation are summarized in the Figure 7.

MEASURING DYNAMIC STABILITY DURING GAIT INITIATION

As stated above, the condition for stability during quiet standing holds that the vertical projection of the center of mass falls within the base of support^[10,11]. As stressed in the literature, this condition is sufficient during quiet standing when the velocity of the center of mass can be neglected. However, during dynamical tasks such as gait initiation, the velocity of the center of mass cannot be neglected and this quantity has to be taken into consideration in the condition for stability^[87,88]. To illustrate this necessity, Hof *et al.*^[87] emphasized “that even if the center of mass is above the base of support, balance may be impossible if the center of mass velocity is directed outward. The reverse is also possible: Even if the center of mass is outside the base of support, but its velocity directed towards it, balance can be achieved”. The former situation is particularly relevant to the gait

initiation process where the center of mass position falls normally within the base of support at the time of foot contact while its velocity is then directed outwards, *i.e.*, towards the swing leg side.

Until recently, authors compared stability across stepping task conditions with measures of mediolateral center of mass shift, velocity and step width at the time of swing foot contact (*e.g.*, Ref^[12,14,29,89,90]). It was assumed that the lower these kinematical center of mass variables are and the larger the step width, the greater the stability. These variables were however considered separately, which made comparison of stability across conditions potentially difficult. Difficulty would indeed arise in a situation where the base of support size is increased, thus yielding a greater stability, and where the center of mass velocity or shift at swing foot contact is also increased, thus yielding a lower stability: It could not be clearly determine whether stability is improved or not.

Hof *et al.*^[87] proposed an extension of the classical condition for stability in static situations to dynamical situations where the position of the vertical projection of the center of mass plus its velocity times a factor (square root L/g) should fall within the base of support, L being leg length and g the acceleration of gravity. These authors suggested naming this vector quantity "extrapolated centre of mass position", because the centre of mass trajectory is extrapolated in the direction of its velocity. According to these authors, the definition put forward the "margin of stability", which was defined as the minimum distance from extrapolated centre of mass position to the boundaries of the base of support, as a measure of dynamical stability. The margin of stability can thus be considered as a "synthetic" variable since it simultaneously takes into account the position of the center of mass, its velocity and the base of support size. Since the publication of Hof *et al.*^[87], this quantity is increasingly used in the literature to quantify stability during dynamical tasks such as steady-state locomotion^[21,91,92], gait initiation^[15,24,60,93], leg flexion^[20,94], sit-to-stand^[95], *etc.*

To summarize, the condition for dynamic stability holds that the position of the vertical projection of a quantity termed the "extrapolated center of mass" should fall within the base of support. The distance between the boundaries of the base of support and the extrapolated center of mass (*i.e.*, "the margin of stability") is increasingly used in the literature to quantify stability during dynamical tasks.

STABILITY-RELATED CONTROLLED VARIABLES

The mediolateral margin of stability was fruitfully used in recent studies which investigated the adaptability of the stabilizing features of various stepping tasks (gait initiation, rapid leg flexion or abduction) to spatial or temporal constraints imposed on the postural system

in young healthy adults and seniors. These constraints included temporal pressure^[15,20,24,94], obstacle clearance^[15,24], fear of falling^[96-98], velocity instruction^[60], and symmetrical or asymmetrical body loading^[93,99]. In brief, these studies have repeatedly shown that participants were able to develop adaptive postural strategies in the forms of changes in the APAs' spatio-temporal features, step width and/or swing foot strike pattern (*cf.* paragraph above) so as to maintain an invariant margin of stability value across the different conditions. A recent study using mechanical modeling of the human body during gait initiation over obstacles of varying heights and distances (*cf.* paragraph Stance leg stiffness) reinforced this idea of adaptive stabilizing features by showing that a negative value of the margin of stability at foot contact would occur (thus yielding an unstable state) should these changes not be developed^[15]. This invariance of the margin of stability under various postural constraints led authors to suggest that this quantity may function as a possible balance control parameter during gait initiation.

As a marked exception, unpublished data obtained in twenty seven healthy young adults showed that unilateral knee joint hypomobility experimentally induced by the wear of an orthosis over the stance or the swing leg induced an increased margin of stability compared to unconstrained gait initiation, thus yielding a more stable state. This result was due to an enlarged step width in the conditions with an orthosis. In addition, participants spontaneously initiated gait with a smaller step length and reduced progression velocity, which allowed them to maintain an invariant peak vertical ground reaction force and associated slope values. This statement was strengthened by the result that participants were in fact able to reach the same step length and progression velocity when instructed to do so. But, in this case, the slope (and to a lesser extent, the peak vertical ground reaction force) was then largely increased compared to the control condition. As an expected consequence, participants reported discomfort at the heel, knee and hip with repetition.

To summarize, these results showed that when a mechanical constraint is applied to the leg, the CNS uses a more protective strategy by giving priority to stability and joint comfort rather than to motor performance. It can thus be proposed that the CNS set reference values for stability and vertical disturbance before stepping. The CNS would then plan the stabilizing features and motor performance of gait initiation so as to reach these desired reference values. These references values may change according to the instructions given to participants and the sensorimotor state of the locomotor apparatus.

CONCLUSION

The findings reported in this review may be replaced

in the broader framework of homeostasis in Physiology^[100]. According to the definition, homeostasis is the tendency of a system, especially the physiological system of higher animals, to maintain internal stability, owing to the coordinated response of its parts to any situation or stimulus that would tend to disturb its normal condition or function. During gait initiation, the regulation of dynamic stability and vertical disturbance at foot collision seems to respond to this definition. Results reported in this review indeed showed that in situations where instability and vertical disturbance may potentially be increased due to internal or external constraints, a compound of postural responses are triggered that allows to keep these biomechanical variables constant. It was thus proposed that the CNS sets reference values to be kept invariant before stepping and that balance control mechanisms would be planned accordingly. In the physiological domain, reference values are also supposed to be set by the CNS for controlled variables such as the neuromuscular spindles sensitivity, glycemia, blood pressure, natremia, etc. As for the maintenance of dynamic stability during gait initiation, the maintenance of these physiological variables requires both anticipatory and reactive mechanisms (cf. for example the anticipatory secretion of insulin before glycemia rises). This review advances the viewpoint that dynamic stability during gait initiation (as measured with the margin of stability) may share a similar principle of functional regulation. Now, the question how these different balance control mechanisms are coordinated to ensure the regulation of dynamic stability remains to be clarified. Specifically, to what extent these mechanisms are complementary and may substitute to each other in case of motor deficiency should be investigated in future studies. This knowledge is important for the clinician to better understand the pathophysiology of balance disorders with aging, neurological and orthopedic conditions. Thus, this review further advances the viewpoint that rehabilitation interventions focused on separate or isolated components of posture, balance, or gait may limit the effectiveness of current clinical practices.

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Basic Study

Biomechanical assessment of new surgical method instead of kyphoplasty to improve the mechanical behavior of the vertebra: Micro finite element study

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Institutional review board statement: The study was approved by the head of animal care center at Department of Biomedical Engineering at the University of Isfahan.

Institutional animal care and use committee statement: The fresh ovine vertebrae were harvested from the dead sheep Carcasses without meaning any harm or pain to the living animals; approved by the University of Isfahan's Animal Care Committee at the time of adoption.

Conflict-of-interest statement: To the best of our knowledge no conflict of interest exists.

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Abstract**AIM**

To reduce post treatments of kyphoplasty, as a common treatment for osteoporotic vertebrae.

METHODS

This study suggests a new method for treating vertebrae by setting the hexagonal porous structure instead of the rigid bone cement mass in the kyphoplasty (KP). The KP procedure was performed on the fresh ovine vertebra of the level L1. Micro finite element modeling was performed based on micro computed tomography of ovine trabecular cube. The hexagonal porous structure was set on one cube instead of the bone cement mass. For the implant designing, two geometrical parameters were considered: Spacing diameter and thickness.

RESULTS

The results of micro finite element analyses indicated the improvement in the mechanical behavior of the vertebra treated by the hexagonal porous structures, as compared to those treated by vertebroplasty (VP) and KP under static loading. The improvement in the

mechanical behavior of the vertebra, was observed as 54% decrease in the amount of maximum Von Mises stress (improvement of stress distribution), in trabecular cube with embedded hexagonal structure, as compared to VP and KP. This is comparable to the results of the experimental study already performed; it was shown that the improvement of mechanical behavior of the vertebra was observed as: 83% increase in the range of displacements before getting to the ultimate strength (increasing the toughness) after setting hexagonal pearls inside vertebrae. Both the material and geometry of implant influenced the amount of Von Mises stress in the structure.

CONCLUSION

The new proposed method can be offered as a substitute for the KP. The implant geometry had a more obvious effect on the amount of Von Mises stress, as compared to the implant material.

Key words: Vertebroplasty; Kyphoplasty; Micro finite element modeling; Hexagonal porous structure; Von mises stress

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Core tip: By embedding the hexagonal porous structure with two variable parameters including spacing diameter and thickness, as a substitute for the bone cement mass in the vertebral kyphoplasty, lower levels of maximum Von Mises stress could be achieved, thereby indicating the reduction of stress concentration in the interface area between the bone cement mass and the cancellous bone, as well as the reduction of post treatments. Furthermore, setting porous structures with different geometries inside vertebrae could provide the possibility of bone regeneration, the transfer of growth factors and recreation of mechanical properties.

Hosseini Faradonbeh SA, Jamshidi N. Biomechanical assessment of new surgical method instead of kyphoplasty to improve the mechanical behavior of the vertebra: Micro finite element study. *World J Orthop* 2017; 8(11): 829-835 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i11/829.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i11.829>

INTRODUCTION

Vertebroplasty (VP) and kyphoplasty (KP) as minimally invasive surgeries, consume poly methyl methacrylate (PMMA) and calcium phosphate as the bone cement for the treatment of patients with osteoporotic disorders in vertebral column. But one important challenge affecting the quality of procedure is the leakage of bone cement. Also the mechanical behavior of treated vertebra can affect biomechanics of the whole spine^[1-3]. It is known that the KP does not guarantee the stoppage of fractures.

Based on the studies of Polikeit *et al*^[4], the strength of the treated vertebrae can be regained by cement augmentation, while it increases the endplate bulge and generates some altered load transfer in adjacent vertebrae. Then the rigid cement augmentation could facilitate the subsequent collapse of adjacent vertebrae.

According to a careful literature review performed by Wilcox^[5], the main factors affecting the spine performance after cement augmentation can be classified in three groups: (1) the cement properties and volume; (2) the features of connection between the structure and vertebra; and (3) the spine properties. The bone and cement interface is important in providing the longer term stability of the construction. Cement augmentation improves motion segment stiffness, while, it alters the bone stress distributions in the treated and adjacent segments.

Keller *et al*^[6], indicated that cement injection affects the stress distribution in both the vertebra and adjacent segments. Rohlmann *et al*^[7] proved that the wedge shaped vertebral body could alter the center of the gravity of the upper body. This shift was compensated by the KP leading to a lower muscle force and an increase in the spinal load. The cement augmentation increases the intradiscal pressure in adjacent discs with a slight increase in Von Mises stress in vertebral endplates. Based on attempts of Liang *et al*^[8], the asymmetrical cement distribution inside the treated vertebra led to the unrelieved pain after percutaneous vertebral augmentation. The insufficient distribution of the bone cement increased the displacement of augmented vertebral body. Tschirhart *et al*^[9] and Xu *et al*^[10], both emphasized that in the case of severe fractures, cement augmentation could worsen the fracture, leading to the cement leakage with subsequent problems; this indicated the uncertainty in the results of VP. Baroud *et al*^[11], emphasized that both experimental study and finite element modeling are often focused on the effect of type of bone cement and volume. To reduce the risk of adjacent fracture after cement augmentation, Boger *et al*^[12] suggested consuming the low modulus cement (consisting of the regular bone cement (PMMA) and the low-modulus cement prepared with Vertecem by the addition of an aqueous fraction of 35% sodium hyaluronate).

Kinzl *et al*^[13], emphasized that stress concentration in trabecular bone is based on cement distribution. Basically, in the KP, the bone cement and trabecular structure are separated. So the whole structure is not homogeneous and the stress concentration can be seen in the interface area which is the reason of occurring micro fractures. The result of studies of Kosmopoulos *et al*^[14] and Kettler *et al*^[15], indicated that the main problems with the cement augmentation are: (1) stress concentration in the interface area; and (2) asymmetrical cement distribution. Baroud *et al*^[16], proved that the wedge shaped vertebrae, induced a shift in the center of gravity of the upper body and therefore increased the intradiscal pressure and stress on endplates. Compensation of this shift by the

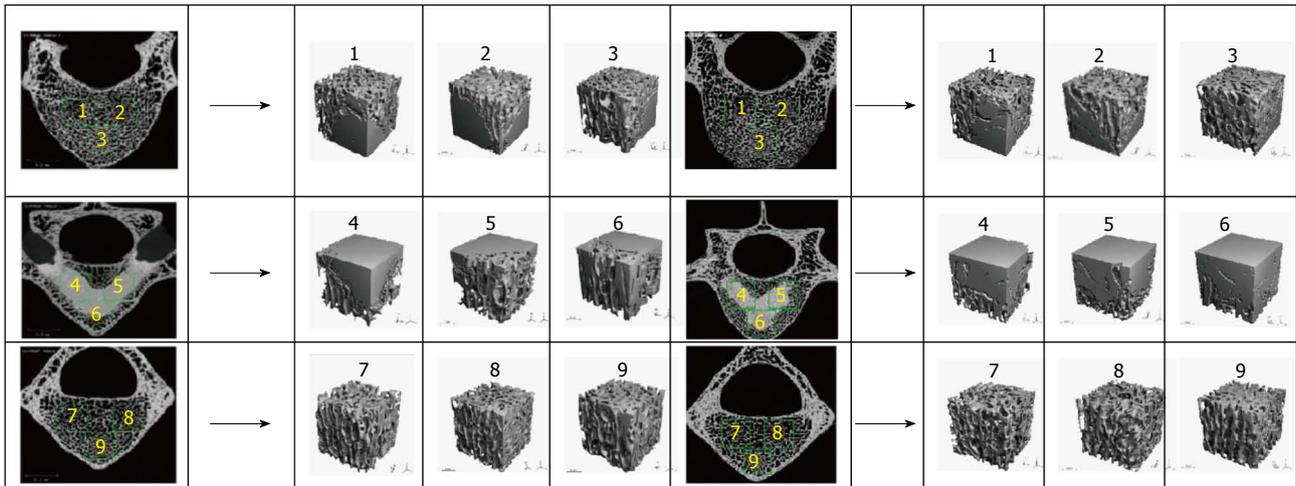


Figure 1 Subdividing the specimens of vertebroplasty (left) and kyphoplasty (right) to 9 smaller cubes in 3 layers in order to evaluate the regional variations in stress distribution.

KP procedure decreased the erector spinae force and also, the axial force in spinal column. Armsen *et al*^[17], emphasized that in the case of the long term stability of the structure build up from the bone cement and trabecular bone, two main factors must be considered. First, it should be noted that the cytotoxicity of poly methyl methacrylate prevents the osteointegration; second, the osteoporosis as a progressive disease weakens the structure of the trabecular bone. Considering the necessity of setting a structure to solve mentioned problems, Garzón-Alvarado *et al*^[18], suggested setting porous structures. Verhulp *et al*^[19], emphasized that the structural complexity in trabecular bone could be the reason of existence of a wide range of differences in the amount of Von Mises stress in the structure. Landgraft *et al*^[20], attempted to simulate the generation of microstructural models of human trabecular bone and the acrylic bone cement injection with the Finite Element Method (FEM) of cement curing inside vertebrae based on micro computed tomography (μ CT) scanning.

Considering the results of all studies conducted to address the limitations of cement augmentation and the problems that patients may encounter after the VP and KP, the main drawbacks of these procedures can be classified as: (1) asymmetrical cement distribution inside the vertebra; (2) stress concentration in the interface area between cement mass and bone in the KP; (3) the risk of occurring fractures in the adjacent vertebrae; (4) the risk of cement leakage while augmenting; and (5) as an important case, different outcomes of patients due to ignoring the morphological parameters of trabecular bone such as trabecular thickness (Tb. Th) and trabecular spacing (Tb. Sp) in treating osteoporotic vertebrae.

In this study, the hexagonal porous structure with the low rate of mass/volume and high stability, is presented with defined geometrical parameters including thickness and spacing diameter, as determining factors to build the implant with optimum design and therefore, to reduce post treatments. Furthermore, setting porous structures

with different geometries inside the vertebra, could provide the possibility of tissue regeneration, the transfer of growth factors and the recreation of mechanical properties.

MATERIALS AND METHODS

Preparation of specimens

Two L1 ovine vertebral bodies were chosen for the VP and KP procedures. Cement augmentation was performed according to common instructions already brought in the literature. The VP and KP procedures were performed by needle insertion through the pedicle. The PMMA was used as the bone cement. The volume fraction for the consumed PMMA was 20% of the whole vertebral volume. The cement distribution was checked by CT scanning of the samples after cement augmentation.

Micro finite element modeling

To reconstruct three dimensional micro structure of trabecular bone, a micro computed tomography (μ CT 100, SCANCO Medical AG, Switzerland) was used for a specimen treated by VP and KP. To evaluate the regional variations of stress distribution inside the vertebrae, each specimen was subdivided to 9 smaller cubes with the size of 5 mm \times 5 mm \times 5 mm in 3 layers (Figure 1). Then the model was imported into the analytical software ABAQUS 6.14.

Implant design

The hexagonal porous structure was set on one cube instead of the bone cement mass. For designing the implant, two geometrical parameters were considered as: Spacing diameter and thickness (Figure 2). The implant design was performed in four groups with different geometries. The geometrical characteristics of the hexagonal structure including thickness and spacing diameter, are presented in Table 1. There was also a pattern among the designed implants: The thickness of

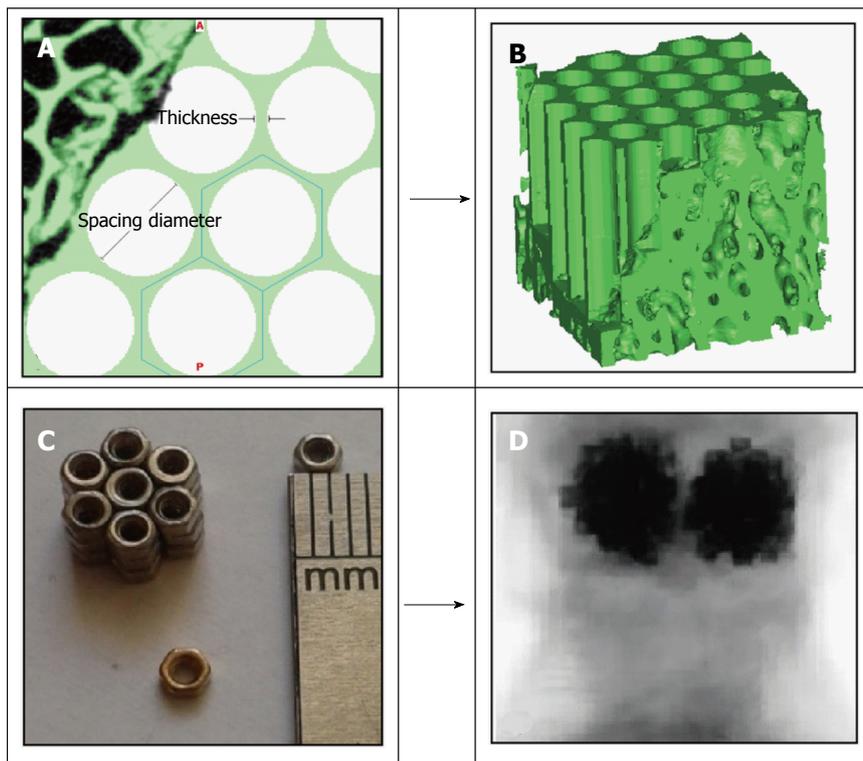


Figure 2 Spacing diameter and thickness. A and B: Design of hexagonal porous structure; C and D: Using a symmetric circle pattern equivalent to; the embedded hexagonal structure in the experimental study (Ref [21]), already performed.

Table 1 Geometrical parameters in implant design				
	Model 1	Model 2	Model 3	Model 4
Thickness (mm)	0.5	0.4	0.3	0.2
Spacing diameters (mm)	1	1.5	2	2.3

Table 2 Material properties used in the finite element method		
Components	Elastic modulus (MPa)	Poisson ratio
Trabecular bone	30	0.2
Bone cement	2530	0.2
Steel	200e3	0.3
Titanium	110e3	0.3

the structure was decreased simultaneously with growing the spacing diameter from the models 1 to 4. The hexagonal porous implants were designed in the way to replace the cement mass on one cube in four models with two groups of materials: Steel and titanium. The porous structure is set in the space already occupied by the cement mass. The symmetric circle pattern was used to construct the hexagonal structure equivalent to the experimental study^[21], previously performed. Material properties including elastic modulus and Poisson ratio used in the FEM are shown in Table 2.

Loading

In accordance with micro finite element analyses (μ FEA) performed by Gong *et al.*^[22], to simulate the experimental testing conditions, a displacement load was applied as 1% compressive strain on the longitudinal direction with the full constraints at the bottom of each trabecular cube.

RESULTS

The results of μ FEA of cubes related to VP and KP indicated that the maximum Von misses stress in the

cubes of the VP was less than that of the KP. Basically, the mechanical behavior of a construction made of the bone cement and trabecular structure is based on the cement distribution. As shown in Figure 3, the cement distribution in trabecular cubes is totally different in the VP and KP.

The results of μ FEA of the cubes surrounding the injected cement mass in both VP and KP indicated the low regional variations in the amount of maximum Von Misses stress in the cubes 1 to 6 with the average value of 21.7 MPa and 36.6 MPa for the VP and KP, respectively. Also, in the third layer without cement penetration, for cubes 7 to 9, the difference between the amounts of maximum Von Misses stress in the cubes was not considerable and had the average value of 7.3 and 7.21 MPa for the VP and KP.

The low regional variation in the cubes with combination of bone cement and trabecular bone in the KP, made the selection of each cube for embedding the hexagonal structure, a reasonable statistical one. Therefore, the results of analyses for the selected cube were generalizable to the whole vertebra. The

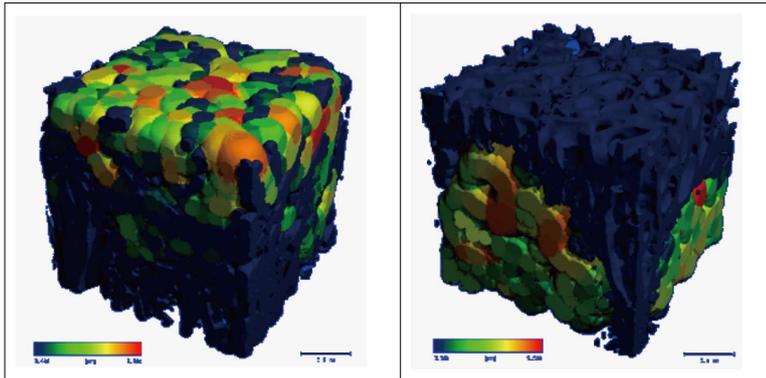


Figure 3 Different cement distribution in the vertebroplasty (left) and kyphoplasty (right).

maximum Von misses stress in the cube 2, with the embedded hexagonal porous structure with different geometries, instead of the cement mass, is shown in Figure 4. The maximum Von Misses stress in the cube with hexagonal structure was more than that of the same cube treated by KP procedures at first. But after implementing different geometrical parameters of the hexagonal structure, the maximum Von Misses stress was decreased in the whole cube. This was the sign of altered stress distribution inside vertebrae.

For the model 1, with the thickness of 0.5 mm and spacing diameter of 1 mm, the maximum Von-Misses stress for the implant material of steel and titanium was 38.2 and 37.8 MPa, respectively. For the model 2, with 0.4 and 1.5 mm for the thickness and spacing diameter, the maximum Von-Misses stress reduced to 34 and 32.2 MPa for steel and titanium implants, respectively. This decreasing trend in the amount of Von Misses stress was continued until reaching to 16.5 and 16.4 MPa for the steel and titanium implants in the model 3, with the 0.3 and 2 mm for the thickness and spacing diameters. But after this, increasing the spacing diameter and decreasing the thickness in the hexagonal structure, caused the enhancement of Von Misses stress in model 4.

The diagrams of vertebrae with hexagonal structure, indicated two main points: (1) after implementing geometrical parameters of the hexagonal structure, the amount of maximum Von Misses stress in the construction was decreased; and (2) the influence of type of material (steel or titanium) on the amount of maximum Von Misses stress was less obvious than the impact of implant geometry.

DISCUSSION

This study was set to compare the mechanical behavior of the vertebrae treated by the VP and KP with the one treated by the hexagonal porous structure having different geometries. In the case of VP, the bone cement filled most of the porous space of the trabecular structure, such that the whole construction was almost homogeneous. This was the reason for increasing the stress in endplates, pressure inside

disks and the bulge of adjacent endplates leading to occurring adjacent fractures^[4]. On the other hand, in the KP, the bone cement mass and the trabecular structure were separated and the whole structure was not homogeneous. So the stress concentration could be seen in the interface area. The stress concentration in the separation region caused high amounts of Von Misses stress in the construction.

The results of an experimental study addressing the differences between the mechanical behavior of the vertebrae treated by hexagonal pearls embedded inside vertebrae and that of the VP and KP^[21], confirmed the results of μ FEA in this study. Based on the results of mechanical tests, by setting the hexagonal porous structure, the toughness of the vertebra was enhanced substantially in the form of increased range of displacement of the vertebrae (83%) before getting to the ultimate strength under static loading. Also, the effect of the type of material in increasing the toughness was less obvious when compared to the effect of implant shape. In the KP, the separation area between the rigid cement mass and the trabecular bone was the most susceptible region for occurring fractures because the stress distribution in the boundary region was not homogeneous. The hexagonal porous structure rendered better stress distribution in the boundary region and reduced the risk of fracture in the future.

The complicated geometry of trabecular bone requires an algorithm to determine the amount and the position of bone cement or any other structure. The improvement in stress distribution inside treated vertebrae leads to the reduction of stress in endplates^[6]. So it could be inferred that the treated vertebrae by the hexagonal structure is likely to encounter a less amount of stress in endplates. As the treated vertebrae by hexagonal structure had better stress distribution, it could be predicted that in the term of long term stability, those vertebrae might show a better performance.

The decreasing trend in the maximum Von Misses stress in the cube with the hexagonal porous structure can be obviously seen in Figure 4. The improvement in the mechanical behavior of the whole vertebra treated by new method, as compared to the common procedures, could be achieved by validating the

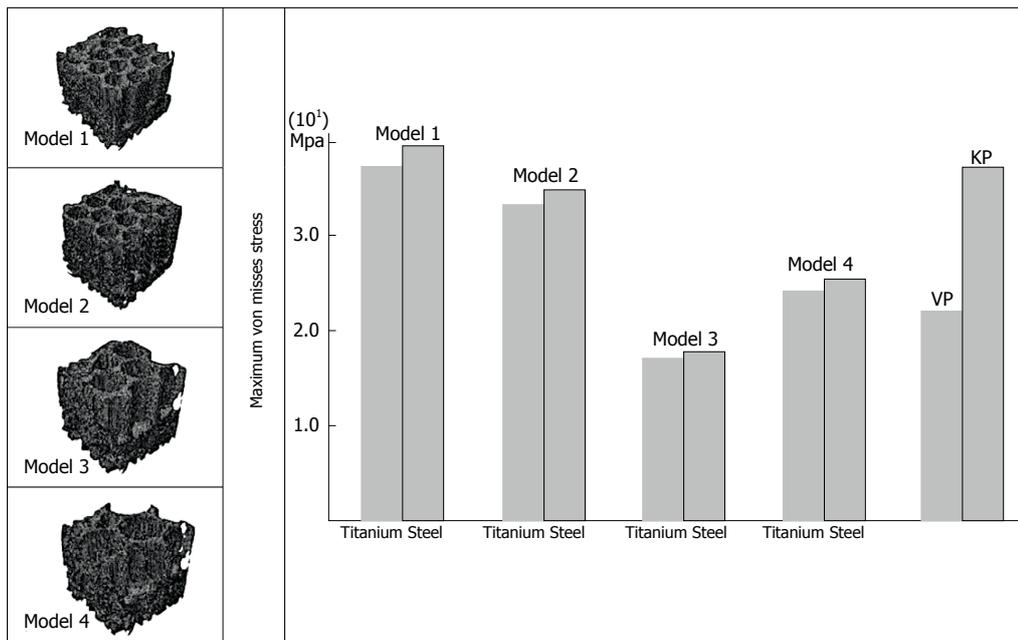


Figure 4 Maximum von mises stress in the cube with geometrically different hexagonal structures: model 1 to 4 and also in the vertebroplasty and kyphoplasty in the form of bar graph.

theoretical results through experimental tests. The reduction of Von Mises stress in the construction after implementing geometrical parameters is comparable to the results of the experimental tests already performed, thereby showing the increased range of displacement before getting to the ultimate strength in the vertebrae treated by the hexagonal structure; this represented the better stress distribution inside the vertebrae under the uniaxial compressive load. The increasing trend in Von Mises stress in the model 4 indicated the existence of an optimal amount for the geometrical parameters of hexagonal structure. Considering the morphological parameters of trabecular cube such as Tb. Th and Tb. Sp, it seems that there is a relationship between geometrical parameters of the embedded structure and morphological parameters of trabecular bone. Therefore, optimizing the design of implants is related to those morphological parameters.

The more dependence of stress distribution on different geometries of implant, compared to the variation of material in the results of μ FEA, was also observed in the experimental study^[21], this showed that the influence of the material of hexagonal structure in increasing the range of displacements before getting to the ultimate strength (improved stress distribution), as compared to the impact of implant geometry, is of secondary importance.

Future studies must be focused on optimizing the geometry of the hexagonal implants based on morphological parameters of trabecular structure in order to provide clear surgical instructions for each patient. In addition to the improvement of mechanical properties of the treated vertebrae, setting porous scaffolds might help better bone regeneration, cell

migration and bone repair.

In conclusion, the new method presented here is based on using hexagonal implants instead of the rigid cement mass. The results of treated vertebrae by hexagonal structures showed that the improvement of the stress distribution inside vertebrae could lead to increasing the toughness and reducing stress in endplates. Also, because the hexagonal porous structure was symmetrical and geometrically optimized, it could solve the problem of asymmetrical cement distribution, a common problem in the VP and KP. The results of this study indicated that a wide range of material could be selected in providing implants due to the low dependence of stress distribution, relative to the implant material variance.

Future studies must be focused on evaluating geometrically different models of implants based on defined parameters of this study: Thickness and spacing diameter; this could lead to optimizing the stress distribution considering the morphological parameters of trabecular bone for each patient. Also, advanced techniques to facilitate the insertion of porous structures inside vertebrae must be considered. In the case of long term stability, *in-vivo* studies could be an effective method to assess the bone repair and evaluating the durability.

COMMENTS

Background

The vertebroplasty (VP) and kyphoplasty (KP) are known as common procedures in treating osteoporotic vertebrae. Although post treatments of KP are less than those of VP, but the stress concentration in the interface area of bone cement and trabecular bone could be regarded as the main reason of occurring micro fractures, pain and aseptic loosening.

Research frontiers

Previous researches have already proved that cement augmentation increases the interdiscal pressure in adjacent discs with a slight increase in Von Mises stress in vertebral endplates. Basically, the main drawbacks of cement augmentation are: (1) stress concentration in the interface area; and (2) asymmetrical cement distribution.

Innovations and breakthroughs

This is the first study addressing the hexagonal porous structure with defined geometrical parameters including spacing diameter and thickness. It was conducted to alter the mechanical behavior of the osteoporotic vertebrae.

Applications

The hexagonal porous structures could be considered as a substitute for bone cement with the variety of geometrical parameters. Furthermore, setting porous structures with different geometries inside vertebrae may provide the possibility of bone regeneration, transfer of the growth factors and recreation of mechanical properties.

Terminology

The hexagonal porous structure could be considered as a substitute for bone cement mass due to lowering the level of the maximum Von Mises stress and reducing the stress concentration and post treatments. Within defined geometrical parameters, thickness and spacing diameter, the structure could be optimized as well.

Peer-review

Good study, subject addressed in this article is worthy of investigation.

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Retrospective Study

Atlantoaxial rotatory displacement in children

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Author contributions: Spiegel D and Dormans J came up with the study questions; Spiegel D, Shrestha S, Sitoula P and Rendon N contributed to the study design and IRB application; Spiegel D, Shrestha S, Sitoula P and Rendon N reviewed all of the studies and collected the data; Spiegel D was the primary author of the manuscript; Shrestha S and Sitoula P were secondary authors; Rendon N and Dormans J reviewed the manuscript and provided critical revisions; all authors provided final approval for the article.

Institutional review board statement: The study was reviewed and approved by the Children's Hospital of Philadelphia's Institutional Review Board.

Informed consent statement: A waiver of informed consent has been granted by the Children's Hospital of Philadelphia's Institutional Review Board to conduct this retrospective study.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest related to this work. Dr. Spiegel has received royalties from Springer for co-editing a textbook.

Data sharing statement: The data is available at request from the corresponding author.

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Abstract**AIM**

To correlate the Pang and Lee class with the clinical course in a consecutive series of patients presenting with painful torticollis.

METHODS

Forty-seven dynamic rotational computed tomography (CT) scans in 35 patients were classified into one of the five types defined by Pang and Li, including types I (atlantoaxial rotatory fixation), II ("pathologic stickiness" without crossover of C1 on C2), III ("pathologic stickiness" with crossover of C1 on C2), IV (normal or muscular torticollis), and V (diagnostic grey zone). The Pang and Li class was then compared with the radiologist's report, which was

graded abnormal, diagnosis of rotatory subluxation or fixation, or non-diagnostic. Medical records were reviewed and the clinical course was compared among the five subtypes.

RESULTS

We reviewed 47 CT scans in 35 patients, and the majority were performed without sedation. The average age was 7.7 years (4-14 years old) and associated conditions included minor trauma (20%), surgical procedures around the head and neck (29%), and Grisel's syndrome (20%). Twenty-six percent of our studies fell within the pathologic spectrum (5% type 1 or rotatory fixation, 21% types 2 and 3 or rotatory subluxation), while 45% were classified as muscular torticollis (45%) and 28% fell within the diagnostic grey zone. Seven radiologists interpreted these studies, and their interpretation was discordant in 45% of cases. Clinical resolution occurred in 27 of 29 cases for which follow-up was available. One of two patients with fixed rotatory subluxation required a C1-C2 arthrodesis.

CONCLUSION

The Pang and Li classification characterizes a spectrum of abnormalities in rotation to facilitate communication, although the indications for dynamic CT scan should be further defined.

Key words: Atlanto-axial rotatory subluxation; Atlanto-axial rotatory fixation; Dynamic rotational computed tomography; Atlanto-axial rotatory displacement

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Core tip: Atlantoaxial rotatory displacement represents a spectrum of pathology. We classified 47 computed tomography (CT) scans in 35 patients presenting with painful torticollis according to Pang and Li, and found that the radiologist's interpretation was discordant in 45%, suggesting the need to develop a common language with our imaging colleagues to accurately describe this pathology in the individual patient. Most patients resolved with non-operative treatment, although one of two with fixed rotatory subluxation required a fusion. As 74% were classified as muscular torticollis (45%) or fell within the diagnostic grey zone (28%), the indications for a dynamic CT scan should be revisited.

Spiegel D, Shrestha S, Sitoula P, Rendon N, Dormans J. Atlantoaxial rotatory displacement in children. *World J Orthop* 2017; 8(11): 836-845 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i11/836.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i11.836>

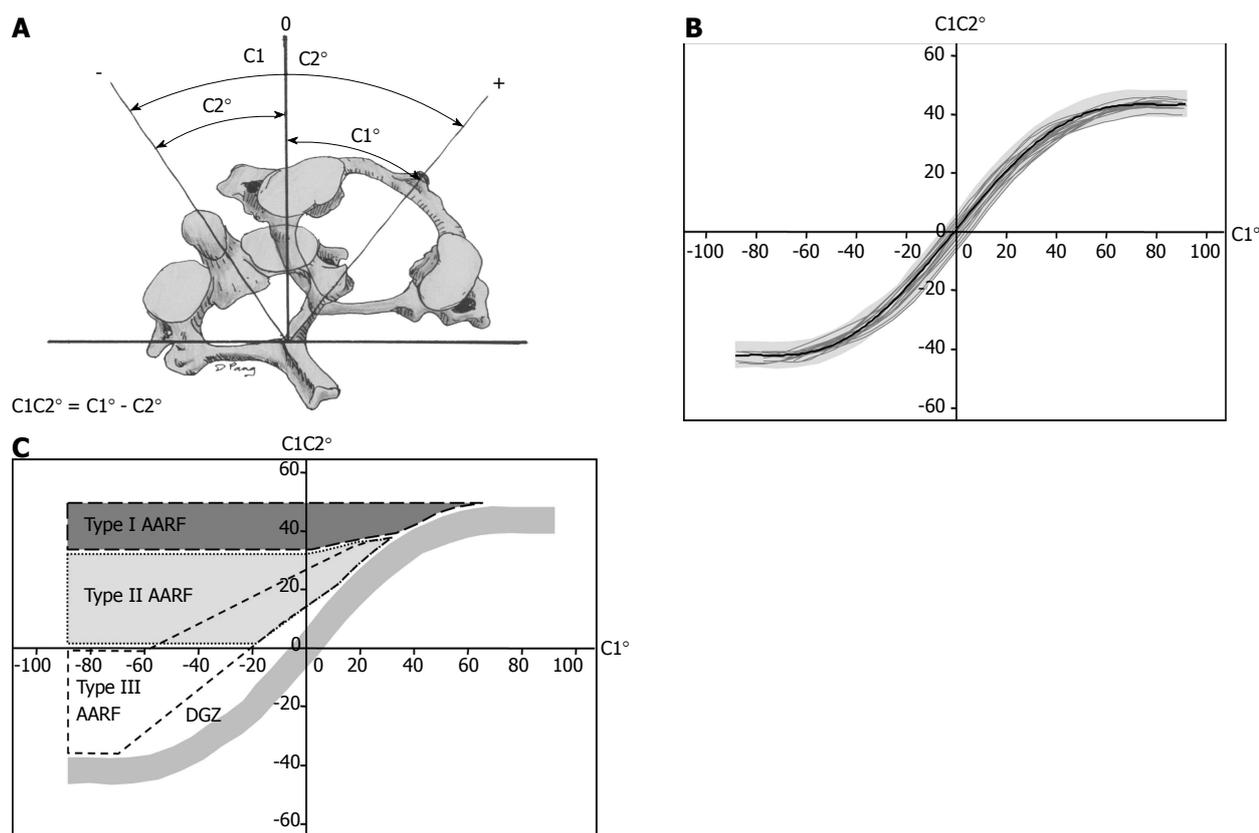
INTRODUCTION

A variety of terms have been used to describe a

spectrum of rotational abnormalities of the atlantoaxial joint observed in the absence of major trauma, most commonly atlantoaxial rotatory displacement, atlantoaxial rotatory subluxation (AARS) and atlanto-axial rotatory fixation (AARF)^[1-12]. This lack of uniformity in terminology reflects the challenges of capturing dynamic rotational abnormalities occurring within the physiologic range of motion. As a loss of contact between the facets at C1 and C2 of up to 85% occurs during the extremes of physiologic rotation, subluxation is a normal finding and "pathologic" cannot be defined by the relationships between C1 and C2 at any particular point within the arc of rotation^[13,14]. The dynamic computed tomography (CT) scan has been utilized to evaluate children presenting with a painful torticollis, although diagnostic imaging criteria have not been established. Pang and Li have developed a diagnostic approach in which measurements extracted from the dynamic rotational CT scan are plotted on a graph and compared with normative data^[5-7]. The goal of this retrospective radiographic and clinical review is to correlate the Pang and Li class with the clinical course in a consecutive series of patients presenting with painful torticollis.

MATERIALS AND METHODS

Pang and Li first defined normal composite rotational motion curves from dynamic rotational CT scans in 21 pediatric patients who had no signs or symptoms of atlanto-axial rotatory dysfunction (3 to 11.5 years of age)^[5]. For each position of cervical rotation, they first measure the angle between the vertical axis and the sagittal axis of the occiput, C1, and C2. They then plot the C1 angle (head position) on the X axis and the C1-C2 angle (angle of separation or divergence) on the Y axis (Figure 1A and B). They identified three distinct phases within the normal motion curve (Figure 1B). C1 rotates in isolation during the first or "single motion" phase (0°-23°), and from 24°-63° both C1 and C2 rotate at different rates increasing the angle of separation or divergence to a maximum of approximately 45°. Rotation beyond 63° occurs through the subaxial spine with no further divergence between C1 and C2. C1 normally crosses over C2 at the zero or null point. This normative data provides a template of how C1 and C2 relate throughout the range of head positions, and was compared with data from patients presenting with painful torticollis to develop a classification system (Figure 1C)^[6,7]. In patients with type I dynamics, C1 and C2 are locked (< 20% correction in separation angle through range of motion). This type might be referred to as AARF. In type II and type III there is a "pathologic stickiness" between C1 and C2; while mobility between C1 and C2 is preserved (> 20% correction in separation angle), C1 either does not (type II) or does (type III) cross over C2. Normal dynamics are observed in type 4 (muscular torticollis). In the type 5 or diagnostic grey zone, C1 crosses over C2 at a point between 8 and 20 degrees beyond the midline;



Figures 1 Classification by Pang and Li. A: Measurements from the dynamic CT scan include the angles between C1 and C2 relative to the vertical axis, and the C1C2 angle is then calculated. By convention, positive values are assigned to the presenting side (side to which the chin points at presentation of torticollis) and negative is assigned to the opposite side (corrected side). Normative data is depicted as motion curves in which the C1 angle is plotted against the C1C2 angle (1B), and the different classes are illustrated as shaded areas in (C) (Figure 1A reprinted with permission from Pang D, Li V. Atlanto-axial rotatory fixation: part 2—new diagnostic paradigm and a new classification based on motion analysis using computed tomographic imaging. *Neurosurgery* 2005; 57: 941-953. Figures 1B and C reprinted with permission from Pang D, Li V. Atlantoaxial rotatory fixation: Part 1-Biomechanics of normal rotation at the atlantoaxial joint in children. *Neurosurgery* 2004; 55: 614-625).

the authors feel that this may represent a transitional type of dynamics which may either revert to normal or progress to one of the more severe forms of the condition. For clinical applications, the authors obtain the CT scan with the patients head in a comfortable position (P or presenting position, side to which the chin is rotated), with the nose pointing straight upwards (P₀ or neutral position, partially corrected), and with the head rotated maximally to the opposite side (P₋, maximally corrected position). By convention all values towards the presenting side are positive, and towards the opposite or corrected side are negative (Figure 1A).

We searched the database from our radiology department to identify all patients who underwent a dynamic rotational CT scan over seven consecutive years since a digital imaging system became available. Approval from the Institutional Review Board was obtained. The imaging protocol involved 1.5 millimeter cuts between the occiput and C3 with the patient's shoulders flat and the head positioned at neutral, and with maximal voluntary rotation to the right and to the left. Digital calipers were used to measure the angle between the vertical axis and the sagittal axis of each bone (occiput, C1, and C2) at all three positions of cervical rotation (right, left, neutral). The angle of

divergence between C1 and C2 (C1-C2 angle) was also calculated for each position of rotation. Three observers evaluated each CT scan independently (PS, SS, DS), and the reviewed each study together and constructed the graphs which were compared with the normative template provided by Pang and Li (types I - III = abnormal or within spectrum of AARS), type 4 = normal, type 5 = Diagnostic Grey Zone) (Figure 1B and 2). We reviewed the radiologist's interpretation, which we graded as (1) positive (diagnosed as AARS or AARF); (2) negative; or (3) non-diagnostic.

We then reviewed each patient's medical records with regard to age, gender, potential associations (minor trauma, inflammatory conditions, recent surgery around the head or neck), delay from symptom onset to presentation, treatment prior to referral, treatment course including immobilization, and outcomes (resolved, persisted, recurrent). We correlated the patient's overall treatment course and outcomes for each of the 5 types. Patients who were imaged more than once were grouped according to their most severe type.

RESULTS

We reviewed 47 CT scans in 35 patients, and only

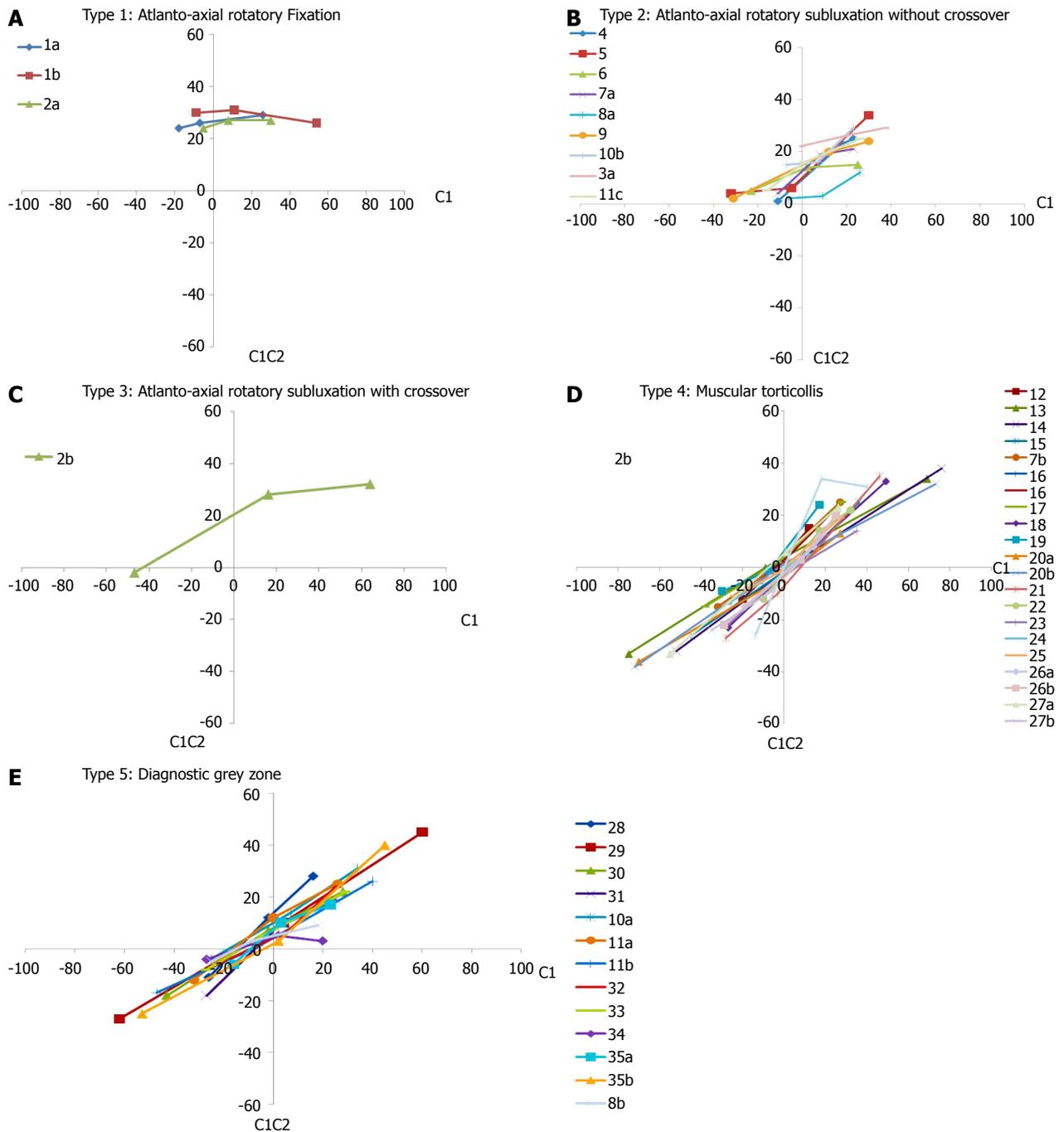


Figure 2 Atlanto-axial rotatory subluxation and fixation. A: Type 1 (fixation). Three studies (two patients) could be classified as a fixed rotatory subluxation, in which there was less than 20% correction of the C1C2 angle on maximal rotation to the opposite side; B: Type 2 (pathologic stickiness without crossover). Eight studies illustrated an improvement in the angle of divergence of more than 20%, but C1 did not cross over C2; C: Type 3 (pathologic stickiness with crossover). In three studies there was improvement in the C1C2 angle and C1 did cross over C1, but well beyond the null point or midline; D: Type 4 (normal dynamics, muscular torticollis). Twenty-one of our studies exhibited normal dynamic curves and could be classified as muscular torticollis; E: Type 5 (diagnostic grey zone). Ten studies fell into the diagnostic grey zone. In these cases the C1 crossover was delayed and occurred at 8°-20° beyond the midline or null point.

26% (12/47) of our studies fell within the pathologic spectrum from rotatory subluxation (21% types 2 and 3) to rotatory fixation (5% type I) (Table 1). Forty-five percent fell within the physiologic range (muscular torticollis), and 28% were in the diagnostic grey zone. Ten of our patients were imaged more than once. Normal dynamics was observed in two separate studies in 3 patients. One follow-up study demonstrated

restoration of normal dynamics, and improvement was observed in 3 cases (type 1-3, type 2-4, type 2-5). There was either no change or progression to a higher class in 3 cases. A single patient had 3 studies performed, and while the first two were classified in the diagnostic grey zone, the third demonstrated type II dynamics. Two of these studies were performed with sedation, and a third in the operating room under

Table 1 Radiographic findings (n = 47)

Pt. #	Rotation	Presenting position (P) (maximum rotation towards presenting side)				Neutral (Po) (partially corrected position)				Corrected position (P-) (best corrected position)				% Correction	Pang class	Rad int	Radiologist
		Oc	C1	C2	C1C2	Oc	C1	C2	C1C2	Oc	C1	C2	C1C2				
1a	R	30	26	-3	29	-1	-7	-31	26	-22	-18	-42	24	17%	1	Yes	4
1b	L	45	54	31	26	13	11	-20	31	-23	-9	-39	30	15%	1	Yes	1
2a	L	17	30	-3	27	-3	8	-21	27	-15	-5	-29	24	11%	1	ND	1
3a	L	38	37	8	29	20	19	-7	26	-2	-1	-23	22	24%	2	Yes	3
4	L	24	23	-2	25	16	18	-5	23	-10	-11	-12	1	96%	2	Yes	2
5	L	29	30	-4	34	4	-5	-11	6	-30	-32	-36	4	88%	2	ND	7
6	L	23	25	10	15	2	2	-12	14	-20	-23	-28	5	66%	2	No	1
7a	R	18	23	2	21	-2	8	-11	19	-19	-11	-15	4	81%	2	Yes	2
8a	R	25	26	14	12	7	9	6	3	-3	-6	-8	2	83%	2	ND	7
9	L	24	30	6	24	4	12	-8	20	-34	-31	-33	2	92%	2	No	3
10b	R	16	23	-6	29	-4	7	-9	16	-22	-7	-22	15	91%	2	Yes	2
11c	L	21	26	1	25	-7	1	-15	16	-25	-16	-21	5	NA	2	Yes	5
2b	L	53	64	32	32	-2	16	-12	28	-61	-47	-45	-2	NA	3	Yes	1
12	L	10	12	-3	15	-2	-4	-4	0	-13	-20	-8	-12	NA	4	No	1
13	L	67	69	35	34	-6	-9	-9	0	-80	-75	-42	-33	NA	4	No	2
14	R	73	76	38	38	2	11	6	5	-58	-52	-20	-32	NA	4	No	1
15	R	34	36	11	25	8	10	6	4	-48	-45	-19	-26	NA	4	No	7
7b	R	27	27	2	25	-10	-10	-7	-3	-30	-32	-17	-15	NA	4	Yes	1
16	R	22	23	2	21	-1	-1	-3	2	-20	-18	-9	-9	NA	4	ND	7
17	R	33	28	3	25	-1	-3	-5	2	-38	-38	-23	-15	NA	4	ND	4
18	R	44	49	16	33	5	10	5	5	-33	-27	-4	-23	NA	4	No	5
19	R	18	17	-7	24	-7	-7	-6	-1	-28	-30	-21	-9	NA	4	No	1
20a	L	24	27	14	13	-6	-1	3	-4	-71	-70	-34	-36	NA	4	ND	3
20b	L	76	73	41	32	-5	1	3	2	-71	-72	-34	-38	NA	4	No	1
21	R	47	46	11	35	-2	-3	7	-10	-29	-28	-1	-27	NA	4	No	2
22	L	20	32	10	22	8	17	6	14	-20	-10	2	-12	NA	4	ND	3
23	L	32	35	21	14	-1	-1	2	-3	-28	-27	-5	-22	NA	4	No	2
24	L	9	11	6	5	9	-12	-6	-6	-22	-27	-13	-14	NA	4	No	7
25	L	27	27	24	19	5	-3	-1	-2	-20	-24	-13	-11	NA	4	No	1
26a	L	15	17	5	12	15	14	6	8	-21	-19	-4	-15	NA	4	ND	7
26b	L	23	25	5	20	7	8	5	3	-29	-29	-7	-22	NA	4	ND	3
27a	L	27	26	3	23	1	1	-5	6	-64	-55	-22	-33	NA	4	ND	1
27b	L	24	20	7	13	-3	-6	3	-9	-30	-35	-11	-24	NA	4	No	3
3b	R	37	40	9	31	16	18	-16	34	-12	-14	12	-26	NA	4	Yes	3
8b	L	18	18	12	9	-6	-9	-12	3	-21	-25	-20	-5	NA	5	ND	5
28	R	18	16	-12	28	1	-2	-14	12	-23	-26	-15	-11	NA	5	No	1
29	L	66	60	16	45	1	4	-6	10	-69	-62	-35	-27	NA	5	No	2
30	R	31	28	6	22	-3	-2	-9	7	-42	-43	-25	-18	NA	5	No	1
31	L	23	25	6	19	3	1	-7	8	-20	-27	-9	-18	NA	5	Yes	2
10a	R	30	34	3	31	-2	7	-7	14	-29	-25	-21	-4	NA	5	Yes	2
11a	L	21	26	1	25	7	0	-12	12	-34	-32	-20	-12	NA	5	Yes	1
11b	L	33	40	14	26	-6	-6	-7	1	-62	-47	-30	-17	NA	5	Yes	6
32	R	25	25	1	24	2	6	-13	7	-25	-27	-19	-8	NA	5	No	3
33	R	29	29	7	22	-2	-4	-9	5	-27	-27	-19	-8	NA	5	No	7
34	L	22	20	23	3	3	2	-3	5	-29	-27	-23	-4	NA	5	No	7
35a	L	21	23	6	17	4	3	-7	10	-18	-16	-12	-6	NA	5	Yes	2
35b	L	41	45	5	40	-1	2	-1	3	-50	-53	-18	-25	NA	5	Yes	1

A variety of data was collected from the imaging studies including patient number, presenting side, measurement angles (occipital, C1, C2, C1C2) for the presenting position, neutral position, and corrected positions, as well as the percentage of correction in divergence angle for types II and III, the type according to Pang and Li, the radiologist's interpretation (Yes, No, Non-diagnostic) and the radiologist who evaluated each study (1-7). For the radiologists interpretation; Yes: AARF; No: Normal or muscular torticollis; ND: No clear diagnosis established; NA: Not applicable.

general anesthesia.

Seven radiologists interpreted these studies. For studies classified as types 1 through 3, the radiologist's interpretation was concordant in 8/13 (62%) (Table 1). Two of the other 5 studies were read as normal and three were non-diagnostic. In the 21 studies graded as type 4 (normal or muscular torticollis), 12 (57%) were read as normal and of the remaining 9 (43%)

were read as AARF (2) or non-diagnostic (7). For those studies in the diagnostic grey zone (type 5), the radiologists interpreted 46% (6/13) as normal, 46% (6/13) as AARF, and 8% (1/13) as non-diagnostic.

Our study population included 19 females and 16 males, and the average age was 7.7 years (range 4-14 years). All patients had neck pain, torticollis, and a normal neurologic examination. Associated conditions

Table 2 Associated conditions

Associations	Pang class and associations	
Minor trauma (7)	I	Minor trauma (2)
ENT or craniofacial procedures (10)	II	Craniofacial procedures (3) ENT procedures (3) Grisels (1) Unknown (2)
Grisels (7)	III	Minor trauma (1)
Unknown (8)	IV	Unknown (6) ENT procedures (3) Grisels (3) Minor trauma (3) Occipital condyle fracture (1)
Occipital condyle fracture (1)	V	Grisels (3) ENT procedures (2)
Down syndrome (1)		Minor trauma (2) Unknown (1)
Congenital muscular torticollis (1)		Down syndrome (1)

The conditions associated with the painful torticollis are illustrated on the left side, and on the right side these associations are grouped according to the Pang and Li type.

are listed in Table 2, and included minor trauma (20%), craniofacial or ENT procedures (29%), and Grisel syndrome (20%). Sufficient clinical information could be retrieved for 29 of 35 patients (Table 3). The time from the onset of symptoms to presentation ranged from three days to five months, and seven of the patients were treated by a variety of methods prior to referral to our orthopaedic service. Three patients were evaluated in our emergency room and were never seen by orthopaedics, while two others were seen once as outpatients for a second opinion. Patients having more than one study are grouped according to their highest grade of involvement.

Two patients were classified as having type 1 dynamics, or a true fixed rotatory subluxation. The first presented after 6 mo of previous treatment with skin traction, skeletal traction and bracing. Reduction was achieved with skeletal traction, but could not be maintained, and a C1-C2 arthrodesis was required. The second patient presented one month after the onset of symptoms and failed two courses of skin traction and bracing, during which her dynamics had improved from type I to type III. She was then treated by skeletal traction, and ultimately reduced and was managed in a pinless halo for 3 mo. She remains asymptomatic at more than 3 years follow-up.

Nine patients had type II (8) or type III (1) dynamics, five of whom were scanned more than once. Six were admitted for soft cervical traction (4-14 d) and then immobilized in a soft collar, hard collar, or pinless halo for an additional 2-8 wk. Two were managed with a soft collar and oral medications. While follow-up was limited, resolution was observed in eight patients. A single patient had persistent and intermittent symptoms, and initially had two studies that were in the diagnostic grey zone, and the third had demonstrated progression to a type II rotatory subluxation.

Sixteen patients exhibited normal dynamics (type 4, muscular torticollis). Four were never evaluated by orthopaedics, and two were seen once for an outpatient consultation. All but one of the remaining patients had clinically resolved at one to twenty weeks follow-up. Four patients were admitted for soft cervical traction, and seven were managed by nonsteroidal anti-inflammatory medications with or without a soft or hard cervical collar, or by physical therapy. A single patient with a history of congenital muscular torticollis and an acute episode of pain was treated by a bipolar sternocleidomastoid release once symptoms had abated.

Eight patients fell within the diagnostic grey zone (type 5). Five patients were effectively treated by soft cervical traction (2-10 d), with no relapse at two to twenty weeks follow-up. Of three patients treated by a soft collar and analgesics, one had resolved at 8 wk follow-up and records could not be obtained for the other two. Due to behavioral issues, a single patient with Down syndrome could not be imaged at presentation, and could not be maintained in halter traction despite oral sedation and analgesics. The decision was made to perform a dynamic rotational CT scan under anesthesia using the O-arm, and the diagnosis was muscular torticollis. The torticollis resolved with immobilization and physical therapy, and has not recurred at more than 2 years follow-up.

DISCUSSION

The terms atlanto-axial rotatory displacement (AARD), subluxation (AARS), and fixation (AARF) have all been used to describe a spectrum of rotational abnormalities of the atlanto-axial joint observed in the absence of major trauma^[1-12]. Associated conditions include minor trauma^[1,15], inflammatory disorders (Grisel syndrome)^[3,16,17], or surgical procedures on the head or neck^[6,7,17-20]. Predisposing factors may include anatomic features (horizontal facet orientation, facets shaped like biconvex discs, joint hypermobility), mechanical loading (intraoperative positioning, loss of normal muscle tone during general anesthesia), and physiologic factors (hyperemia from infection or inflammation) associated with increased mobility. Anatomic barriers to achieving reduction include inflamed synovial and/or capsular tissues^[1,2,10] or abnormalities of a meniscus like synovial fold at the periphery of the joint (inflammation, rupture, in-folding)^[21]. Pathologic findings identified in chronic cases include contracture of periarticular soft tissues, interposition of fibrous tissue, osseous cross union, and adaptive changes in facet morphology^[1,7,15,22-24]. A timely diagnosis is critical, and the results following treatment are less predictable when the condition presents at a subacute (> 1 mo) or chronic stage^[1,7], recurs, or presents with a fixed subluxation between C1 and C2^[7].

Normal cervical rotation is approximately 70°-80° to each side in both children and adults^[13,14], and the maximum divergence between C1 and C2 during

Table 3 Clinical findings

Pt #	Pang	Age	Gen	History	Delay to initial presentation	Prior treatment	1° Rx.	Dur Results (d)	2° Rx.	Dur Results (d)	3° Rx.	Dur (wk)	Outcome	Immobilization	FU (wk)	Final results
1	1,1	8	F	Fell backwards while walking	3 wk initial, referred after 6 mo	3, 5	5	14	3	6	1			PH × 6 wk, SC × 1 wk	108	1
2	1,3	8	F	Shaking water from ear	4 wk	3, PT	4	7	3	4	3	5	3	PH × 3 mo	150	1
3	2,4	7	M	Goldenhar syndrome, ear reconstruction	7 d	None	4	8	1	-	-	-	-	PH × 4 wk	NR	1
4	2	6	F	Crouzon syndrome, midfacial advancement	None	None	4	10	1	-	-	-	-	PH × 4 wk	2	1
5	2	10	F	Pharyngitis	7 d	None	4	14	1	-	-	-	-	PH × 2 mo	6	1
6	2	7	M	Awakened with stiff neck	10 d	None	4	3	2	4	2	-	-	None	2	1
7	2,4	13	F	ADN	7 d	None	4	7	1	-	-	-	-	HC × 6 wk	2	1
8	2,5	7	M	Tonsillectomy/ADN, Klippel-Feil	5 d	None	4	7	1	-	-	-	-	SC	2	1
9	2	8	F	Tonsillectomy/ADN	4 d	None	1	10	2	NR	2	NR	NR	SC	1.5	1
10	5,2	5	M	Goldenhar Syndrome, Hemifacial microsomia. 2 episodes S/P mandibular reconstruction and zygoma and mandible reconstruction	4 d	None	4,4	4,5	1	-	-	-	-	PH × 4 wk, HC × 3 wk		1
11	5,5,	9	M	Neck pain	Unknown	None	4	5	3	-	-	-	-	PH × 3 wk	18	3
12	4	6	M	Unknown	Unknown	None	1	-	-	-	-	-	-	-	-	No Ortho
13	4	5	M	Unknown	4-5 mo	None	Outpatient consult	-	-	-	-	-	-	None	NA	1
14	4	6	F	Scarlet fever	6 wk	6 wk of oral antibiotics	Outpatient consult	-	-	-	-	-	-	-	NA	1
15	4	6	M	Unknown	ER	None	1	-	-	-	-	-	-	-	-	No Ortho
16	4	8	M	Unknown	ER	None	3	-	-	-	-	-	-	PH × 8 wk	-	No Ortho
17	4	9	M	All terrain vehicle injury, occipital condyle fracture	None	None	1	1	-	-	-	-	-	-	20	1
18	4	6	F	Cervical lymphadenitis	None	2	4	-	-	-	-	-	-	HC × 1 wk	1	1
19	4	5	F	Congenital muscular torticollis	1 mo	Torticollis sx at 1.5 yr of age	Bipolar Release	-	1	-	-	-	-	-	-	-
20	4,4	12	F	Retropharyngeal abscess	3-4 d	None	4	10	1	-	-	-	-	SC × 2 wk	3	1
21	4	6	M	Throwing ball	2 wk	4	4	14	2	-	7	2	2	Persistent	1	1
22	4	9	F	Unknown	None	None	PT	-03/17/003	-	-	-	-	-	Recurrence	18	-
23	4	7	F	Choanal Atresia repair, ADN	2 d	2	1	2	2	4	-	-	-	CTO × 6 wk	9	1
24	4	8	M	Wrestling	None	None	3	-	-	-	-	-	-	HC	-	No FU
25	4	10	M	ADN	None	None	3	-	-	-	-	-	-	-	-	-
26	4,4	8	F	Minor trauma doing handstand	None	None	4	5	1	-	-	-	-	-	18	1
27	4,4	4	F	None	NA	None	3 PT	2	1	-	-	-	-	SC × 2 wk	2	1
28	5	12	F	Turning head during sleep	1 d	None	3	-	-	-	-	-	-	-	-	No FU
29	5	14	F	Down syndrome	None	None	4	10	2	-	-	-	-	PH × 6 wk/SC, PT	8	1

30	5	6	F	ADN	3-4 d	None	4	2	1	-	-	-	SC × 3 wk, PT	8	1
31	5	5	F	Pharyngitis	3-4 d	None	3	-	1	-	-	-	SC × 2 wk	8	1
32	5	7	M	Lymphadenitis	4 wk	PT	4	7	1	-	-	-	HC × 6 wk	20	1
33	5	6	6	ADN	None	None	4	3	1	-	-	-	HC × 6 wk, PT	6	1
34	5	6	F	Serving tennis	4 wk	None	3	10	1	-	-	-	-	1.5	No FU
35	5	9	M	URI	2 d	None	4	7	3	4	3	1	PH × 8 wk	10	1

All patients had neck pain, torticollis, and a normal neurologic examination. Clinical information includes age, gender, historical features, delay to presentation, previous treatment, treatment course and duration, immobilization, results and follow-up. Delay: Time from symptoms to evaluation in days; HC: Hard cervical collar; SC: Soft cervical collar; CTO: Cervicothoracic orthosis; PT: Physical therapy; AND: Adenoidectomy; URI: Upper respiratory infection; Treatment: 1: Analgesic with or without an antibiotic; 2: Analgesic, muscle relaxant, with or without an antibiotic; 3: Soft or hard collar; analgesic, muscle relaxant with or without an antibiotic; 4: Admission, skin traction, analgesics, muscle relaxant; 5: Skeletal traction; 6: C1-C2 arthrodesis; Results of treatment: 1: Resolved; 2: Persistent; 3: Relapse; Final results: 1: Asymptomatic, normal activities; 2: Persistent tilt, no pain, no other symptoms; 3: Persistent torticollis, pain and/or other symptoms.

normal rotation to either side ranges from 29° to 45°^[5,13,25,26]. As a loss of contact between the C1 and C2 facets of up to 85% occurs at the extremes of physiologic rotation, subluxation is a normal finding during rotation^[13,14]. This has led to the use of a dynamic CT scan as a diagnostic modality^[5,7,9,26-28], although diagnostic criteria have yet to be established. Important concerns include how C1 and C2 move relative to one another throughout the arc of rotation (C1-C2 angle or angle of separation) and whether C1 crosses over C2. Mönckeberg *et al.*^[14] suggested that an angle of separation of less than 36° coupled with facet uncoverage of less than 60% were sufficient for a diagnosis. McGuire *et al.*^[27] recognized that both the separation angle and crossover of C1 were important, and attempted to classify patients as follows: I (normal), II (< 15° of separation between C1 and C2, C1 crosses over C2), and III (C1-C2 angle is fixed or C1 does not cross over C2). In contrast, several studies have questioned the value of dynamic CT scans. Hicazi *et al.*^[28] found no significant difference between the presenting and corrected sides in atlantoaxial rotation, the atlanto-dens interval, or

the center of rotation. Alanay *et al.*^[29] found that both the intra-observer and inter-observer reliability were poor.

Pang and Li have developed a classification scheme relative to normative data, encompassing a spectrum from AARF (type I), through "pathologic stickiness" (types 2 and 3), and finally to muscular torticollis (type 4)^[5-7]. They also defined a diagnostic grey zone in which dynamics may presumably return to normal or progress to one of the more severe forms of the condition. Recognizing the limitations of this retrospective review, our impression is that the classification adequately describes the spectrum of pathology, although it is clear that there was discordance with the radiologist's interpretation in many cases.

Several technical points are worth mentioning. Care should be taken to ensure that the patient's shoulders remain flat in the scanner to avoid a false positive result (rotation occurs through trunk rather than cervical spine). It is also prudent to remove the metal arc from the head frame, as this may restrict the active or passive range of cervical rotation. As rotation may also be limited by pain or muscle spasm, some have suggested that the study be performed under sedation, or even general anaesthesia^[11,14]. While the 3 data points required to construct a line for the graph can be obtained even with a relatively limited arc of motion, it is possible for example that with greater rotation towards the corrected side, that a patient with type II dynamics could achieve cross over and be classified as type III.

Only 26% of studies in our series fell within the pathologic spectrum (types I - III), including just two cases of fixed rotatory subluxation, calling into question the indications for obtaining a dynamic CT scan. A number of these were obtained in the emergency room prior to orthopaedic consultation. Recognizing that an early diagnosis improves outcomes, consideration could be given to empiric treatment for patients presenting within several days of symptom onset with characteristic signs and symptoms of atlanto-axial rotatory pathology, reserving the dynamic CT scan for those failing initial management and/or those presenting in a delayed fashion. Although detailed follow-up information was mainly available for those patients with a greater severity of involvement, the majority of patients resolved with non-operative treatment measures. The two patients with a fixed rotatory subluxation had a protracted course, one of whom presented after 6 mo of previous treatment and ultimately required an arthrodesis. The second responded after three courses of traction and 3 mo of additional immobilization in a pinless halo. For patients with type II or type III dynamics, all but one resolved with treatment. One patient has relapsed on two occasions but has responded to symptomatic treatment, however the long-term prognosis remains uncertain. We found that all but two patients with normal dynamics or who were classified as being in the diagnostic grey zone resolved clinically, and records were

unavailable for the other two. These clinical observations are consistent with a majority of studies^[8,16,18,20,27-31].

There are several limitations of this study to be discussed, including the fact that the intra and inter-observer reliability of this scheme has not been reported. We attempted to minimize variations by having each study graded by three examiners, who then reviewed each study together prior to assigning a final class. From a technical standpoint, our scans were obtained in neutral and maximal voluntary rotation to the right and left, in contrast to Pang and Li who obtain their studies at the position of comfort (rotated to right or left), neutral, and toward the opposite or corrected side. Our angle of rotation towards the presenting side might be slightly greater than their "presenting" position, altering one data point on the graph. While our angle of divergence might be slightly greater for the "presenting" side, this should have minimal if any impact on classification. Our follow-up period was limited for all but the most severe cases, and we cannot provide a detailed quantitative assessment of cervical range of motion or of clinical outcomes. Our impression supports previous studies in suggesting that the vast majority of cases resolve without chronic residua. We have not routinely obtained dynamic CT scans after clinical resolution, and cannot prove that normal dynamics were restored in patients who resolved clinically. Persistent abnormalities in rotatory dynamics may be compensated for by an increase in motion at the occiput-C1 articulation or through the subaxial spine.

COMMENTS

Background

Atlantoaxial rotatory displacement represents a spectrum of rotational malalignment between C1 and C2, and Pang and Li have described a classification scheme which explains this spectrum, based on dynamic computed tomography (CT) imaging. The authors classified a group of patients presenting with painful torticollis according to Pang and Li and compared findings with the interpretation by the authors' radiologists and with each patient's clinical course.

Research frontiers

There is limited information in the literature on atlantoaxial rotatory displacement, and a variety of terms have been utilized to describe the condition, suggesting that there is a need for a common language to describe the pathology.

Innovations and breakthroughs

There are few studies concerning the Pang and Li classification, and while this classification is able to capture a spectrum of pathology, it has not achieved wide clinical use to our knowledge. The authors sought to determine whether the Pang and Li class correlated with our radiologist's interpretation of dynamic rotational CT scans.

Applications

The Pang and Li classification has practical applications and may be used by the clinician to characterize the findings on a dynamic CT scan. The findings allow the clinician to be more specific in articulating the nature of the pathology.

Terminology

Atlantoaxial rotatory displacement: Abnormal relationship between C1 and C2 in the axial plane in which there may or may not be mobility between the two

segments; Atlantoaxial rotatory subluxation: abnormal relationship between C1 and C2 in the axial plane in which there is mobility between the two vertebrae; Atlantoaxial rotatory fixation: fixed abnormal relationship between C1 and C2 in the axial plane.

Peer-review

The current study focused on an original issue. It is well-organized.

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Randomized Controlled Trial

Hypothenar fat pad flap vs conventional open release in primary carpal tunnel syndrome: A randomized controlled trial

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Abstract**AIM**

To compared outcomes between the hypothenar fat pad flap (HTFPF) and conventional open carpal tunnel release (COR) in primary carpal tunnel syndrome (CTS).

METHODS

Forty-five patients (49 hands) were enrolled into the study from January 2014 to March 2016, 8 patients were excluded. Randomization was conducted in 37 patients (41 hands) by computer generated (Block of four randomization) into COR and HTFPF group. Nerve conduction study (NCS) included distal sensory latency (DSL), distal motor latency (DML), sensory amplitude

(S-amp), motor amplitude (M-amp) and sensory nerve conduction velocity (SCV) were examined at 6 and 12 wk after CTR. Levine score, grip and pinch strength, pain [visual analog scale (VAS)], 2-point discrimination (2-PD), Semmes-Weinstein monofilament test (SWM), Phalen test and Tinel's sign were evaluated in order to compare treatment outcomes.

RESULTS

The COR group, 19 patients (20 hands) mean age 50.4 years. The HTFPF group, 20 patients (21 hands) mean age 53.3 years. Finally 33 patients (36 hands) were analysed, 5 patients were loss follow-up, 17 hands in COR and 19 hands in HTFPF group. NCS revealed significant difference of DSL in HTFPF group at 6 wk ($P < 0.05$) compared with the COR group. S-amp was significant improved postoperatively in both groups ($P < 0.05$) but not significant difference between two groups. No significant difference of DML, M-amp and SCV postoperatively in both groups and between two groups. Levine score, pain (VAS), grip and pinch strength, 2-PD, SWM, Phalen test and Tinel's sign were improved postoperatively in both groups, but there was no significant difference between two groups.

CONCLUSION

There is no advantage outcome in primary CTS for having additional HTFPF procedure in CTR. COR is still the standard treatment. Nevertheless, improvement of DSL and S-amp could be observed at 6 wk postoperatively.

Key words: Hypothenar fat pad flap; Randomized controlled trial; Carpal tunnel release; Carpal tunnel syndrome; Nerve conduction study

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Core tip: The study conducted a randomized controlled trial to compare between the hypothenar fat pad flap additional and conventional open carpal tunnel release in primary carpal tunnel syndrome. The study showed no advantage, however improvement of nerve conduction study was observed in the early postoperatively.

Kanchanathepsak T, Wairojanakul W, Phakdepiboon T, Suppaphol S, Watcharananan I, Tawonsawatruk T. Hypothenar fat pad flap vs conventional open release in primary carpal tunnel syndrome: A randomized controlled trial. *World J Orthop* 2017; 8(11): 846-852 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i11/846.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i11.846>

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common compression neuropathy in the upper extremity^[1]. The worldwide incidence is 5.8% in women and 0.6% in

men^[2], while the pathology and the causes are unclear. Several studies describe that the symptoms caused by direct nerve compression and nerve ischemia^[3,4].

Fullerton^[4] found that the numbness symptom of CTS may arise from the nerve ischemia. The median nerve ischemia alters axonal threshold and significantly increases both sensory and motor refractoriness resulting numbness and paresthesia in CTS patients^[3]. Furthermore, the nerve ischemia may cause by venous return obstruction due to external pressure that increases pressure in the region of entrapment, leading to nerve edema and eventually resulting in nerve damage and fibrous tissue^[5,6] and also can be provoked by ganglia, neoplastic masses, vascular abnormalities, ligamentous attachments, and also different various structures (anomalous muscles, bifid median nerve, persistent median artery)^[7].

Carpal tunnel release (CTR) is a standard treatment for patients who indicated to surgery of CTS and the success rate was 75%-98%. However, several studies^[8] found that some patients who had persist or recurrent compressive symptoms after this surgery was as high as 2%-25%. Nancollas *et al*^[9], a retrospective review of 60 cases with an average of 5.5 years follow-up, had reported 57% recurrent symptoms within 2 years after surgery.

The hypothenar fat pad flap (HTFPF) procedure, first described by Cramer and refined by Strickland *et al*^[10] is usually utilized in recurrent CTS, there is a adipose tissue from hypothenar eminence as a pedicle flap to cover the median nerve that provides vascularity, enhance nerve gliding property and prevent adhesion to the median nerve. This procedure had an excellent result and low rate of complication^[8,10,12]. We hypothesized that increasing vascularity to the median nerve by HTFPF procedure could improve the nerve recovery and the success rate of CTR in primary CTS compared to the conventional CTR alone.

MATERIALS AND METHODS

Forty-five patients (49 hands) who diagnosed with primary carpal tunnel syndrome were enrolled into the study during January 2014 and March 2016 while 8 of them were excluded from the study. Thirty-seven patients (41 hands) were conducted in this prospective randomized controlled trial study according to consort diagram (Figure 1). The study was approved by the local institutional review board and all patients signed an informed consent.

The inclusion criteria were primary idiopathic carpal tunnel syndrome, age 20-60 years, duration of symptoms at least 3 mo and no improvement of symptoms after conservative treatment. The exclusion criteria were previous CTR or trauma in affected hand, history of steroid injection, cerebrovascular disease, cervical radiculopathy, combined other nerve compression, diabetes mellitus, cognitive impairment and unwilling to participate.

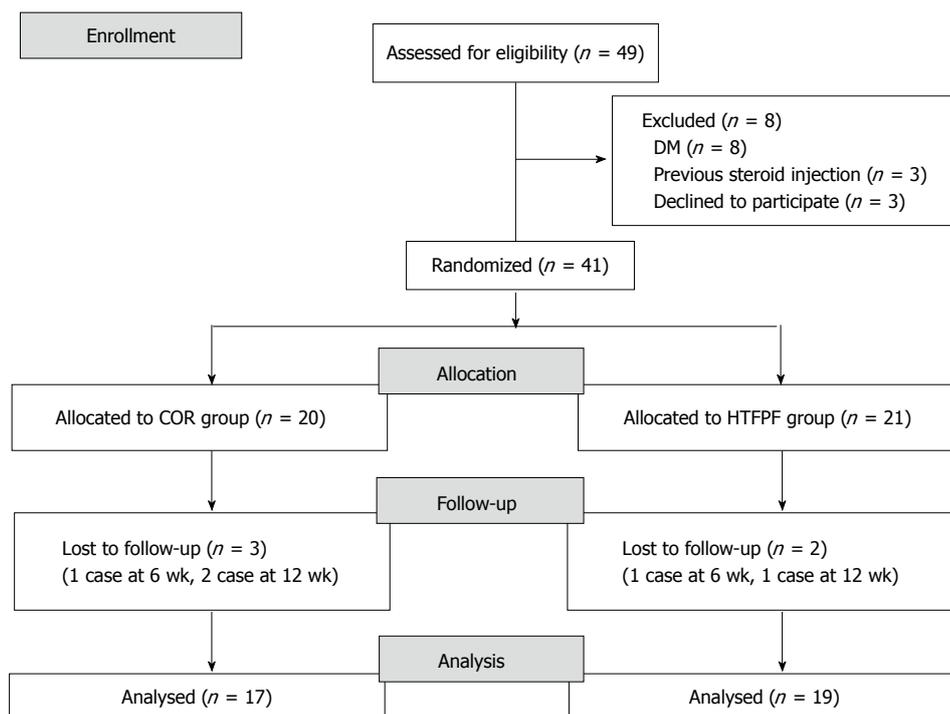


Figure 1 Consort flow diagram showed the randomization process. COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

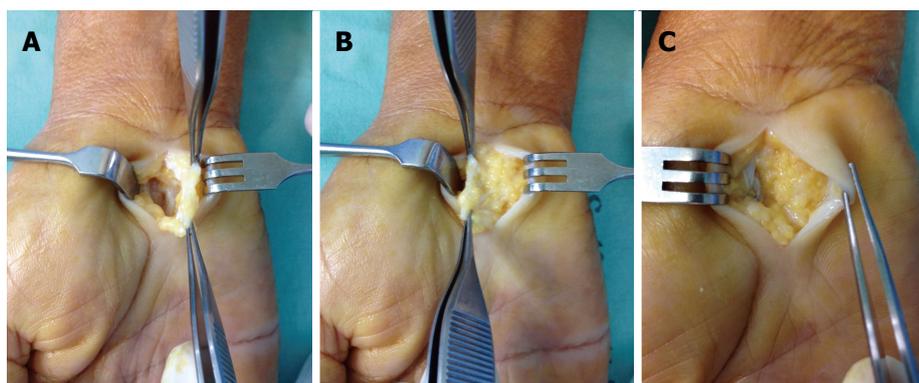


Figure 2 Transverse carpal ligament was exposed. A: Dissecting the hypothenar fat pad after complete released of transverse carpal ligament (TCL); B: Harvested hypothenar fat pad flap (HTFPF) was prepared to cover the median nerve; C: HTFPF was sutured to radial half of TCL remnant and covered the median nerve.

Patients were randomized into either conventional open carpal tunnel release group (COR) or HTFPF group by using a computer generated table, STATA 12.0, Statacorp, college station, TX, United States (Block of four randomization) and concealed with sealed envelopes which were opened during the operation after transverse carpal ligament was released. All of the patients and assessors in this study were blinded after the interventions assignment.

Surgical technique

The only one senior hand surgeon performed CTR throughout the study. All patients were injected with 1% lidocaine without adrenaline for local anesthesia. A tourniquet was inflated 250 mmHg. Longitudinal skin incision was made from distal to the distal wrist

flexion crease and 5 mm ulnar to thenar crease along the Kaplan’s line about 3 cm in length. Subcutaneous tissue and palmar fascia were dissected and retracted by Ragnel retractors. The transverse carpal ligament (TCL) was exposed and released by Stevens tenotomy scissors until clearly identified the median nerve (Figure 2A).

The concealed envelopes were opened to allocate the group of patients. In COR group, normal saline was irrigated and skin sutured with nylon no 5-0. In HTFPF group, superficial dissection at hypothenar fat was performed deep to palmaris brevis muscle and care should be taken to avoid digital nerve injury of ring and small fingers. The hypothenar fat pad with its vascular from ulnar artery was harvested (Figure 2B) then sutured HTFPF to radial half of TCL remnant

Table 1 Demographics data of conventional open carpal tunnel release and hypothenar fat pad flap groups

	COR group (n = 17)	HTFPF group (n = 19)	P value
Age (yr) mean ± SD	50.4 (1.5)	53.3 (1.5)	0.182
Gender (%)			0.231
Male	0 (0)	2 (11)	
Female	17 (100)	17 (89)	
Body mass index mean ± SD	28.4 (1.3)	25.5 (0.9)	0.064
Hand dominant (%)			1
Right	15 (88)	17 (90)	
Left	2 (12)	2 (10)	
Side of operation (%)			0.017
Right	6 (35)	15 (79)	
Left	11 (65)	4 (21)	
Onset of duration mo mean ± SD	11.8 (2.3)	13.3 (2.5)	0.675

COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

with absorbable suture material for coverage over the median nerve (Figure 2C). Normal saline was irrigated and skin was sutured with nylon no 5-0. Wound dressing was applied in both groups.

All of patients were followed up 6 and 12 wk after surgery and nerve conduction study (NCS), physical examination, pain [visual analog scale (VAS)], symptom severity scale and functional status scale (Boston questionnaire) were recorded at each visit. Sutured was removed 2 wk after surgery in all patients.

Study factors and measurements

The primary outcome was NCS including distal sensory latency (DSL), sensory amplitude (S-amp), distal motor latency (DML), motor amplitude (M-amp) and sensory conduction velocity (SCV). Self-administered questionnaire described by Levine *et al*^[13], which also known as Boston questionnaire was used to evaluate the hand function. Boston questionnaire consists of symptom severity scale (SSS) which includes 11 questions which each answer score from 1 (best) to 5 (worst), making a total score of 55 and functional status scale (FSS) which includes 8 questions which each answer score from 1 (best) to 5 (worst), making total score 40.

Age, gender, body mass index (BMI), onset of duration, side of operation and hand dominant were collected. Pain (visual analog scale, VAS), Tinel's sign, Phalen test, grip strength, pinch strength, 2-point discrimination (2-PD), Semmes-Weinstein monofilament test (SWM) and complication were evaluated in all patients.

NCS, pain (VAS), Levine score and all examination were compared between two groups at preoperatively, and 6 and 12 wk postoperatively. The NCS was performed as described in the previous literature^[17] by the same physician.

Statistical analysis

The demographic data including age, gender, BMI, onset of duration, side of operation, hand dominant and examination (Tinel's sign and Phalen test) were

collected with excel version 2013. All of the continuous data were normally distributed and were presented with mean ± SD, while the categorical data were shown in percentage.

The primary and secondary outcomes were analyzed with the repeated ANOVA and Graphpad software version 6.0 and the relationship between groups and time to follow-up were evaluated. These data include NCS, Levine score, pain (VAS), 2-PD, grip strength, pinch strength and SWM. $P < 0.05$ was used to determine the correlation between two groups and time to follow-up postoperatively.

RESULTS

The COR group consists of 19 patients (20 hands, $n = 20$), all were female with the mean age of 50.4 years (41-62 years). The HTFPF group consists of 20 patients (21 hands, $n = 21$); 2 males (11%) and 16 females (89%) with the mean age of 53.3 years (42-63 years). Five patients were lost to follow-up; 3 cases in COR group and 2 cases in HTFPF group. Finally 33 patients (36 hands) were analysed in this study with 17 hands in COR group and 19 hands in HTFPF group. The demographic data of the included patients are summarized in Table 1.

NCS revealed the improvement of DSL in HTFPF group at 6 and 12 wk postoperatively and statistically significant difference at 6 wk ($P < 0.05$) comparing with the COR group (Figure 3). S-amp was statistically significant improved postoperatively in both groups ($P < 0.05$) but not significantly different between two groups (Figure 4). There were no statistically significant differences of DML, M-amp and SCV between preoperative and postoperative in both groups and no statistically significant different of DML, M-amp and SCV between two groups (Figures 5-7).

Postoperative pain (VAS) was decreased in both groups but there was no significantly different between two groups. Negative result in both Tinel's sign and Phalen test were detected in both groups postoperatively. Grip strength, pinch strength, 2-PD, SWM and Levine

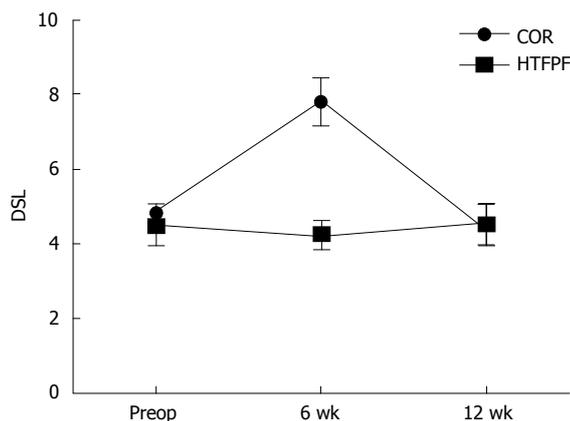


Figure 3 Distal sensory latency was significantly improved in hypothenar fat pad flap group at 6 wk postoperatively, $P < 0.05$, but not significant different in between groups at 12 wk postoperative. DSL: Distal sensory latency; COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

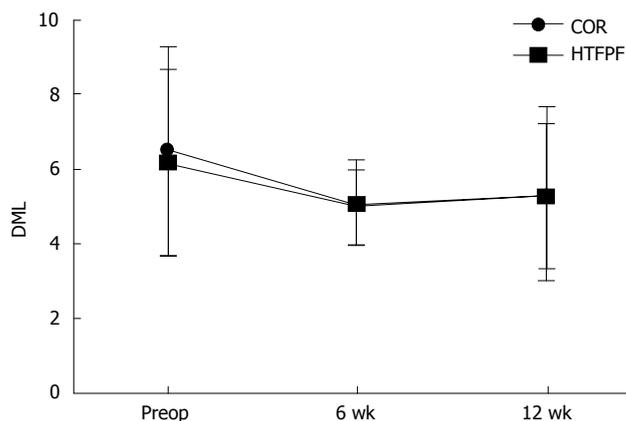


Figure 5 Distal motor latency was not significantly improved postoperatively in both groups and not significant different in between groups. DML: Distal motor latency; COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

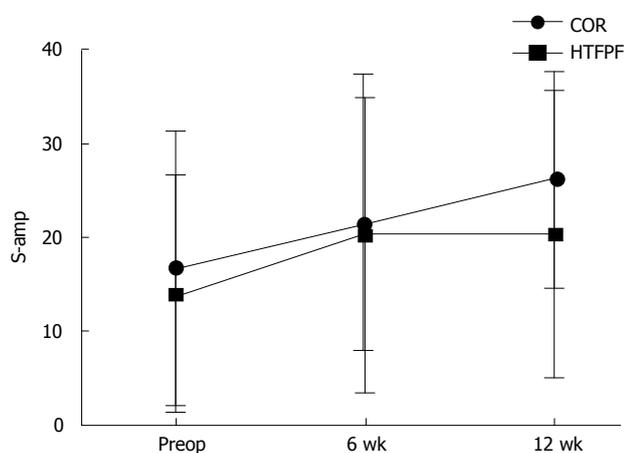


Figure 4 Sensory amplitude was significantly improved in both groups postoperatively. S-amp: Sensory amplitude; COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

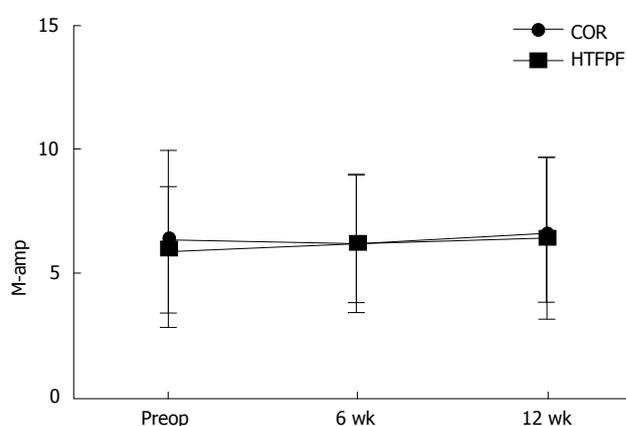


Figure 6 M-amp was not significantly improved postoperatively in both groups and not significant different in between groups. M-amp: Motor amplitude; COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

score were improved in both groups, however there was no statistical difference between two groups was shown (Tables 2-4).

At 6 wk after operation, painful scar was occurred 11.76% and 31.58% in COR and HTFPF groups respectively, eventually the symptom was resolved in both groups at 12 wk and there were no statistically significant difference between two groups. Two of 19 cases in HTFPF group had pain over hypothenar eminence at 6 wk, however this symptom was disappeared at 12 wk.

DISCUSSION

The HTFPF is vascularized pedicle flap that supplied by branches of ulnar artery and widely used for recurrent or persistent CTS with median nerve hypersensitivity. Most authors reported an excellent result of HTFPF^[8,10-12], even though had some modification by Craft *et al.*^[12] suggested the combination of microneurolysis of the median nerve and HTFPF.

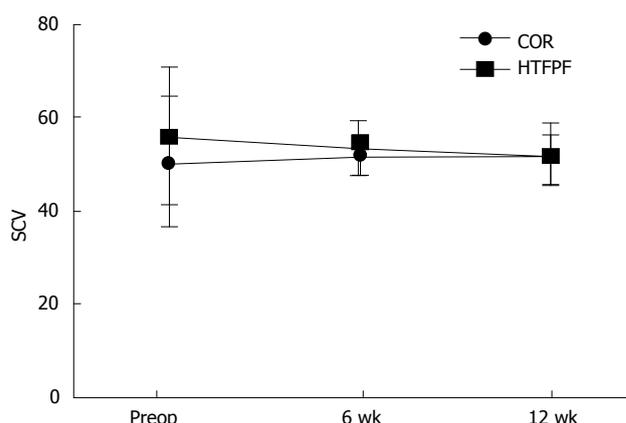


Figure 7 Sensory nerve conduction velocity was not significantly improved postoperatively in both groups and not significant different in between groups. SCV: Sensory nerve conduction velocity; COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

It is limited evidence in the flap coverage procedure on the median nerve in primary CTS. Increasing vascularity to the median nerve may result in rapid

Table 2 Results of levine score

Levine score	Preop., mean \pm SD		6 wk postop., mean \pm SD		12 wk postop., mean \pm SD		P value
	COR	HTFPF	COR	HTFPF	COR	HTFPF	
Symptom severity scale	2.6 (0.6)	2.5 (0.5)	1.7 (0.5)	1.7 (0.5)	1.5 (2.5)	1.1 (0.1)	> 0.05
Functional status scale	2.4 (1.0)	2.5 (0.9)	1.8 (0.7)	1.7 (0.6)	1.4 (0.6)	1.1 (0.2)	> 0.05

COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

Table 3 Results of grip and pinch strength

	Preop., mean \pm SD		6 wk postop., mean \pm SD		12 wk postop., mean \pm SD		P value
	COR	HTFPF	COR	HTFPF	COR	HTFPF	
Grip strength (Pound)	29.2 (15.0)	28.9 (14.1)	22.3 (12.8)	21.4 (10.4)	30.4 (13.0)	31.4 (10.8)	> 0.05
Pinch strength (Pound)	12.0 (3.3)	11.9 (3.9)	11.0 (2.8)	11.5 (3.4)	13.3 (3.3)	15.5 (3.0)	> 0.05

COR: Conventional open release; HTFPF: Hypothenar fat pad flap.

Table 4 Results of pain (Visual analog scale), 2-point discrimination and semmes-weinstein monofilament

	Preop., mean \pm SD		6 wk postop, mean \pm SD		12 wk postop, mean \pm SD		P value
	COR	HTFPF	COR	HTFPF	COR	HTFPF	
Pain (VAS)	4.6 (3.4)	4.4 (3.4)	0.4 (1.0)	0.5 (1.1)	0 (0)	0 (0)	> 0.05
2-PD (mm)	3.5 (1.0)	4.7 (2.9)	3.1 (0.8)	2.9 (0.7)	2.5 (0.5)	2.7 (0.8)	> 0.05
SWM	3.7 (0.3)	4.1 (1.0)	3.4 (0.4)	3.4 (0.5)	3.3 (0.4)	3.1 (0.4)	> 0.05

COR: Conventional open release; HTFPF: Hypothenar fat pad flap; VAS: Visual analog scale; 2-PD: 2-point discrimination; SWM: Semmes-weinstein monofilament.

nerve recovery and improve success rate. For that reason this study was conducted to add this procedure during CTR. This study used NCS for detection of nerve electrophysiology in short-term follow-up since there was no difference in the outcome of mid-term and long-term follow-up^[9,14].

The advantage of HTFPF procedure are well-vascularized pedicle flap, could be harvested from same incision use of CTR with no donor site morbidity and sufficient to cover the median nerve in carpal tunnel^[10,15].

The result of NCS revealed better nerve recovery in DSL in HTFPF group at 6 wk but not different at 12 wk compared to COR group. The S-amp was improved after surgery in both groups, however no significant difference between two groups was observed. There was no advantage outcomes of HTFPF procedure compared to COR in primary CTS. There were few studies performed the NCS in early postoperative, however this study shows an early detect of the electrophysiological conduction change in median nerve. This result was similar to study of Ginanneschi *et al.*^[14] reported at one month after CTR, SCV and DML were improved.

Conversely, El-Hajj *et al.*^[16] compared the DML and DSL, M-amp and S-amp, and SCV preoperatively and postoperatively, the result showed an improvement in all studied variables, except the DSL at 18 wk after surgery which improved only at 42 wk. The author explained that recovery of the sensory was delayed

compare to motor, because the sensory fibers were affected more than motor fibers, and the myelin sheath more than the axons in most cases of CTS. Tahririan *et al.*^[17] study showed significant improvement in DSL, DML and SCV 6 mo postoperatively.

The strength of this study is the prospective randomized controlled trial, while small number of cases in each group is the limitation. Increased risk of painful scar and pain over the hypothenar eminence was found in HTFPF group. However, there was no statistical difference between two groups.

This study concluded that there was no advantage outcome in primary CTS for having additional HTFPF procedure in CTR compared with conventional technique. COR is still the standard treatment in primary CTS. Nevertheless, improvement of DSL and S-amp could be observed at 6 wk postoperatively. However, the interesting point is the recurrent rate in long-term follow-up between two groups and further data collection and analysis should be carried out in the future.

COMMENTS

Background

Carpal tunnel syndrome is the most common compression neuropathy. Carpal tunnel release is a standard treatment for patient who indicated for surgery although complete nerve recovery was not achieved for all of patients. This study hypothesized that increasing vascularity to the median nerve by hypothenar fat pad flap procedure could improve the nerve recovery of carpal

tunnel release in primary carpal tunnel syndrome.

Research frontiers

Many recent studies used flap coverage procedure on the median nerve for recurrent or persistent carpal tunnel syndrome.

Innovations and breakthroughs

There is no other studies have done the comparison between hypothenar fat pad flap and conventional carpal tunnel release in primary carpal tunnel syndrome before.

Applications

Although no advantage outcome in primary carpal tunnel syndrome for having additional hypothenar fat pad flap procedure in carpal tunnel release. However, improvement of distal sensory latency and sensory amplitude could be observed at 6 wk postoperatively.

Terminology

Hypothenar fat pad flap is vascularized pedicle flap that supplied by branches of ulnar artery.

Peer-review

It is a well presented prospective randomized controlled trial comparing the hypothenar fat pad flap with conventional open techniques for carpal tunnel syndrome.

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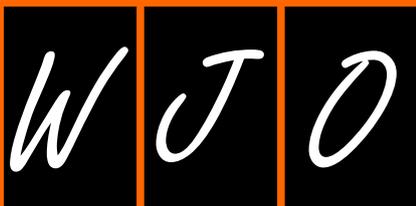
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Update on mesenchymal stem cell therapies for cartilage disorders

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Abstract

Cartilage disorders, including focal cartilage lesions, are among the most common clinical problems in orthopedic practice. Left untreated, large focal lesions may result in progression to osteoarthritis, with tremendous impact on the quality of life of affected individuals. Current management strategies have shown only a modest degree of success, while several upcoming interventions signify better outcomes in the future. Among these, stem cell therapies have been suggested as a promising new era for cartilage disorders. Certain characteristics of the stem cells, such as their potential to differentiate but also to support healing made them a fruitful candidate for lesions in cartilage, a tissue with poor healing capacity. The aim of this editorial is to provide an update on the recent advancements in the field of stem cell therapy for the management of focal cartilage defects. Our goal is to present recent basic science advances and to present the potential of the use of stem cells in novel clinical interventions towards enhancement of the treatment armamentarium for cartilage lesions. Furthermore, we highlight some thoughts for the future of cartilage regeneration and repair and to explore future perspectives for the next steps in the field.

Key words: Stem cell; Cartilage; Chondral defect; Management; Bone marrow; Mesenchymal stem cells; Adipose

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Core tip: An increasing interest in stem cell application for cartilage defect repair is recently expressed, as a consequence of advancements demonstrating the critical function of mesenchymal stem cells as a potential alternative cell source for cartilage repair, as well as of recent clinical data exhibiting the effectiveness of these management strategies. Future research will determine the role of combining stem cells, primary chondrocytes,

and signaling molecules towards cartilage regeneration.

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INTRODUCTION

Cartilage lesions are among the most often recognized pathologies in young adults undergoing arthroscopy. Approximately 60% of the patients treated arthroscopically for any reason had at least one chondral lesion at their knee^[1]. Due to the relatively young age of these patients (mean age ranged from 37 to 43 years old) and because the majority of lesions has been graded as II or III, it was suggested that impending osteoarthritis would be inevitable without treatment in these patients^[1].

Effective management of these lesions can be extremely challenging, thus, creating a burden for both patients and physicians. With conservative treatment being unsuccessful, several surgical interventions have been proposed for focal cartilage lesions, including microfracture, autologous chondrocyte implantation [with either periosteum (ACI) or matrix-assisted (MACI)], osteochondral autograft or allograft transplantation, and particulated autologous or allogeneic articular cartilage^[2-4]. Despite the plethora of available techniques, the effectiveness of these in terms of preventing or delaying the development of osteoarthritis is questionable.

In the armamentarium against cartilage defects, stem cell-based interventions have gradually taken a more prominent role. As shown in Figure 1, there is an exponential growth in the number of published studies that deal with stem cell use in cartilage disorders (Figure 1). Mesenchymal stem cells (MSCs) are multipotent cells that have been isolated from a variety of tissue types, including bone marrow, synovium, and adipose tissue^[5-7]. MSCs have been observed to undergo differentiation down osteogenic, chondrogenic, myogenic, and tenogenic lineages, making them of great importance to the orthopedic and tissue engineering communities.

The regenerative potential of marrow-derived elements was determined in the 1960's, long before the discovery of MSCs, with the observation that superficial chondral defects exhibit limited healing potential, while defects penetrating the subchondral plate result in fibrocartilaginous ingrowth^[8]. This observation ultimately led to the development of marrow stimulating techniques for chondral repair such as microfracture^[9]. Penetrating the subchondral bone allows bleeding, and formation of a clot containing MSCs and various other bone marrow elements to form. While this technique has been shown to produce improved patient-reported outcomes at short time-points, the repair tissue is fibrocartilaginous in

nature, and exhibits poor mechanical properties when compared to native cartilage. At longer time-points, this tissue may become fibrillated and require further management.

The premise behind the use of MSCs for cartilage repair was supported on two characteristics of the stem cells. These multipotent cells, under the appropriate environmental conditions, could differentiate into chondrocytes and repair the chondral defect^[10]. Differentiation of both adipose-derived and bone marrow MSCs towards chondrocytes can be enhanced with the use of growth factors^[11,12]. Thus, the ideal perspective would be to promote MSC differentiation towards chondrocytes and to utilize the healing response with new chondrocyte-like cells.

Another equally important ability has been revealed for MSCs, *i.e.*, their capacity to actively interact with primary cells and extracellular matrix *via* continuous feedback mechanisms^[13]. As a consequence, stem cells could act as advocators of the existing chondrocytes *via* their anti-inflammatory and immunomodulatory effect. In addition, this interaction can formulate an appropriate response towards differentiation, proliferation or secretion of supportive molecules that allows stem cells to be actively engaged in the cartilage healing response^[14].

MSC transplantation is a technique that offers several potential benefits over other cartilage repair methods. MSCs may be isolated from adipose tissue, which is much less invasive than the harvest of chondrocytes for ACI. MSCs are also phenotypically stable during cell culture expansion, while chondrocytes undergo dedifferentiation. Furthermore, MSCs may be isolated in greater quantities than chondrocytes, allowing for the possibility of single-step procedures, which could decrease economic burden for the patient. Currently, clinical studies involving MSC transplantation are limited.

The aim of this editorial is to summarize the recent work in basic science and clinical interventions in an attempt to provide an update on the recent advances in stem cell treatment options for cartilage disorders. Furthermore, some thoughts for the future of cartilage regeneration and repair *via* stem cell application will be discussed. Due to the plethora of studies in the literature, the main focus of this study would be on clinical interventions for focal cartilage defects.

BONE MARROW DERIVED MSCs

Update on basic science

A better understanding of the pathogenetic phenomena that initiate the process of cartilage degeneration is of paramount importance, as this would allow the formulation of therapeutic approaches that aim to prevent osteoarthritis at its infancy. TGF-beta1 is proven to be a key factor for cartilage homeostasis, and its function is utilized in tissue engineering for chondrocyte proliferation and enhancement of functional properties^[15]. Recently, an interesting aspect of the role of transforming growth factor-beta (TGF-beta) in osteoarthritis has been

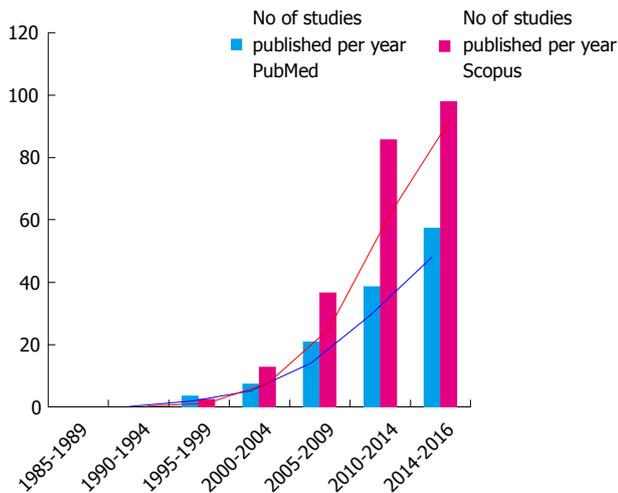


Figure 1 An increasing number of studies about stem cell use in cartilage disorders is published, especially in the last decade.

proposed. Specifically, it was found that mechanical load increases in ACL-deficient knees result in recruitment of additional osteoclasts at the subchondral bone. This leads to activation of TGF- β 1 that assists in recruitment of MSCs that causes atypical subchondral bone formation, a potential initial step in the osteoarthritic pathogenetic cascade^[16].

Cell to cell and cell to extracellular matrix interactions are important in the mechanical environment of the joint for suitable response to injury or degeneration. Stem cells appear to play a major role in these interactions with numerous applications in both therapeutic strategies but also in the design of tissue-engineered scaffolds. A recent study demonstrated that interactions of N-cadherin in MSCs could modify the perception of the mechanical properties of the microenvironment, and thus, generate corresponding response of stem cells towards proliferation and differentiation^[17]. Furthermore, mechanical stimuli including tension stimulation can result in significant improvement of the functional properties of tissue-engineered human cartilage that could be used for replacing chondral defects^[18].

Update on clinical studies

The initial reports for the use of autologous bone marrow-derived MSCs for focal cartilage defects used marrow obtained from the iliac crest and, *via* a subsequent surgery using an open approach, the stem cells were injected into the defect with a periosteal cover sutured on top of the lesion. In the first study, two patients with patellar cartilage defects underwent treatment with MSCs. Significant improvement in pain and functional outcome was maintained for at least 4 years after surgery^[19]. In a case report involving a patient with a defect of the medial femoral condyle, autologous transplantation of bone marrow derived MSCs was also associated with improved outcome. Second-look arthroscopy revealed full coverage of the lesion 7 mo after surgery with hyaline-like cartilage as well as significant improvement in clinical symptoms.

However, MRI showed irregularities of the repair tissue^[20]. The favorable outcome of autologous bone-marrow derived MSCs for cartilage defects at the patellofemoral joint was confirmed by another report of three cases demonstrating clinical improvement in kissing lesions which are usually more challenging to treat^[21].

In recent years, as arthroscopic techniques have evolved, all-inside arthroscopic techniques for cartilage repair using MSCs developed with favorable outcome. In a case report, after microfracture, a collagen membrane that was immersed in bone marrow derived MSCs were secured with fibrin glue. MRI imaging at 12 mo demonstrated filling of the cartilage defect, while the patient remained asymptomatic until at least 24 mo^[22]. In addition, single stage arthroscopic techniques were also described. In a prospective study, 30 patients with cartilage defects at the knee joint were treated using a combination of microfracture and subsequent application of a mixture gel containing bone marrow aspirated cells, hyaluronic acid (HA), and fibrin. A significant improvement was recorded with an improvement in Lysholm score from 50.8 to 80.1 and subjective IKDC from 39 to 83 preoperatively and postoperatively, respectively^[23]. An analogous technique where bone marrow-derived cells were mixed with collagen powder or HA membrane and platelet gel was used for osteochondral defects of the talus^[24]. In these patients, a significant improvement in the AOFAS score was recorded with an increase from 64.4 to 91.4, preoperatively to postoperatively, respectively^[24]. Furthermore, using bone marrow cells aspirated from the iliac crest, isolated *via* centrifugation and embedded in a HA membrane, 20 patients with chondral defects at their knee experienced significant improvement in pain and function^[25]. Both MRI and histological analysis confirmed the presence of regenerated cartilaginous tissue^[25]. Nine patients with focal cartilage defects were treated with microfracture supplemented with coverage of a polyglycolic acid/hyaluronan matrix membrane with autologous bone marrow concentrate cells. A significant improvement in IKDC, Lysholm and Tegner scores was reported at 22 mo follow up^[26]. The recent advancements in the field have allowed for the successful combination of autologous stem cells with therapeutic interventions already employed in cartilage repair.

When evaluating studies that compared outcomes with or without stem cell augmentation, promising findings are reported. The first attempt to compare clinical outcome between patients treated with autologous chondrocyte implantation and patients treated with autologous bone marrow-derived MSCs, showed that bone marrow MSCs could be equally effective as chondrocytes for focal cartilage lesions. Indeed, both groups demonstrated significant improvement postoperatively with no statistical difference between the groups in Lysholm IKDC and Tegner activity scores^[27]. In a comparative study for patellofemoral chondral lesions, 18 patients were treated with bone marrow cells embedded in a biodegradable HA-based scaffold while 19 patients were treated with matrix-

induced autologous chondrocyte implantation (MACI). At 2 year follow up, both groups showed a significant improvement in clinical outcome and pain scores, but bone marrow aspirate concentrate treated patients had significantly better subjective IKDC score^[28]. In another study that combined therapeutic approaches, two different techniques using marrow derived MSCs were compared. One combined microfracture with subsequent injection of MSCs with HA. In the other group, MSCs were seeded in a periosteal patch that was sutured over the cartilage defect. Both groups showed improvement postoperatively with a trend towards better outcome for the MSC/HA group^[29]. Combination of intra-articular injections of autologous bone marrow-derived MSCs and HA 3 wk after microfracture and medial opening-wedge high tibial osteotomy in 28 patients resulted in approximately 7.6 added improvement for IKDC and Lysholm scores compared to HA injections alone. In this randomized controlled trial an improvement in Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score at 1 year was also seen^[30]. Further improvement in the current armamentarium against cartilage defects has leads to technical adaptations that explore the potential use of autologous MSCs instead of primary chondrocytes. The above findings suggest that the use of MSCs result in analogous - if not better - outcomes.

Several carriers have also been successfully used recently for autologous MSCs. In a case series, platelet rich fibrin glue was successfully used as a cell carrier for autologous bone marrow derived MSCs that were subsequently sutured with a periosteal flap. All five patients experienced improvement in clinical scores, while second look arthroscopy performed in two patients demonstrated good integration and healing of the repair area^[31]. A type I collagen scaffold was used as a carrier for autologous MSCs in two patients with periosteal graft sutured on top. Both KOOS and IKDC score improved significantly postoperatively at 30 mo follow up^[32]. In a pilot clinical study application of a poly-ethylene glycol diacrylate (PEGDA) hydrogel biomaterial after microfracture in 15 patients was compared with the outcome of microfracture alone in three patients. It was suggested that pain was improved in the biomaterial group, however, additional data are necessary before making safe conclusions^[33].

Finally, a recent randomized trial used allogeneic MSCs for patients with osteoarthritis. It was suggested that allogeneic bone marrow MSCs resulted in improvement in pain, quality of life and cartilage quality as evaluated by MRI compared to HA^[34]. Based on these promising data, use of allogeneic bone marrow MSCs may be a viable solution for focal cartilage lesions in some patients.

ADIPOSE AND SYNOVIAL DERIVED STEM CELLS

Update on basic science

Since their identification as a potential source of cartilage

matrix molecules, adipose derived MSCs (ADSCs) have become a valuable source in several models for cartilage regeneration^[7,35]. A primary advantage of ADSCs is their abundance and the relative ease of obtaining cells from the patient^[14,36]. Another advantage of ADSCs is that they have been demonstrated to have a prominent chondro-inductive effect. As shown in an *in vitro* co-culture model, the combination of articular chondrocytes with ADSCs resulted in a two-fold increase in GAG content and increased collagen II gene expression^[37].

Expression of pro-chondrogenic genes in ADSCs *via* adenovirus-mediated gene transfer of TGF beta2 could lead to ectopic neocartilage formation, while recently a combined expression of IGF-1 and FGF-2 in ADSCs demonstrated a synergistic effect towards enhanced chondrogenic differentiation^[38,39]. Towards this direction, poly lactic-co-glycolic acid (PLGA) nanoparticles that deliver a specific plasmid of bone morphogenetic protein 4 (BMP-4) into rabbit ADSCs significantly enhanced chondrogenesis and appear to benefit cartilage repair *in vivo*^[40].

Concerns about the degree of stemness of ADSCs have been raised since ADSCs demonstrate an inferior chondrogenic potential when compared to BMSCs^[41]. Indeed, ADSCs may need specific conditions to chondro-differentiate and this process may require a prior step of pre-differentiation^[42]. However, the immunosuppressive effect and the chondroprotective role of ADSCs should not be underestimated. In a mice model of osteoarthritis injection of ADSCs resulted in inhibition of cartilage destruction and synovial thickening^[43]. Similarly, in a rabbit model, intra-articular injections of ADSCs delayed the progression of osteoarthritis and meniscus damage *via* inhibition of metalloproteinase and TNF α expression^[44]. In one study performed in a rat OA model, fluorescein-labeled ADSCs were injected into an arthritic knee joint and were detectable *via* non-invasive bioluminescence imaging for up to 10 wk post-injection. Histological analysis confirmed that injected cells were present and proliferating in synovial, meniscal, and articular cartilage tissues. Furthermore, ADSC-treated rats showed a significantly increased O'Driscoll histological score, suggesting a chondro-protective or regenerative effect from these cells^[45]. Additional research is needed to better understand the protective or reparative mechanism of ADSCs. Recently, a similar role in chondroprotection has been demonstrated for synovial derived MSCs^[46].

Update on clinical studies

Interest in ADSCs increased considerably after a case series reported that patients that received intra-articular injection of ADSCs had reduced pain and improved knee function^[47,48]. In humans, ADSCs have been used in intra-articular injections since 2011. To date, eleven studies have been recorded. ADSCs have been isolated either from the abdominal area, buttocks, or infrapatellar fat pad. In all studies, ADSC injection showed improved clinical outcome in terms of reduced pain and

improvement in functional scores. Data obtained from MRI at 6 mo showed promising data suggesting cartilage regeneration^[47]. Also, macroscopic appearance from second-look arthroscopy showed hyaline-like cartilage with smooth surface^[47]. Finally, histology in a specimen obtained also confirmed characteristics of hyaline cartilage. Unfortunately, there are some disadvantages in these clinical studies. First, most are case reports without a control group. Another limitation is the fact that in most cases an additional therapeutic intervention was simultaneously performed^[49]. High-level of evidence studies are necessary in order to confirm the promising results of the clinical cases described.

In a randomized single blinded study evaluating only 14 patients synovial mesenchymal cells were used in a matrix collagen membrane and were compared with matrix autologous chondrocyte implantation^[50]. Functional outcomes were similar between the two groups, while mesenchymal cells were reported to have better outcome in certain outcomes, such as KOOS score^[50].

Synovial MSCs, cultured in autologous human serum, arthroscopically implanted in 10 patients with single cartilage defect showed promising results^[51]. Specifically, synovial cells were harvested and were cultured in autologous human serum^[51]. At 3-year follow up, improved MRI features and Lysholm score were reported, however no benefit was seen in Tegner activity level^[51].

Another type of stem cells used in clinical studies is the autologous peripheral blood progenitor cells (PBPCs). Specifically, one week after arthroscopic drilling of a cartilage defect, 8 mL of PBPCs were injected at the knee together with 2 mL of HA^[52]. Articular cartilage biopsies in five patients showed the presence of hyaline cartilage^[52]. Clinical outcomes from the same group have been reported in a randomized study that compared the outcomes in patients that underwent subchondral drilling and subsequent HA injections with and without PBPCs^[53]. It was shown that the presence of PBPCs did not result in better clinical outcome (IKDC scores of 74.8 vs 71.1 for PBPC and no PBPC group, respectively). However, PBPC group exhibited better histologic and MRI scores compared to control^[53].

OTHER TYPES OF STEM CELLS

Other types of stem cells have been proposed as potential candidates for cartilage repair treatment. In a recent animal model, weekly injections of embryonic MSC-derived exosomes demonstrated restoration of osteochondral defects and presence of hyaline cartilage^[54]. Chondrocytes have also been demonstrated to adopt stem cell-like characteristics when cultured under specific biochemical and mechanical conditions^[55]. In this study, dedifferentiated chondrocytes were found to be highly proliferative and chondrogenic, making them an attractive source for cartilage repair. Additional research should identify additional progenitor cell

populations that may be used in cartilage repair and should focus in further characterizing their properties.

CRITICISM

Autologous MSCs have demonstrated potential in the repair of cartilage defects, and that lead to an increased interest has been expressed for the use of stem cells in cartilage lesions (Figure 1). However, an analysis of these studies in terms of level of evidence shows that less than 10 studies are randomized and approximately 15 studies have a control group. Additional randomized controlled clinical studies are necessary to determine whether isolated MSCs or ADSCs offer any benefits over traditional marrow stimulating techniques such as microfracture. Furthermore, long-term follow-up with MRI or second-look arthroscopy will be critical for determining the durability of repair tissue generated by MSC implantation, particularly before utilizing these techniques in younger, active patients.

The use of MSCs is not without clinical limitations or disadvantages. Cost of stem cell preparation represents an unknown factor that needs to be included in the equation of their application. Detailed cost effectiveness studies are needed to clarify the potential benefit for their use in comparison to the current strategies for cartilage repair. Moreover, the use of autologous MSCs has a certain amount of donor morbidity. Iliac crest marrow aspiration has been associated with chronic pain, dysesthesia, potential wound drainage and scarring^[56]. These complications are relatively minor and occur rarely, but it is important to establish a better understanding of the potential problems that are associated with stem cell use, as these techniques become more popular. For adipose and synovial derived MSCs donor morbidity is significantly less, but future studies should focus on potential withdraws for their use as well. Finally, the use of allogeneic MSCs in co-culture systems could offer a potential solution, but again, additional research should determine whether the potential risk of immune response related complications outweighs their benefits^[14].

From a basic science perspective, the mechanisms underlying chondrogenic differentiation of MSCs and subsequent matrix production require elucidation. As it stands, the quality of repair tissue generated by marrow stimulation is known to be mechanically inferior to native articular cartilage. It may be the case that disruption to the subchondral plate contributes to this phenomenon, and implantation of autologous MSC or ADSC could circumvent this issue.

FUTURE PERSPECTIVES

The success of autologous MSC implantation is dependent on determining their benefit over simpler techniques such as microfracture. Studies will also be necessary to determine which delivery method is most appropriate. An appealing aspect of MSC implantation

is that it has the potential to be performed in a single surgical procedure. However, MSCs can also be isolated at an earlier time point and pre-differentiated prior to implantation. Studies comparing the efficacy of the multitude of cell delivery techniques are necessary to determine a standard of care.

A lot of interest has been focusing in the field of lubricin expression from MSCs^[57,58]. This potential may indicate that tissue engineering of cartilage from stem cell sources could ensure the presence of lubricin in the superficial cartilage^[59].

Finally, effective application of stem cells appears to be linked with the presence of primary cells, and the interactions between primary chondrocytes and MSCs may worth to be examined further. This is an attractive field that may attract a lot of interest since recent work have shown that endogenous stem cells may have the capacity for cartilage repair and regeneration^[55,60]. Additional research is also necessary to incorporate the advances in the field of tissue engineering and explore the potential of capitalizing the benefit from combining successful approaches from basic science to clinical practice.

CONCLUSION

Over the recent years, a growing number of studies arise in the field of MSCs use in cartilage repair, building a progressively stronger foundation for their clinical applications. With the assistance of basic science, a better understanding of their exact role in cartilage physiology is established. New studies initiate to demonstrate the critical role of MSCs in the initial steps of cartilage degeneration, opening a new horizon full of possible alternative methods to address the complicated problem of cartilage repair and regeneration. Clinical work has shared valuable data that confirm their effectiveness as an alternative cell source for cartilage repair. More importantly, recent clinical findings revealed the advantages and disadvantages of each type of MSCs signifying the importance of combining chondrocytes with different types of stem cells. The effective combination of different treatment approaches showed that careful selection of the treatment plan should be based on the characteristics of the patient.

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New insights in the treatment of acromioclavicular separation

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Abstract

A direct force on the superior aspect of the shoulder may cause acromioclavicular (AC) dislocation or separation. Severe dislocations can lead to chronic impairment, especially in the athlete and high-demand manual laborer. The dislocation is classified according to Rockwood. Types I and II are treated nonoperatively, while types IV, V and VI are generally treated operatively. Controversy exists regarding the optimal treatment of type III dislocations in the high-demand patient. Recent evidence suggests that these should be treated nonoperatively initially. Classic surgical techniques were associated with high complication rates, including recurrent dislocations and hardware breakage. In recent years, many new techniques have been introduced in order to improve the outcomes. Arthroscopic reconstruction or repair techniques have promising short-term results. This article aims to provide a current concepts review on the treatment of AC dislocations with emphasis on recent developments.

Key words: Acromioclavicular dislocation; Rockwood classification; Coracoclavicular ligament reconstruction; Hookplate; Arthroscopically assisted acromioclavicular reconstruction; Weaver and Dunn procedure; Conoid and trapezoid ligaments

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Core tip: Current literature suggests that the decision for treatment of type III injuries should be made on a case-by-case basis, with an emphasis on initial nonoperative treatment. Early operative treatment for grades III-VI dislocations may result in better functional and radiological outcomes than delayed surgery. There are numerous surgical techniques presented in the literature. The authors prefer an autograft tendon reconstruction of the coracoclavicular joint without bone tunnels in combination with direct suture fixation of the acromioclavicular joint. Arthroscopic techniques are evolving but there is currently

no evidence to support arthroscopic over open surgery.

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INTRODUCTION

The interest in acromioclavicular (AC) joint injuries dates back to the time of Hippocrates (460-377 BC) and Galen (129-199 AD)^[1]. These ancestors already noted the difficulties in correctly diagnosing and treating this type of injury. Naturally, many developments have been made since then. New insights have led to the introduction of numerous treatment techniques during the past few decades^[2]. However, to date, much controversy still exists, and the optimal treatment is not available yet. Moreover, the best timing of surgery remains a topic of debate. This current concepts review aims to provide an up-to-date and evidence-based overview of relevant treatment options for AC joint dislocations, with special emphasis on most promising recent techniques.

Etiology

AC joint dislocations are common injuries among an athletic population. They account for approximately 12% of injuries of the shoulder girdle. The patient is typically male, < 30 years of age and involved in (contact) sports^[3]. The typical trauma mechanism is a force that depresses the shoulder girdle, such as occurs during a fall from a cycle or during a collision in contact sports. The force depresses the scapulohumeral complex (rather than the clavicle being elevated), resulting in tears of the AC ligament and the coracoclavicular (CC) ligaments. Associated shoulder injuries are present in 18% of patients with type III to V dislocations; superior labral anterior posterior (SLAP) lesions being the most common^[4].

Anatomy

The AC joint is a diarthrodial joint, consisting of a thin cartilage surface and an interposed fibrocartilaginous meniscoid disk. The joint capsule or AC ligament (*i.e.*, thickenings in the capsule) and the extracapsular CC ligaments provide static stability. Physiologic forces and the weight of the arm place significant translational forces in the vertical, anteroposterior and axial planes of the AC joint. Based on cadaveric studies, the AC ligaments contribute 20% to 50% of resistance to superior migration and 90% to anterior-posterior translation. The CC ligaments are formed by the conoid medially and the trapezoid laterally. They are the primary restraint to inferior and medial translation of the scapulohumeral

complex in relation to the clavicle^[5]. The conoid ligament is attached proximally on the posteromedial undersurface of the clavicle, typically 4.5 cm from the AC joint (47.2 mm in men and 42.8 mm in women)^[6]. It tensions under loads that force the clavicle superiorly (or the scapula inferiorly). The trapezoid attaches proximally on the anterolateral aspect of the inferior clavicle, approximately 2.5 cm from the joint (25.4 mm in men and 22.9 mm in women)^[6]. It tensions under medialization of the scapulohumeral complex, *i.e.*, compression of the AC joint. The delto-trapezial fascia provides dynamic stabilization to the AC joint, especially the anterolateral deltoid insertion.

Symptomatology

Patients commonly present with pain at the AC joint, following a trauma such as a fall on the shoulder. The pain is often accompanied by soft tissue swelling as well as a prominent lateral clavicle. Because of the pain, shoulder motion is reduced and patients are limited in their daily and athletic activities. Chronic instability of the AC joint can lead to tremendous impairment of shoulder function including muscle fatigue, scapular dyskinesia, subjective sensation of heaviness of the injured upper limb, and painful horizontal adduction^[7].

DIAGNOSIS

The history and physical examination often provide clues to the diagnosis. The patient frequently reports a fall on the shoulder or a collision and has pain localized at the AC joint and often the trapezius muscle (pars ascendens). The patient may also note a swelling, which can be confirmed on physical examination. The patient is examined while standing or sitting. On inspection, a high lateral clavicle can be seen, compared to the uninjured side. The AC joint is tender on palpation. One should compare with the uninjured side. The shoulder range of motion is usually reduced because of the pain in the acute phase. The examiner should check the stability of the AC joint in the superior-inferior and anterior-posterior directions. For types III and V, the joint feels unstable when the lateral clavicle is depressed manually ("piano key" phenomena). The shoulder is passively adducted in the horizontal plain to test anterior-posterior stability^[8] (Figure 1). Chronopoulos *et al*^[8] reported a sensitivity of 77% for the cross body adduction test, 72% for the AC resistance test and 41% for the active compression test; the combination of all 3 tests showed a specificity of 95%.

Standard radiographs of the shoulder are obtained, including a true anterior-posterior view, a scapular Y lateral view, an axillary view (or Velpeau view modification if unable to abduct the arm), and a Zanca view of the AC joint (performed by tilting the X-ray beam 10° to 35° toward the cephalic direction and using only 50% of the standard shoulder anteroposterior penetration strength) (Figure 2). It may be useful to obtain radiographs of the opposite side for comparison. A bilateral Zanca view visualizes the ipsilateral and contralateral AC joints on one



Figure 1 Digital pictures of a patient with a type-V acromioclavicular dislocation. A: Anterior view; B: Lateral view: The shoulder is passively adducted in the horizontal plain to test horizontal stability. Note the horizontal instability in this case.

X-ray cassette, while the same orientation of the beam is maintained^[9] (Figure 2). In addition, a cross-body adduction radiograph may differentiate between a stable and unstable AC joint by assessment of the degree to which the clavicle overlaps the acromion^[10]. The additional value of stress views with distal traction by weights on the arms is questionable. More precise imaging techniques, such as computed tomography or magnetic resonance imaging, are normally unnecessary, unless associated injuries are suspected.

The radiographic images are assessed on the relation between acromion and clavicle, as well as the CC distance, ideally comparing left and right. Associated injuries of the shoulder girdle must be ruled out.

CLASSIFICATION

Rockwood has made a classification that is used the most widely nowadays (Figure 3)^[11,12]. In type I, neither AC nor CC ligaments are disrupted. In type II, the AC ligament is disrupted and the CC ligament is intact (50% vertical subluxation of the distal clavicle). In type III, both ligaments are disrupted. In type IV, the ligaments are disrupted and the distal end of the clavicle is displaced posteriorly into or through the trapezius muscle. An axillary radiographic view is particularly helpful in identifying type IV injuries. In type V, the ligaments and muscle attachments are disrupted, and the clavicle and acromion are widely separated. In type VI, the ligaments are disrupted, and the distal clavicle is

dislocated inferior to the coracoid process and posterior to the conjoint tendon. Type VI lesions are extremely rare but do occur^[13]. Reproducibility and interobserver reliability of the classification is only moderate and is likely limited by the inability of a classification based on plain radiographs to fully assess a soft tissue injury^[14].

In practice, the difference between type III and V can be subtle and confusing. There is no clear definition or consensus on how to differentiate between these types. A suggested definition is 25% to 100% superior displacement of the distal clavicle in type III dislocations and 100% to 300% displacement in type V^[15,16]. Others describe more than 100% clavicle displacement in type III and more than 300% displacement in type V^[7]. The CC distance can also be used to differentiate between the two types (CC distance 20% or 25% to 100% of contralateral side in type III; CC distance more than 100% of the contralateral side in type V)^[7].

The International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) Upper Extremity Committee has made a subdivision of type III dislocations in order to better identify patients who would benefit from surgery^[15]. Type IIIA is defined as a stable AC joint with normal scapular function and no overriding of the clavicle on the cross-body adduction view. Type IIIB is defined as unstable with scapular dysfunction and an overriding clavicle on the cross-arm adduction view. However, it is unclear to what extent this subdivision predicts treatment outcomes.

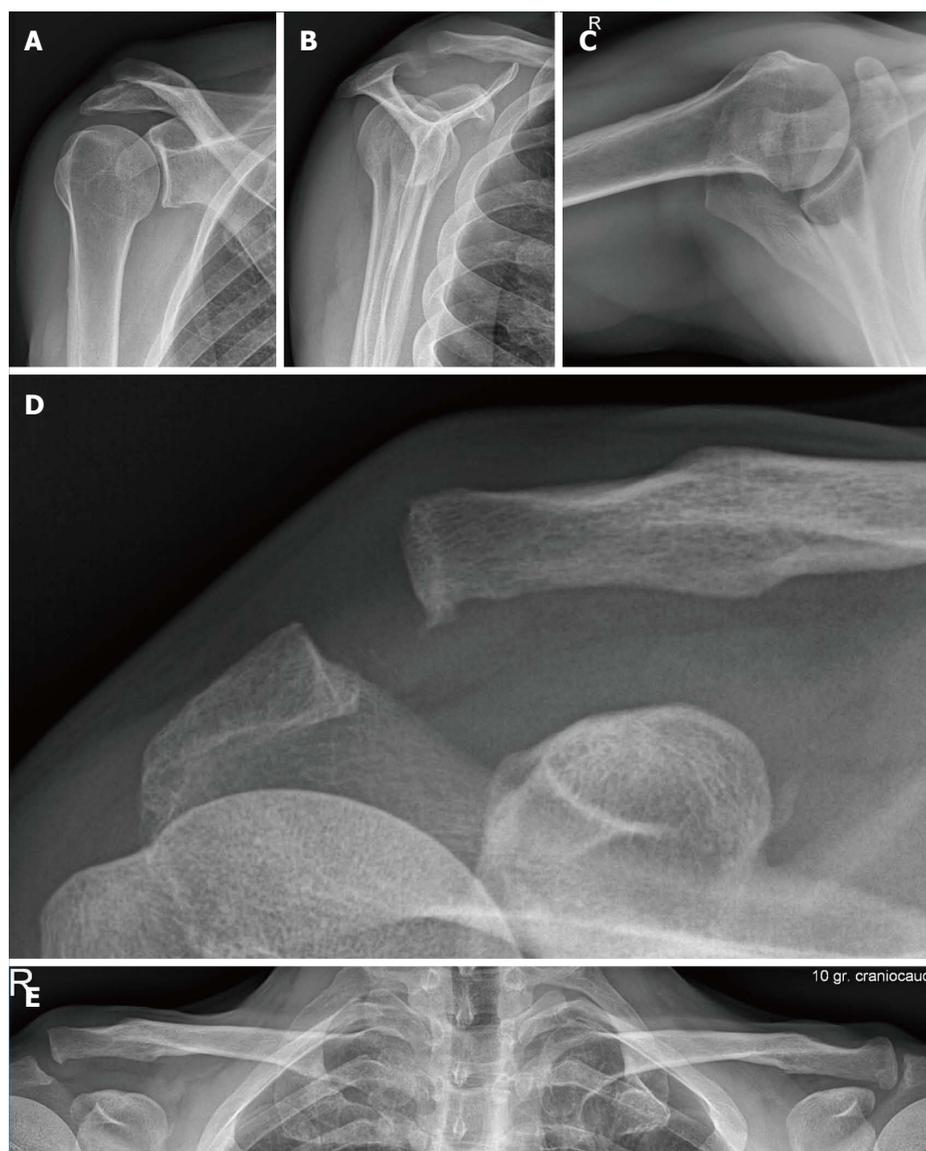


Figure 2 Standard radiographic series of the shoulder. A: A true anterior-posterior view; B: Scapular Y lateral view; C: Axillary view; D: Zanca view; E: In case of acromioclavicular separation, a bilateral Zanca view can be useful.

TREATMENT

There is general agreement that types I and II injuries should be treated nonoperatively in all cases^[2]. Most authors suggest that types IV, V and VI should be treated operatively^[5,7]. In contrast, type III separations have caused much debate during the past decades. In the past, many type III lesions were treated surgically. However, it has turned out that there is no clear superior outcome after surgical treatment^[17,18]. Operative treatment of type III is sometimes reserved for high-demand laborers and athletic patients^[17]. Most surgeons now generally agree that nonoperative treatment is indicated initially in all patients with type III injuries; if unsuccessful, operative reconstruction of the AC and CC ligaments can be provided at a later stage^[19,20].

Nonoperative

Nonoperative treatment is indicated for types I and II

dislocations and consists of temporary immobilization with a sling or collar and cuff for 1 to 3 wk. Early range-of-motion exercises are encouraged. Daily and athletic activities are resumed when the pain permits. Heavy lifting and contact sports are usually postponed until 6 wk. Unsatisfactory outcomes in conservative treatment may be explained by persistent instability, especially a horizontal component of instability^[21].

Open surgery

Numerous surgical repair or reconstruction techniques have been published. In 2013, the number of different surgical techniques described was 162^[2]. These techniques can basically be grouped in four categories: (1) Fixation of the AC and/or CC with hardware including screws and K-wires; (2) hook plates; (3) fixation of the CC with suture buttons; and (4) reconstruction of the CC ligaments with autograft or allograft tendon^[16]. Whichever construct is used, it needs to maintain the

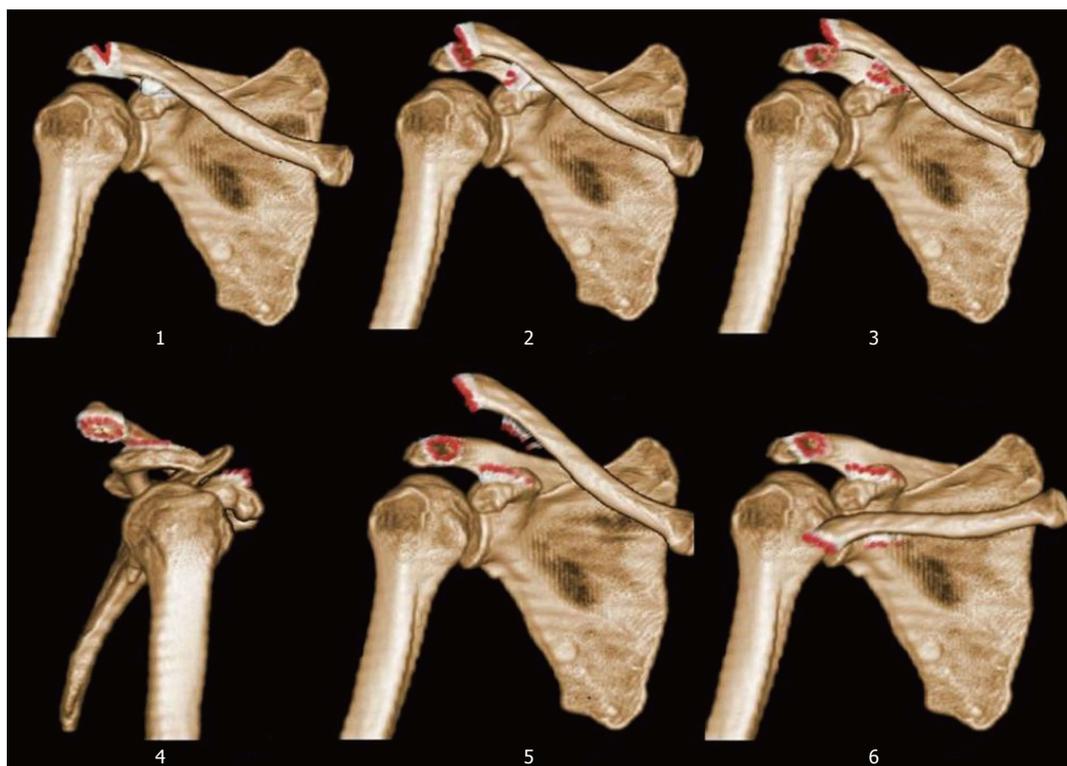


Figure 3 Rockwood classification (Case courtesy of Dr Roberto Schubert, Radiopaedia.org, rID: 19124).

reduction long enough for the biological healing process to be able to take place.

Hardware fixation: Previously, temporary trans-articular K-wire fixation of the AC joint has been used in combination with direct ligament repair. However, this technique has led to unsatisfactory outcomes, including K-wire breakage, migration and loss of reduction^[7]. Likewise, CC cerclage or screw fixation such as the Bosworth screw have led to unacceptable risk of screw breakage^[10]. Some remove the screw after 6 to 8 wk to avoid this complication. Even with adequate screw positioning, hardware failure and obligatory screw removal have decreased the popularity of this technique.

Hook plate fixation: The hook plate is a metal device that keeps the AC joint in a reduced position by hooking its tip under the acromion and fixing it to the clavicle with screws^[18]. It can be used alone or in conjunction with other methods of ligament repair.

The joint separation is either reduced and then the hook plate is positioned, or the hook plate is inserted with the hook under the posterior aspect of the acromion and then pushing the plate segment against the distal end of the shaft of the clavicle, in that way levering the clavicle downwards. Most of the time the 4-hole (shortest) hook plate can be used. Either the hook can be adjusted to the morphology of the acromion or the plate can be adjusted to the morphology of the distal clavicle.

The advantage of this technique is that it provides a

strong and stable construct. There are case series that report acceptable results of hook plate fixation^[22,23]. A disadvantage is that the plate crowds the subacromial space, causing subacromial impingement, rotator cuff lesions, and even acromial stress fractures due to the hook^[24]. The hook makes a pinpoint contact with the undersurface of the acromion, which might explain why complications commonly occur after hook plate fixation^[25]. Furthermore, pain or discomfort is experienced because of the hardware^[16]. Because of these reasons, removal of the plate is routinely required after 3 to 4 mo, making a second operation necessary^[18,22,23]. This in turn can lead to loss of reduction^[22,23].

The Canadian Orthopaedic Trauma Society recently completed a multicenter-randomized clinical trial involving hook plate fixation vs nonoperative treatment of 83 AC dislocations^[18]. Disability and Constant scores were better in the nonoperative group after 3 mo but the differences disappeared at 1 and 2 years. In contrast, radiographic reduction was better in the operative group at all time points but there were more complications and reoperations in this group^[18]. The necessity of implant removal, uncertain superiority over nonoperative management, and the higher incidence of complications are important considerations of hook plate fixation.

Suture button CC fixation: Suture buttons have been introduced as an alternative to simple suture fixation to anatomically repair the CC ligaments. These devices consist of two metal buttons that are connected by thick nonabsorbable sutures. The buttons are locked behind

the clavicle and coracoid drill holes and the sutures function as the CC ligaments^[16,26]. Biomechanical studies have shown that suture buttons have comparable biomechanical strength as compared to the native ligaments^[26,27].

The technique has the advantage of allowing minimally invasive implantation as well as sustaining some range of motion between clavicle and scapula. However, single CC suture button fixation has appeared to be biomechanically inferior to the native CC ligaments *in vivo*^[26]. The single-button technique has resulted in high failure rates due to knot slippage, suture breakage, button migration, fractures^[28-30] and large or misdirected drill holes^[29] as well as failure to address the AC joint capsule^[31-33]. Because of high rates of failure with the use of single buttons, the use of multiple suture buttons is now advocated to restore both the conoid and trapezoid ligaments (improving horizontal and vertical instability) and reduce the failure risk^[26]. For example, Struhl and Wolfson^[34] used a mini-open technique with a continuous loop double endobutton in combination with a lateral clavicle resection. Recently, these authors have added a figure-of-8 ultratrape suture through drill holes in the acromion and clavicle to directly augment AC joint stability^[34].

Suture button fixation has several advantages, particularly the ability for minimal soft tissue disruption and generally satisfactory outcomes. However, caution should be used as these constructs have been associated with remaining anterior-posterior instability and a risk of hardware issues^[35]. Suture button fixation has higher shoulder function scores and lower postoperative pain when compared to hook plate fixation; however, there are higher complication rates^[36].

CC ligament reconstruction: The Weaver and Dunn procedure was first described in 1972 and utilizes the native coracoacromial (CA) ligament in AC joint reconstructions. This technique involves the distal clavicle excision in combination with transfer of the CA ligament from the acromion to the distal clavicle remnant in an attempt to restore AC stability^[37]. The procedure has been studied extensively, demonstrating up to a 30% failure rate and only approximately 25% biomechanical strength when compared to intact CC ligaments^[16,38]. The modified procedure supplements the ligament transfer with a direct CC fixation or hook plate^[38,39]. There are a few studies that reported inferior results of the modified procedure compared to anatomic CC ligament reconstruction technique using autogenous semitendinosus graft^[40-43].

The utilization of autograft or allograft for the anatomic reconstruction of the CC and AC ligaments in acute AC joint dislocation has rapidly gained popularity in the past few decades. In 2003, Lee *et al*^[42] biomechanically compared the strength and stiffness of the native CC ligament with that of reconstructions with CA ligament or free tendon grafts. They reported that tendon grafts had strengths equivalent to the native CC ligament strength,

and were significantly stronger than the CA ligament reconstruction.

There are numerous techniques to reconstruct the CC ligaments. Mazzocca *et al*^[38,44] used a semitendinosus autograft to reconstruct the anatomical configurations of the trapezoid and conoid ligaments, as well as the AC ligaments, without use of supplemental CC or AC stabilization. With this technique, the lateral 1 cm of the clavicle is excised. A soft-tissue tunnel is created under the coracoid. Two bony tunnels are drilled in the clavicle; one 4.5 cm from the AC joint (positioned slightly posteriorly to reconstruct the conoid ligament) and one 2.5 cm from the AC joint (positioned slightly anteriorly to reconstruct the trapezoid ligament). The graft is passed through the tunnels in a figure-of-eight fashion, and fixed proximally using interference screws while the AC joint is reduced with upper displacement of the scapulohumeral complex. Finally, the lateral limb of the graft is sutured to the acromion to reconstruct the AC ligament.

We use an autograft tendon reconstruction technique of the CC joint without bone tunnels in combination with direct suture fixation of the AC joint (Figure 4). The semitendinosus tendon is harvested. A Sabelhouw incision is made and the lateral clavicle is resected. A double nonabsorbable suture is passed through small drill holes in the lateral clavicle and the acromion for AC joint repair. The coracoid process is exposed through the deltopectoral interval. The semitendinosus tendon is directed under the coracoid and over the clavicle for CC joint repair (it is passed from the medial aspect of the coracoid to the posterior aspect of the clavicle to mimic the conoid ligament and from the lateral aspect of the coracoid to the anterior aspect of the clavicle to mimic the trapezoid ligament). The AC joint is reduced by elevation of the arm, the AC joint sutures are tightened, and the semitendinosus is secured with interrupted nonabsorbable sutures over the clavicle. Advantages of this technique without bone tunnels or interference screws are low costs, avoidance of iatrogenic fracture risk, no foreign body use (except for sutures), and the same biomechanical strength as anatomic repair with bone tunnels^[45]. We have treated 23 patients with Rockwood type 4 or 5 lesions with use of this technique, of whom five were failures from elsewhere. All patients indicated that they would undergo the procedure again and were satisfied with the cosmetic outcome. They were able to participate in work and sports without restrictions. Two complications occurred; one patient had a temporary frozen shoulder and another had a recurrence due to a fall after 6 wk.

Arthroscopic surgery

Minimally invasive AC joint reconstruction and repair techniques have been developed since the introduction of arthroscopic shoulder surgery. Although arthroscopically assisted AC reconstruction should be used by skilled arthroscopists only, it has the possible advantages of the minimally invasive nature, direct visualization of

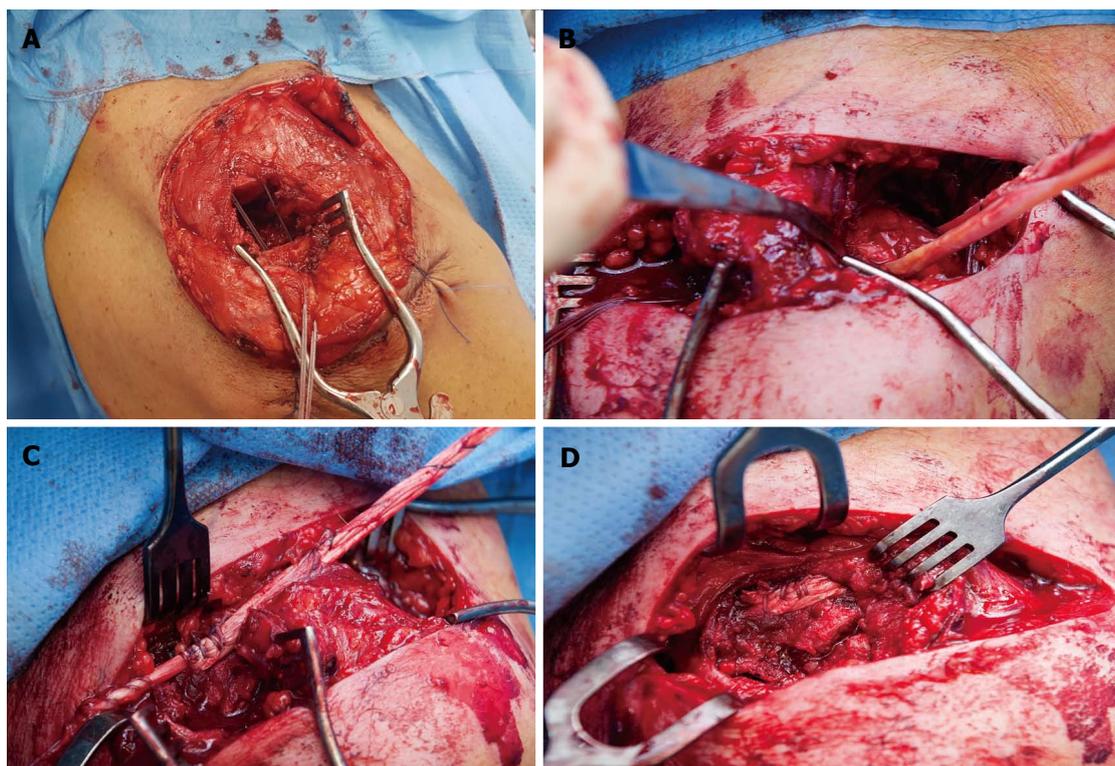


Figure 4 Intra-operative pictures of an autograft tendon reconstruction technique of the coracoclavicular joint without bone tunnels in combination with direct suture fixation of the acromioclavicular joint. A: The lateral clavicle is resected, and a double nonabsorbable suture is used for AC joint repair; B-D: A semitendinosus tendon is passed under the coracoid and over the clavicle for CC joint repair. AC: Acromioclavicular; CC: Coracoclavicular.

the reduction and placement of coracoid fixation, the possibility to address additional pathologies, and the deltotracheal fascia can remain attached^[46,47]. A further advantage of arthroscopic treatment is a diagnostic glenohumeral arthroscopic evaluation. Concomitant injuries are common in AC joint dislocations and may occur in up to 20%-25% of patients^[47-49].

Suture button fixation is typically used with arthroscopically assisted AC repair. Initially, one button was used for repair. Murena *et al.*^[49] described arthroscopic treatment of type III-IV acute AC dislocation with a double flip button. They found excellent clinical results in terms of Constant score (mean 97 points) and patient satisfaction, but a disappointing radiological result with a partial loss of reduction due to distal migration of the flip button within the upper third of the clavicle in one-fourth of the cases, at a mean follow-up of 31 mo. However, because of a high failure risk of one-button repair, either multiple suture buttons or augmentation techniques are used nowadays. An example of a multiple suture button technique is that by Imhoff *et al.*^[47]: Anatomic CC ligament reconstruction utilizing double Tight Rope (Arthrex Inc., Naples, FL, Italy) suspensory fixation. This dual anatomic technique aims to reproduce the native conoid and trapezoid ligaments. The surgical procedure is begun with a diagnostic shoulder joint arthroscopy, followed by arthroscopic preparation of the coracoid undersurface through the rotator interval. After a guided superior skin incision and AC joint reduction, the conoid and trapezoidal tunnels are drilled with use of a drill guide system. The two TightRope devices are inserted

through the tunnels and fixated. The longest follow-up case series of double suture button fixation in 23 patients reported a high satisfaction rate (96%) after 58 mo but eight radiographic failures were noted^[47].

An example of augmentation in arthroscopic-assisted reconstruction of AC joint instability is the technique by DeBerardino *et al.*^[46]: CC ligament reconstruction with an allograft augmented GraftRope (Arthrex Inc., Naples, FL, Italy) system. This technique utilizes an arthroscopically placed fixation with a GraftRope construct augmented with an allograft (or autograft) centrally. After glenohumeral joint arthroscopy, the subacromial bursa is debrided and the AC joint visualized. Joint reduction is checked with fluoroscopy. Following clearance of the coracoid base, the tunnel is drilled with use of a drill guide through a small incision over the clavicle. A semitendinosus or tibialis tendon is passed through the implant system before it is inserted with use of a passing suture. An interference screw is placed between the graft limbs for final construct fixation.

A technique to perform the Weaver-Dunn procedure in an all-arthroscopic way is described by Boileau *et al.*^[50] This procedure also starts with debridement of the undersurface of the base of the coracoid process through the rotator interval. Then the scope is moved to anterior, where the CA ligament is released from the acromion (with a chip of bone remained attached to the ligament). Thereafter, a lateral clavicle resection is performed, and the medullary canal of the clavicle is enlarged and deepened with a burr. Then, the CC reduction and

fixation is performed with use of a double-button system. Finally, the bone-ligament transfer of the CA ligament is pulled in the created cavity of the lateral clavicle and fixed through a second drill hole on the superior cortex. A mean follow-up of 36 mo is now available for a group of 57 patients^[51]. Two patients experienced a recurrent dislocation and 6 patients a partial loss of reduction. The Subjective Shoulder Value ranged from 54% to 85%, and 96% of the patients were satisfied with the procedure and the cosmesis^[51]. There are no randomized controlled trials comparing the outcomes of open vs arthroscopically assisted or all-arthroscopic techniques. Arthroscopic techniques in case series are relatively safe procedures, with equivalent outcomes to open surgery, but demonstrate a distinct complication profile^[39,46,47,52-58]. Arthroscopic suture button techniques generally demonstrate good radiographic outcomes but significant hardware irritation.

Postoperative management

The rehabilitation programs differ between surgical techniques. In general, a sling is provided and progressive range-of-motion exercises up to 90 degrees elevation are begun early after surgery for 6 wk. After this initial period, range-of-motion and strengthening exercises are gradually increased. Non-contact sports can be resumed after 3 mo. Generally, contact athletes are allowed unrestricted sport activities after 6 mo.

TIMING OF SURGERY

Accurate reduction in AC dislocation is considered easier when surgery is performed earlier after injury^[59,60]. However, there is no clear definition of early and delayed surgery. Rockwood and Young^[12], have noted that acute pain generally disappears 2-3 wk after an AC dislocation. Therefore, approximately 3 wk seems a clinically relevant dividing line.

A recent review of Song *et al.*^[60] summarized eight studies comparing acute and delayed surgical treatment of AC dislocation. The dividing line between early and delayed surgery was defined as 3, 4 and 6 wk after injury. They concluded that early surgery (< 3 wk) has better reduction and clinical outcomes than delayed surgical treatment (> 3 wk) and no significant difference in the complication rate^[60]. The studies included in this review used several different methods of reconstruction and this limits the strength of this conclusion.

Delayed surgery is necessary for patients with AC dislocations that failed conservative treatment or with intolerance for early surgical treatment. Adam *et al.*^[3] reported higher rates of deformity recurrence and poorer functional outcome in chronic cases. On the other hand, other studies report satisfactory results after surgical treatment of chronic AC dislocations^[48,52,59,61].

In conclusion, early surgery for grade III-V dislocations may result in better functional and radiological outcomes, with a reduced risk of loss of reduction compared with delayed surgery^[7,54,60]. However, a nonoperative trial

period of 6 mo seems justified for type III lesions, based on high satisfaction rates and normal functionality in 80% of patients^[62]. For example, Rolf *et al.*^[63] treated patients early at a mean of 10, or delayed at a mean of 7.7 mo (after failure of conservative treatment).

OUTCOMES

Many shoulder scoring systems are used to determine functional outcomes in the literature. Unfortunately, none of these is specific for AC dislocations. In a review of eight studies, more than 30 shoulder scoring systems were applied^[60]. This makes reliable comparison of studies difficult.

A Cochrane review in 2010 reported data from three studies (174 participants) and found no significant difference in movement, strength, or function between surgically and conservatively treated patients^[64]. Another review in 2013, which specifically looked at Rockwood type III AC dislocations in eight studies (247 participants), showed the objective and subjective shoulder function outcome was better in the operative group (especially in young adults), though the rate of complications and radiographic abnormalities were higher^[17]. The rehabilitation time was shorter in the conservative group but the cosmetic outcome was worse.

AC dislocation is a typical sports related injury^[65]. Therefore, resumption of sports and work are important outcome aspects. Recently, a retrospective review of Dunphy *et al.*^[66] showed that most patients (77%) were able to return to work following nonsurgical management of type V injuries after six months but had limited functional outcome scores. Patients who are treated nonoperatively for a Rockwood type III AC dislocation need roughly half the time to return to work and sport, compared with patients treated operatively^[2,7,67]. Manual workers treated surgically returned to work after an average of 11 wk, compared with 4 wk after nonsurgical treatment^[67]. Gstettner *et al.*^[68], however, reported that operative treatment of Rockwood type II AC dislocation resulted in more patients returning to the same level of activity at work (82% vs 63%). The level of sports did not differ (67% vs 65%). In Rockwood type V, overhead athletes require more time to resume their sports activity^[69]. In minimally invasive anatomic CC reconstructions of type III AC dislocation, 100% return to sports rates has been reported; however, the influence of type of sport was not considered^[56,70].

The main concern when comparing outcome data is the lack of long-term outcome studies. We performed a literature search of comparative studies with a minimum of 4 years of follow-up (Table 1). We found five studies and classified the operative techniques in the four categories described above^[39,52-59]. There were one randomized controlled trial and four retrospective cohort studies. The studies described early and delayed treatment of type III-V dislocation, as well as different operative techniques. Generally, few statistically significant differences were found between the groups

Table 1 Characteristics of comparative studies with a minimum 4-yr follow-up

Ref.	Type of study	LE	Rockwood classification (No. of patients)	Operative technique (No. of patients)	Category ¹	FU (yr)	Outcome
Boström Windhamre <i>et al</i> ^[55] 2010	Retrospective case control	III	Delayed type III-V (47)	Weaver-Dunn and PDS suture (23)	3	6.1	Constant score: $P > 0.05$ SPADI: $P \geq 0.05$ QuickDASH: $P > 0.05$ VASa: $P = 0.03$ (in favor of PDS) Subluxation: $P > 0.05$
				Weaver-Dunn and hookplate (24)	2		
Kovilazhikathu Sugathan <i>et al</i> ^[56] 2012	Retrospective cohort	IV	Early type III (7) Delayed type III (11)	Open reduction and internal fixation + tension band wiring (7)	1	6.3	OSS: $P = 0.05$ Complications: 71% (early), 9% (delayed)
				Modified Weaver-Dunn procedure with PDS suture (11)	3		
Motta <i>et al</i> ^[52] 2012	Retrospective case control	III	Early type III-V (34) Delayed type III-V (17)	CC reconstruction with LARS (34)	3	5.4	Reduction ^a : $P < 0.05$ (in favor of early reconstruction) Constant score: $P > 0.05$ SST: $P > 0.05$
				CC reconstruction with LARS (17)	3		
Fauci <i>et al</i> ^[59] 2013	RCT	I	Delayed type III-V (40)	Allograft (semitendinosus) (20) Synthetic ligament (LARS) (20)	4 3	4	Constant score ^a : $P = 0.01$ Reduction: $P > 0.05$
Jensen <i>et al</i> ^[39] 2014	Retrospective comparative study	III	Early type III-V (56)	Hookplate (30)	2	4	VAS: $P > 0.05$ SST: $P > 0.05$
				Double TR technique (26)	3		

^aStatistically significant difference ($P < 0.05$); ¹Four categories: (1) fixation of the AC and/or CC with hardware including screws and K-wires; (2) hook plates; (3) fixation of the CC with sutures or suture buttons; and (4) reconstruction of the CC ligaments with autograft or allograft tendon. LE: Level of evidence; FU: Follow-up; SPADI: Shoulder pain and disability index; QuickDASH: Disabilities of the arm, shoulder and hand score; VAS: Visual analogue scale; OSS: Oxford shoulder score; LARS: Ligament augmentation and reconstruction system; RCT: Randomised controlled trial; SST: Simple Shoulder Test; TR: Tight rope.

(Table 1). The main differences included more pain experienced by patients treated with a hookplate vs PDS sutures, a better reduction and less complications after early reconstruction vs late reconstruction, and better Constant scores in allograft vs artificial ligament reconstruction^[39,52,55,56]. Literature showed no conclusive evidence for outcome of conservatively or operatively treatment of Rockwood type III-V AC dislocations. Overall, physically active young adults seem to have a slight advantage in outcome when treated operatively. Randomized controlled trials that compare long-term outcomes of nonoperative treatment with different surgical techniques are needed in order to draw firm conclusions.

COMPLICATIONS

Patients with complications have significantly lower clinical scores, suggesting that the presence of complications appears to be the only predictor of poorer clinical outcomes^[13,14,35,71]. Complications after surgical treatment range from 27% to 44%^[13,28]; the main being infection (4% to 8%), hardware complications (4%) and further surgery (13%)^[68]. In a recent review of four studies, 12 (13%) complications were found in 96 patients after early surgery and 14 (18%) complications are occurred in 79 patients after delayed surgery^[60].

Hookplate fixation has an overall complication rate of 11%^[23] and an infection rate of 5%^[7]. Long-term retention of the plate may lead to acromial osteolysis or

fracture, which implies that a second surgery is required to remove the plate after 3 mo, when the ligaments have healed^[52,55,57].

Clavert *et al*^[35] prospectively reported a complication rate of 27% in 116 primary anatomic button fixations. There were 16 cases of hardware failure resulting in symptoms or loss of reduction. Forty-eight patients also had persistent dislocation of $> 150\%$. Singh^[72] reported secondary progressive loss of reduction in 7 out of 9 patients after a mean of 3.1 mo. Three patients underwent revision.

Millet *et al*^[73] presented a review of 12 studies that reported complications following anatomic CC ligament reconstruction with biologic grafts and described an overall complication rate of 40%. The most serious complications were graft failure, hardware complications, and distal clavicle and/or coracoid fractures as a result of the bone tunnels. Coracoid/clavicle fractures remain a significant complication that occur predominately in techniques utilizing bone tunnels^[74].

The rate of surgical complications in the literature following arthroscopic reconstruction of the CC ligaments varies from 13% to 27% and can reach 40% if postoperative loss of reduction is taken into account^[27]. The five most commonly documented complications of arthroscopic fixation are superficial infection (4%), shoulder pain (27%), CC calcification (32%), fracture (5%), and loss of reduction (27%)^[74].

Thus, many studies have reported postoperative loss of reduction (17% to 80%) after open anatomic

reconstruction with autogenous tendon graft or arthroscopic assisted fixation with suture buttons^[13,14,28,35,75]. However, a partial loss of reduction does not appear to influence the overall functional results^[22,63].

Nowadays, the cosmetic outcome is becoming more and more important for patients. However, the surgeon should consider the preference of a better cosmetic outcome against the higher complication rate in surgically treated patients.

RECENT DEVELOPMENTS

There has been an exponential increase in the number of publications on surgical AC joint reconstruction and repair over the past few years^[2]. Recent studies have concentrated on minimally invasive or arthroscopic anatomical reconstruction of the CC ligaments^[2,7,13,58,76]. Although many improvements have been made, some questions still remain: How many drill holes are needed in the coracoid and clavicle? Which type of graft should be used? And, should only the CC ligaments be reconstructed or both the CC and AC?

Bone tunnels are commonly used for anatomic reconstruction of the CC ligaments. Because the conoid and trapezoid ligaments attach in different areas of the clavicle and the coracoid, making two holes in both bones looks appealing. However, the use of multiple tunnels is technically demanding and increases fracture risk^[27,74]. Jerosch *et al*^[77] in a biomechanical study evaluated eight different AC reconstruction techniques. They found the best restoration of anatomy with suture anchor fixation in the base of the coracoid process.

The historical choice of material for stabilization of the CC ligament mainly depends on the clinical setting and timing of surgery, with synthetic material (sutures or tape) in the acute and tendon graft in the chronic injury^[75]. Today, most surgeons agree that a biological augmentation is required in chronic cases to enhance the healing potential of the torn structures^[5,59,63]. Laboratory studies have shown that anatomic reconstruction with double graft tendons have native-like biomechanical properties^[19] and clinical data are promising^[52].

Since horizontal instability of the AC joint may result in chronic pain and functional shoulder impairment^[78], there is a raising focus on the relevance of specific techniques to improve horizontal stability. Schneibel *et al*^[78] described persistent horizontal instability in 41% of cases after isolated CC double ligament stabilization, and developed an all-arthroscopic, radiographically assisted technique that uses a triangular AC cerclage in conjunction with the CC reconstruction to provide better horizontal stability^[51,78]. Saier *et al*^[79] showed biomechanically that only combined AC and CC reconstruction can adequately restore physiological horizontal AC joint stability. In addition, a recently published study showed that triple-bundle reconstruction including AC graft augmentation yielded superior clinical and radiological outcome than single-bundle CC reconstruction^[52].

CONCLUSION

The aim of the current review was to provide an up-to-date and evidence-based overview of relevant treatment options for AC joint dislocations.

The recently published literature has significant limitations, namely a paucity of high quality trials and long-term follow-up. Most of the studies include heterogeneous populations with varying severities and chronicity of injury. Also, the existence of many different surgical techniques prevents the drawing of firm evidence-based conclusions.

The available evidence does provide some important clues. Operative treatment of Rockwood III AC joint dislocations results in better cosmetic and radiological results and similar function but longer time off work and increased complication rates compared with conservative treatment^[7,17,61]. Current literature suggests that the decision for treatment of type III injuries should be made on a case-by-case basis, with an emphasis on initial nonoperative treatment^[2]. Early operative treatment for grades III-V dislocations may result in better functional and radiological outcomes, with a reduced risk of infection and loss of reduction compared with delayed surgery.

Various operative techniques have been described. However, most techniques do not anatomically restore the complex articulation of the AC joint. Anatomical CC ligament reconstruction may result in optimal functional and radiological outcomes. The conoid and trapezoid ligaments have unique anatomic alignments and different functions. Each ligament should be considered during operative treatment^[39,43].

Arthroscopically assisted AC reconstruction has the possible advantages of the minimally invasive nature, better visualization of the coracoid and the possibility to detect associated glenohumeral lesions, but demonstrates a distinct complication profile in the less experienced arthroscopist. There is currently no evidence to support arthroscopic rather than open surgery, as comparative studies are not available.

Further studies are needed especially in terms of randomized controlled trials and long-term outcomes to confirm stability of the AC joint and optimal functional results.

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Transforaminal Percutaneous Endoscopic Discectomy using Transforaminal Endoscopic Spine System technique: Pitfalls that a beginner should avoid

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Abstract

Transforaminal Percutaneous Endoscopic Discectomy (TPED) is a minimally invasive technique mainly used for the treatment of lumbar disc herniation from a lateral approach. Performed under local anesthesia, TPED has been proven to be a safe and effective technique which has been also associated with shorter rehabilitation period, reduced blood loss, trauma, and scar tissue compared to conventional procedures. However, the procedure should be performed by a spine surgeon experienced in the specific technique and capable of recognizing or avoiding various challenging conditions. In this review, pitfalls that a novice surgeon has to be mindful of, are reported and analyzed.

Key words: Transforaminal Percutaneous Endoscopic Discectomy; Transforaminal Endoscopic Spine System; Lumbar disk herniation; Pitfalls; Spine surgery

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Core tip: Transforaminal Percutaneous Endoscopic Discectomy (TPED) is an evolving minimally invasive technique that has been proven to be safe and effective in treating symptomatic lumbar disc herniation (LDH). However, this relatively new therapeutic approach requires special training and expertise so as to evade complications that may endanger the safety of the patient. In this review, current concepts regarding challenging indications

and contraindications of this novel technique are analyzed focusing on several conditions and pitfalls that a beginner spine surgeon should avoid when treating LDH using TPED with Transforaminal Endoscopic Spine System technique, so as to eliminate possible risks and thus improve outcomes.

Kapetanakis S, Gkasdaris G, Angoules AG, Givissis P. Transforaminal Percutaneous Endoscopic Discectomy using Transforaminal Endoscopic Spine System technique: Pitfalls that a beginner should avoid. *World J Orthop* 2017; 8(12): 874-880 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i12/874.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i12.874>

INTRODUCTION

Symptomatic lumbar disc herniation (LDH) is a common etiology for spine surgery. Although microdiscectomy is considered to be the gold standard method, the need for minimally invasive techniques and the improvements in the use of optics and surgical instruments have led to the utilization of Transforaminal Percutaneous Endoscopic Discectomy (TPED) using the Transforaminal Endoscopic Spine System (TESSYS) technique^[1-3].

TPED has several advantages such as direct visualization of the pathology, reduced soft tissue trauma, reduced blood loss, quicker recovery and preservation of the adjacent anatomy. It can be an effective and safe method in the hands of an experienced spine surgeon if specific steps are followed^[1]. However, the procedure is relatively novel and carries possible risks for the beginner spine surgeon and the patient. Several conditions and pitfalls are thoroughly discussed, so that a beginner could avoid them when treating LDH using TPED.

Indications

Generally, the indication for TPED, in compliance with clinical findings, is usually found to be persistent sciatica caused by LDH. There are several inclusion criteria such as radiculopathy, positive nerve root tension sign, sensory or motor neurological lesion on clinical examination, cauda equine syndrome, hernia confirmed by magnetic resonance imaging (MRI) of the lumbar spine. Failure of 12-wk conservative treatment is also a strong indication^[2,3].

Challenging conditions

Various conditions have been reported as contraindications for TPED including: Recurrent herniated disc, migrated LDH, sequestration of the disc, central or lateral recess spinal stenosis, or previous surgery at the affected level, segmental instability or spondylolisthesis, spinal tumor or infection and vertebral fracture^[1,4-6]. The following conditions should draw the maximum attention in the hands of an inexperienced spine surgeon.

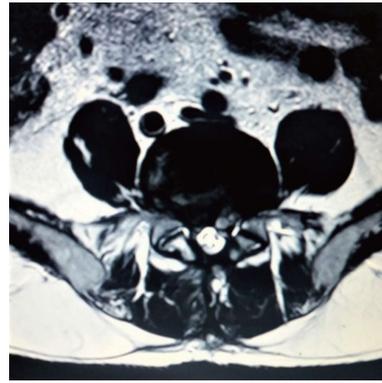


Figure 1 Case of recurrent disc herniation after open discectomy.

SURGICAL TECHNIQUE-RELATED CONDITIONS

Recurrent disc herniation

The gold standard treatment for recurrent LDH is considered to be open discectomy (Figure 1). However, in the hands of an experienced spine surgeon, TPED for recurrent LDH is a feasible and effective alternative to conventional repeated discectomy, while reducing tissue damage, scar tissue formation and instability^[7].

Scar tissue formation

Conventional microdiscectomy is an open surgery with high risk of scar tissue formation contrary to endoscopic discectomy. In case of recurrent LDH and repetitive procedures scar tissue formation is almost inevitable. These cases can be difficult to manage with TPED. The altered anatomy of the region, the possible nerve tension and the difficult visualization of the anatomic structures are major obstacles for a beginner spine surgeon. Recently, percutaneous endoscopic interlaminar lumbar discectomy with dissection of the scar tissue from the medial facet joint rather than from the neural tissue has been proposed as an effective alternative surgical method on the background of recurrent disc herniation^[8]. Also, less systemic cytokine response in patients following microendoscopic vs open lumbar discectomy has been found to exist, indicating the minimally invasive character of the first one^[9]. Additionally, microendoscopic discectomy has been associated with lower risks for surgical site infection and major complications contrary to open discectomy^[10].

Migrated or extruded LDH

TPED is usually appropriate for normal or caudal LDHs. Pediclectomy or translaminar approach may be required to remove an upward- or downward-migrated LDH^[11,12] (Figures 2 and 3). Dorsal LDH located behind the dural sac is not treated with TPED. Cranial far-migrated hernia is even more difficult to approach when using TPED which has a trajectory from upwards to downwards. Open surgery is also proposed for far-migrated disc



Figure 2 T2 weighted sagittal magnetic resonance imaging demonstrating a disc herniation located at the L5/S1 level.

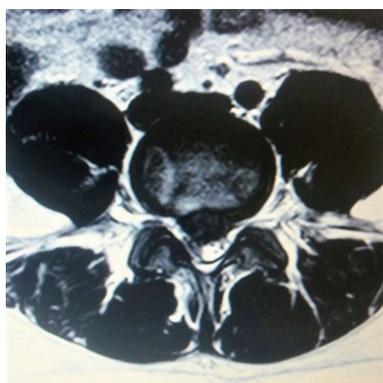


Figure 3 Case of a migrated central hernia.

herniations^[12]. Even for extruded disc fragments endoscopic transforaminal discectomy has been proposed as a safe and effective alternative^[13].

PATIENT-RELATED CONDITIONS

Intracanal LDH at the L5/S1 level with a high and steep iliac crest

High iliac crests refer usually to men contrary to women^[14] (Figure 4). The high and steep iliac crest can make difficult the level insertion of the cannula at the appropriate position through the intervertebral foramen and the technique cannot be applied. In high iliac crest cases where the iliac crest is above the mid L5 pedicle, foraminoplasty may be considered for transforaminal access of L5-S1 disc herniation^[15]. Lee *et al.*^[16] also proposed the foraminoplastic approach in order to facilitate the insertion of the cannula. Tezuka *et al.*^[17] indicated that treatment for the central type of LDH at the L5-S1 disc level is more difficult than at the L4-L5 due to the iliac crest. This can be solved by using a more perpendicular approach with the possible addition of a foraminoplasty^[17]. Interlaminar approach can escape the blockade of crista iliaca, and offer several advantages including a faster puncture orientation, a shorter operation time, and less intraoperative radiation exposure^[18]. Application of transiliac approach to



Figure 4 Case of high and steep iliac crests.

intervertebral endoscopic discectomy in L5/S1 LDH has also been suggested^[19]. Additionally, it is reported that compared with the L5/S1 level, the L4/5 level might be easier to master after short-term professional training^[20]. It is true that some propose the percutaneous endoscopic discectomy as the treatment of choice for foraminal and extraforaminal disc herniations at the L5-S1 level on appropriately selected patients^[21]. Since this is considered the most difficult level, we can forecast that TPED might be established as a treatment for all lumbar levels.

Scoliosis

Scoliosis is a form of deformity which results in misalignment of the spine. Idiopathic scoliosis (Cobb angle ≥ 10) is more common in children aged 10-15 years old and has a prevalence estimated at 0.5%^[22]. Degenerative scoliosis is observed in more than 30% of elderly patients with no history of spinal abnormalities and is typically diagnosed in patients older than 40 years^[23]. The prevalence of 10°, 10°-20° and > 20° curves is 64%, 44% and 24%, respectively^[24]. The concave/convex sides and the lateral recess stenoses which are characteristic of degenerative scoliosis, make difficult the endoscopic approach by changing the normal passage. Basically, the Kambin's triangle is altered making difficult the safe passage of the endoscopic instruments^[4]. In coronal projection, the deformation of the lumbar spine affects the form of the meninge something which makes its traumatization more possible. Nevertheless, the use of TPED for LDH on the background of lumbar scoliosis has been recently attempted^[25,26].

Spondylolysis-spondylolisthesis

Spondylolysis is a unilateral or bilateral stress fracture of the pars interarticularis and is usually combined with spondylolisthesis. In spondylolistheses, alteration of the normal anatomy of the lumbar intervertebral foramen and its dimensions resulting in foraminal narrowing and disc bulging is observed^[27]. The measurement of spondylolisthesis is based on the widely recognized method proposed by Meyerding^[28] in 1932 (Figure 5). Meyerding defined the slippage on plain X-ray imaging in accordance to the vertebra below. The caudal

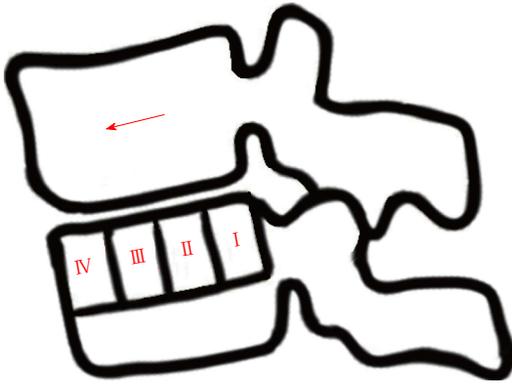


Figure 5 Meyerding's grading of spondylolisthesis regarding cranial anterior vertebral slippage in accordance with the vertebra below.



Figure 6 Case of an obese patient to be treated with Transforaminal Percutaneous Endoscopic Discectomy for lumbar disc herniation.

vertebra is divided into four parts. Grade I means a translation of the cranial vertebra of up to 25%, Grade II of up to 50%, Grade III of up to 75%, and Grade IV up to 100%^[28]. Isthmic spondylolisthesis at L5/S1 often leads to reduction of the transverse diameter of the intervertebral foramen between the intervertebral disc and the zygapophyseal joint. The normal shape of the intervertebral foramen is altered, while spinal nerves and roots, sinuvertebral nerves, spinal arteries, and intervertebral veins are compressed between transforaminal and extraforaminal ligaments^[29]. The radicular symptoms are usually caused by compression of the exiting L5 nerve root and its adjacent vessels in the L5-S1 foramen. In these cases the only surgical options have been lumbar laminectomy and lumbar fusion, however TPED with foraminoplasty appears as an effective upcoming treatment^[30,31]. We believe that beginners should avoid TPED when dealing with spondylolistheses of 2nd grade and greater^[32]. Using TPED, the conditions of spondylolysis and spondylolisthesis can not be treated.

Obese patients

In obese patients, a beginner spine surgeon will have to deal with technical considerations due to increased fat tissue, such as bad fluoroscopic verification and

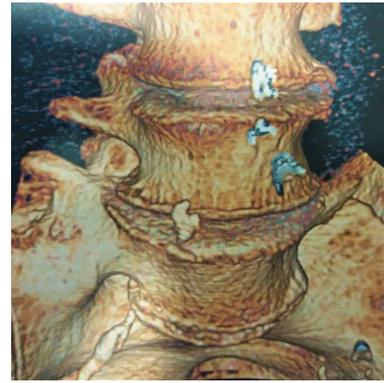


Figure 7 Case of Bertolotti's syndrome.

difficult transforaminal approach. TPED for LDH in obese patients has shown satisfactory early results, however more studies are needed to confirm its efficacy^[33,34] (Figure 6).

Muoskeletal malformations

Several variations of the lumbar spine can be an obstacle for the realization of TPED with Bertolotti's syndrome being a common etiology of low back pain, especially for young people^[35]. Lumbosacral transitional vertebrae are increasingly recognized as a common anatomical variant associated with altered patterns of degenerative spine changes. Bertolotti's syndrome refers to the association between lumbosacral transitional vertebrae and low back pain^[36] (Figure 7). On the co-existence with LDH, Bertolotti's syndrome makes difficult the transforaminal passage through the Kambin's triangle during TPED^[27].

High LDH levels in conjunction with abnormal location/ variations of adjacent anatomic formations

Kidneys are important retroperitoneal organs adjacent to the lumbar spine. They are normally located between the transverse processes of T12-L3 vertebrae, with the left kidney typically more superior in position than the right^[14] (Figure 8). Treating high level LDHs, especially T12-L1, L1-L2 and L2-L3, using TPED in accordance with abnormal location and possible variations of adjacent organs such as kidneys may result in their traumatization during the passage of the reamers and the cannula.

SURGICAL PROCEDURE

TPED using the efficacy of TESSYS technique is performed under local anesthesia and mild sedation^[1,3]. Patients are initially placed at the lateral decubitus position, lying down on the opposite side (Figure 9). Lesion is thus confronted upwards. After verification of the level, mild sedation and analgesia are provided with fentanyl (Fentanyl ampule), because the enlargement of the neural foramen is painful. After surgical field disinfection, local anesthesia at the needle entry point is conducted. This point is anatomically about 11 cm away from midline defined. Transforaminal promotion of the

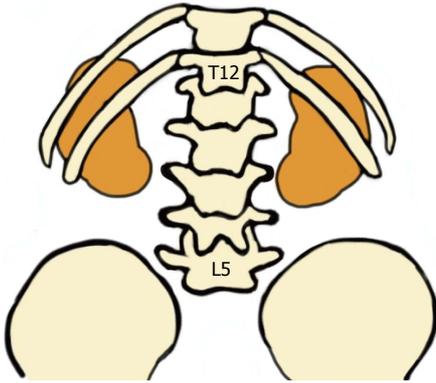


Figure 8 Posterior schematic illustration of the location of kidneys in accordance with lumbar spine levels.

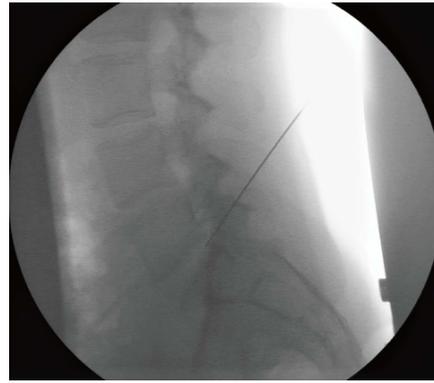


Figure 11 Fluoroscopic verification of the operated level and insertion of the needle.

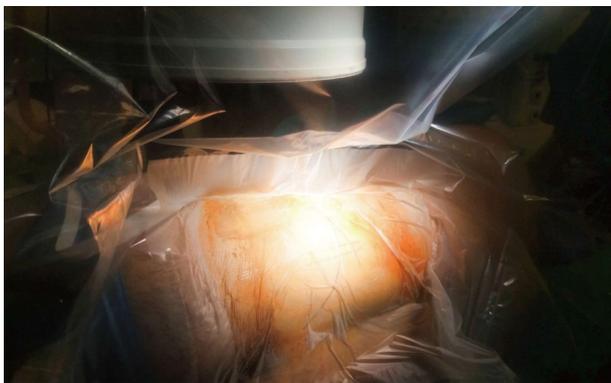


Figure 9 Placement of the patient at the lateral decubitus position and disinfection of the surgical field.

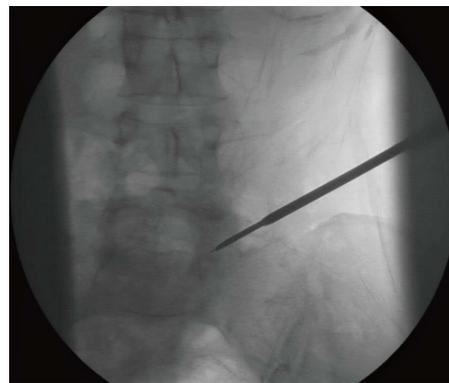


Figure 12 Sequential transforaminal passage of different size reamers.

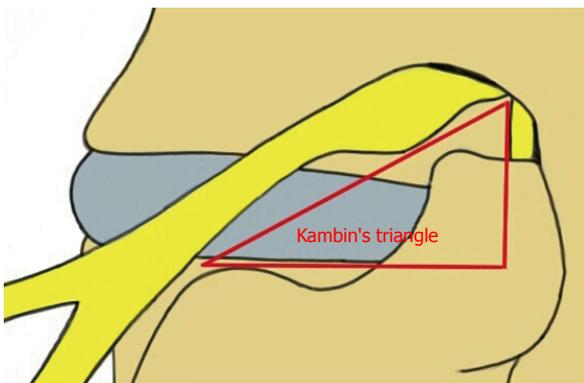


Figure 10 Kambin's triangle. The hypotenuse is parallel to the exiting nerve root, the base is according to the superior border of the transverse process of the caudal vertebra, and the height represents the trajectory of the traversing nerve root.



Figure 13 Insertion of the cannula and the endoscope afterwards.

needle through the anatomic triangle of Kambin (safe zone) is subsequently performed^[4] (Figures 10 and 11). Sequential transforaminal passage of three different size reamers (5.5, 6.5, 7.5 mm, joimax GmbH) constitute the next step (Figure 12). The cannula and endoscope are afterwards carefully inserted, in order to ensure nerve root preservation (Figure 13). Removal of herniated disc material is finally accomplished with

graspers (Figure 14). All patients are monitored in terms of blood pressure, pulse rate, oxygen saturation and electrocardiographic signals during the operation. Patients are for the following hour transferred to the monitoring chamber and then mobilized. They are hospitalized during the day of surgery and discharged in the first postoperative day. Possible complications could be: Nerve root damage, postoperative dysesthesia, dural tears, post-operative hematoma, wood infection and visceral injury^[5,37,38]. Patients are usually scheduled to have a check-up 6 wk after the surgery

Table 1 Summary of the indications, contraindications, advantages and disadvantages of the technique

Indications	Contraindications (for the beginners)
Radiculopathy	Surgical technique-related conditions
Positive nerve root tension sign	Recurrent disc herniation
Sensory or motor neurologic lesion on clinical examination	Scar tissue formation
Cauda equine syndrome	Migrated or extruded LDH
Hernia confirmed by MRI of the lumbar spine in compliance with clinical findings	Patient-related conditions
Failure of 12-wk conservative treatment	Intracanal LDH at the L5/S1 level with a high and steep iliac crest
	Scoliosis
	Spondylolysis-Spondylolisthesis
	Obese patients
	Muoskeletal malformations
	High LDH levels in conjunction with abnormal location/ variations of adjacent anatomic formations
	Disadvantages
Advantages	Careful selection of patients is needed
Safe and effective technique	Limited space for surgical maneuvering
Direct visualization of the pathology	Long learning curve
Less blood loss	
Less trauma and scar tissue	
Faster rehabilitation	
Preservation of the spine stability and the adjacent anatomy	

LDH: Lumbar disc herniation; MRI: Magnetic resonance imaging.

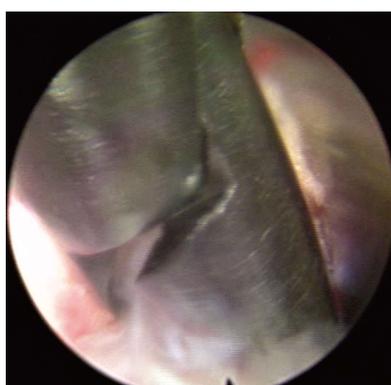


Figure 14 Removal of herniated disc material with a grasper.

at the outpatient clinic. Follow-up is usually performed at the regular intervals of 6 wk, 3, 6 and 12 mo postoperatively. The indications, contraindications, advantages and disadvantages of the procedure are summarized in Table 1.

CONCLUSION

TPED is an evolving minimally invasive technique which requires training and expertise. Every condition which alters the normal architecture of the spine and makes the access to the LDH difficult tests the abilities of the spine surgeon and sets a question mark on the feasibility and limits of TPED. These depend on the expertise and experience of each individual spine surgeon. It should be kept in mind that TPED is a combination of two interventional approaches involving the percutaneous and the endoscopic aspect; both of them indicate its demanding character. However, good training and coaching may overcome such difficulties offering a safe and efficient procedure to patients with

LDH.

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Basic Study

Role of fast-setting cements in arthroplasty: A comparative analysis of characteristics

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Abstract**AIM**

To evaluate the behaviour of two fast-setting polymethyl-methacrylate (PMMA) cements CMW® 2G and Palacos® fast R + G, as reference: Standard-setting Palacos® R + G.

METHODS

The fast-setting cements CMW® 2G and Palacos® fast R + G were studied, using standard-setting high viscosity Palacos® R + G as a reference. Eleven units (of two batch numbers) of each cement were tested. All cements were mixed as specified by the manufacturer and analysed on the following parameters: Handling properties (mixing, waiting, working and hardening phase) according to Kuehn, Mechanical properties according to ISO 5833 and DIN 53435, Fatigue strength according to ISO 16402, Benzoyl Peroxide (BPO) - Content by titration, powder/liquid-ratio by weighing, antibiotic elution profile by High Performance Liquid Chromatography. All tests were done in an acclimatised laboratory with temperatures set at 23.5 °C ± 0.5 °C and a humidity of > 40%.

RESULTS

Palacos® fast R + G showed slightly shorter handling

properties (doughing, hardening phase, $n = 12$) than CMW® 2G, allowing to reduce operative time and to optimise cemented cup implantation. Data of the quasistatic properties of ISO 5833 and DIN 53435 of both cements tested was comparable. The ISO compressive strength (MPa) of Palacos® fast R + G was significantly higher than CMW® 2G, resulting in ANOVA ($P < 0.01$) and two sample t -test ($P < 0.01$) at 0.05 level of significance ($n = 20$). Palacos® fast R + G showed a higher fatigue strength of about 18% mean (ISO 16402) of 15.3 MPa instead of 13.0 MPa for CMW® 2G ($n = 5 \times 10^6$ cycles). Palacos® fast R + G and CMW® 2G differed only by 0.11% ($n = 6$) with the former having the higher content. The BPO-content of both cements were therefore comparable. CMW® 2G had a powder/liquid ratio of 2:1, Palacos® fast R + G of 2.550:1 due to a higher powder content. Despite its higher gentamicin content, CMW® 2G showed a significantly lower antibiotic elution over time than Palacos® fast R + G ($n = 3$).

CONCLUSION

Both cements are compliant with international standards and are highly suitable for their specified surgical indications, affording a time-saving measure without detriment to the mechanical properties.

Key words: Polymethylmethacrylate; Elution; Fast-setting; Viscosity; Antibiotic; Fatigue; Arthroplasty

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Core tip: Polymethylmethacrylate (PMMA) cements provide reliable fixation of the implants in joint arthroplasty. Fast-setting high viscosity PMMA cements exist that have altered setting characteristics compared to standard setting cements. These potentially offer benefits to surgeons based upon their handling properties. Such cements have gained popularity in arthroplasty surgery as described in the United Kingdom and Australian National Joint Registries. The use of fast-setting cements has various beneficial as well as economic effects, such as time-saving and better antibiotic elution.

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INTRODUCTION

Polymethylmethacrylate (PMMA) cements provide reliable fixation of the implants in joint arthroplasty^[1,2]. The chemical composition of each bone cement accounts for its mechanical and handling properties. The polymerization reaction of PMMA is divided in to four phases: Mixing, waiting, working and setting.

Bone cements are classified based upon the amount of time they spend in each of these phases. The most popular cements are high viscosity varieties which have the best results in registry figures but also offer the surgeon short waiting and extra-long working phases^[3]. However, high viscosity cements can take up to 13 min to set^[4].

Fast-setting high viscosity cements exist that have altered setting characteristics compared to standard setting cements. These potentially offer benefits to surgeons based upon their handling properties. Such cements have gained popularity in arthroplasty surgery as described in the United Kingdom and Australian National Joint Registries^[2,5].

Fast-setting high viscosity cements are characterised by a short mixing, moderate working and very short hardening phase in comparison to standard-setting high viscosity PMMA cements^[6,7]. They potentially offer benefits to both surgeon and patient based on their handling properties. These benefits might include: (1) Reduced operative time. Fast setting cements are homogenised quickly and demonstrate very short mixing and waiting phases, allowing them to be applied rapidly^[8,9]. Usually, fast setting cements are setting at the same time that a standard high viscosity cement is reaching the end of their working properties. By reducing the operative time, they may offer an economic advantage^[10-12]. Of more importance, as longer operative time is correlated with increased risk of prosthetic joint infection, they may also offer an advantage in reducing infection^[13,14]; (2) cemented cup implantation. The short waiting phase of fast setting cements might have the advantage of minimising the risk of bottoming out of the socket during insertion^[15]. A high viscosity, fast setting cement flows away less readily during pressurisation and thus, once the correct cup position is achieved, it can be kept under pressure during the working phase with less progressive movement^[16]; (3) cemented knee arthroplasty. Some authors have advocated the use of a sequential mixing technique to ensure even cement mantles in total knee arthroplasty^[6]. Fast setting cements are central to this technique in order to avoid excessive operative time. In addition, others state that high viscosity fast setting cements tend to penetrate the cancellous bone less deeply. This reduces the peak temperature at the interface and facilitates cement removal at revision arthroplasty^[17]; (4) cement spacer and bead production: The handling properties of fast setting cements allows manipulation of the dough more rapidly, facilitating the production of hand-made spacers and beads^[18]; and (5) augmentation surgery. The short waiting phase of fast setting high viscosity cements leads to the dough sticking less to surgeon's gloves. These favourable handling properties will be of benefit when filling bone defects or augmenting the fixation of screws in osteoporotic bone^[19].

There is extensive published data on the mechanical properties of standard-setting high viscosity cements.

Table 1 Testing material

Product	Powder (g)	Liquid (mL)	Batch number	Viscosity
DePuy CMW® 2G	40	20	#3620322	Very high-viscosity
			#3572255	Very high-viscosity
Palacos® fast R + G	51	20	#7743	Very high-viscosity
			FZ52#050214	Very high-viscosity
Reference: Palacos® R + G	40.8	20	#7735	Standard high viscosity
			#7753	Standard high viscosity

However, the varied possible clinical applications, described above, for the use of fast-setting cements demands a similar detailed knowledge of their properties. There is therefore a need to describe the clinically relevant cement properties of these newer cements including, handling behaviour, antibiotic elution, quasistatic and dynamic mechanical properties.

The aim of this research is to study the behaviour of two fast-setting cements and compare these against the "gold-standard" clinically proven standard-setting high viscosity cement, Palacos® R + G. The design was an *in vitro* non-interventional, experimental and prospective comparative study.

MATERIALS AND METHODS

Materials

The fast-setting cements CMW® 2G and Palacos® fast R + G were studied, using standard-setting high viscosity Palacos® R + G as a reference^[20-22]. Eleven units (of two batch numbers) of each cement were tested (Table 1).

Methods

All cements were mixed manually as specified by the manufacturer, in porcelain crucibles with metal spatulas by our team, consisting of experienced laboratory technicians of Heraeus Holding GmbH and me, after intense training for several weeks with different cements.

All cements were analysed on the following parameters: (1) Handling properties (mixing, waiting, working and hardening phase) according to Kuehn^[7]; (2) Mechanical properties according to ISO 5833^[23] and DIN 53435^[24]; (3) Fatigue strength according to ISO 16402^[25]; (4) Benzoyl Peroxide (BPO) - content by titration, powder/liquid-ratio by weighing; and (5) Antibiotic elution profile by High Performance Liquid Chromatography (HPLC)^[26] (Table 2). All tests were done in an acclimatised laboratory with temperatures set at 23.5 °C ± 0.5 °C and a humidity of > 40%.

Fatigue testing: Fatigue was tested according to ISO 16402^[25]. The run follows the four-point bending test method described in ISO 5833^[24]. The dynamic testing

is executed with a pulsating sinusoidal loading under force control. The tests are continued until failure occurs or the specimen reaches a predetermined maximum number of cycles ($n = 5 \times 10^6$). The specimens had the dimensions 3.3 mm × 10 mm × 70 mm^[27].

Gentamicin elution: Cylindrical cement specimens ($d = 25$ mm, $h = 10$ mm) with a surface of approximately 3.1 cm² were used. For the dissolution the PMMA cement samples were stored at 37 °C in dissolution medium (0.1 M phosphate buffer, pH 7.4). Aliquots were taken and the dissolution medium was renewed at day 1, 3, 7, 14, and 21. An appropriate amount of dissolution medium was added to ensure that the samples were completely covered. The dissolution medium samples were stored at -20 °C until analysis. Sample preparation and the determination of concentrations were done at AZB (Analytisches Zentrum Biopharm GmbH Berlin).

Sample preparation: For the preparation of calibration standards 7.646 mg gentamicin sulphate (equivalent to 5.0 mg gentamicin) were dissolved in 25 mL water to achieve a 200 µg/mL gentamicin stock solution. Working solutions were prepared at 100, 250, 500, 750, 1000, 2500, 5000 and 7500 ng/mL by serial dilutions with water. Tobramycin was used as an internal standard. The internal standard working solution was prepared at a concentration of 25 µg/mL in water.

Up to eight calibration standards from 100-7500 ng/mL were prepared by spiking 200 µL of gentamicin working solutions with 18 µL internal standard working solution. The study samples were diluted by a factor of 20 with water and prepared according to the calibration standards by adding internal standard working solution^[26].

Determination of concentrations: Concerning the liquid chromatography (LC) mass spectroscopy (MS) conditions, chromatographic separation was performed on a modular HPLC 1200 Series (Agilent Technologies, Waldbronn, Germany) using a Luna C18 (II) column, 150 mm × 2 mm, with two C18, 4 mm × 2 mm, guard columns (Phenomenex, Aschaffenburg, Germany) thermostated at 25 °C (gentamicin), respectively.

For gentamicin the mobile phase A was 0.11 mol/L trifluoroacetic acid/methanol (50:50) and mobile phase B was acetonitrile. An isocratic separation was achieved with an A:B ratio of 95:5 at a flow rate of 0.25 mL/min. The run time was 2.5 min and the total cycle time was less than 3 min. Injection volume was 2 µL. Under the described conditions the four gentamicin components C1, C2, C2a and C1a co-eluted. The HPLC method was previously used by Heller *et al.*^[26] to determine gentamicin in biopsy samples. The detection of the co-eluted gentamicin components was carried out using an API 4000 QTrap (Applied Biosystems, Darmstadt, Germany). Ionisation was carried out with an electrospray interface (positive polarity) using the mass selective detector in the multiple reaction monitoring

Table 2 Test parameters

Parameter	Characteristics	More details	Sample size	Scale of measure - Ratio scale	Descript. + analyt. statistics
Handling properties <i>in vitro</i>	Mixing, doughing and waiting phase	Elapsed time	12	Duration	Median, quartile, boxplot
	Working phase	Elapsed time	12	Duration	
	Hardening phase	Elapsed time	12	Duration	
Quasistatic mechanical properties	ISO bending strength	In MPa	12	Metric	Median, quartile, boxplot, arithmetic mean, ANOVA, independent two-sample <i>t</i> -test
	ISO flexural modulus	In MPa	12	Metric	
	ISO compressive strength	In MPa	20-24	Metric	
	Dynstat notched impact strength	In kJ/m ²	16	Metric	
Dynamic mechanical properties	Dynstat bending strength	In MPa	16	Metric	Chart, bar graph and standard deviation
		In MPa	5	Metric	
BPO-content		In %	6	Metric	Arithmetic mean, standard deviation, bar graph
Powder/liquid-ratio		g:mL		Ratio	Bar graph
Elution profile	Gentamicin release per mould body	In µg/FK	3	Metric	Table, S/N-curve

mode (MRM). The extracted ion chromatograms of the following ion transitions were stored and calculated: 478.4 → 322.3 m/z (gentamicin C1), 464.4 → 322.3 m/z (gentamicin C2 and C2a), 450.3 → 322.3 m/z (gentamicin C1a.) and 468.4 → 163.1 m/z (internal standard). The three ion transitions of gentamicin components were summed with Analyst (Applied Biosystems, Darmstadt, Germany) and concentrations were calculated with Excel (Microsoft, Unterschleißheim, Germany).

Statistical analysis

The differences of the middle level (= mean) were analyzed by univariate ANOVA (analysis of variance) with repeated measures for more than two paired samples compared with *post-hoc* Tukey test. The method *P* values, adjusted according to the Tukey-method were compared with the significance level $\alpha = 0.05$, and a comparison was considered statistically significant if $P < \alpha$. In addition, the average group differences and the associated 95%CIs were estimated from this model.

The metric ISO variable mechanism and handling properties were tested descriptively by median, quartile, box plot and span and presented summarized in tabular form for all ISO and DIN mechanical results and as a bar chart for all tested handling results.

By calculating the mean values including the standard deviation and a bar chart, the metric parameters of the (di) benzoyl peroxide content (BPO-content) was descriptively displayed three times for each batch of fast-setting cements. The ratio of polymer powder to monomer liquid was presented with metric parameters as a bar graph. The metric data for all antibiotic elution data were tabulated after the 1st, 3rd and 5th day and presented with its standard deviation as a curve diagram.

Metric data of all fatigue strength data were shown as follows: The quasi-static ISO flexible strength in MPa were indicated by mean and its standard deviation,

the fatigue strength in MPa at 5×10^6 cycles and the consequent percentage share of the quasi-static bending strength as a table. It was prepared as SN curve (= S/N curve) in a 95%CI^[27].

RESULTS

Handling properties under *in vitro* condition

For CMW® 2G the polymer powder is filled into the vessel before the monomer liquid. This is contrary to the Palacos® fast R + G and Palacos® R + G process, which both require the filling of the monomer liquid first followed by the polymer powder. The latter technique seems to allow better initial mixing of the liquid and powder moieties. The handling properties of both tested fast setting cements are similar ($n = 12$), but the differences are as follows. CMW® 2G reached the end of the doughing phase according to ISO 5833 at 50 s, approximately 20 s later than Palacos® fast R + G (Figure 1). Palacos® fast R + G was workable at 35 s, immediately after mixing because the dough was no longer sticky and an additional waiting phase is not necessary. CMW® 2G showed a small waiting phase (when still sticky to touch) of approximately 15-20 s after the end of mixing and thus could not be applied until approximately 60 s. Both fast setting cements tested had a similar end of working phase at 3 min after start of mixing. Palacos® fast R + G showed a slightly shorter setting time than CMW® 2G.

Quasistatic mechanical properties

Both fast setting cements tested fulfilled the quasistatic properties of ISO 5833 and DIN 53435^[23,25]. Data of ISO bending strength (MPa) of both cements were similar with no statistical difference due to the one-way analysis of variance (ANOVA) ($P = 0.06$) and independent two sample *t*-test ($P = 0.058$) at 0.05 level of significance ($n = 12$). ISO flexural modulus (MPa) of both cements was also similar, resulting in: ANOVA ($P = 0.869$) and independent two sample *t*-test ($P = 0.868$) (for both α

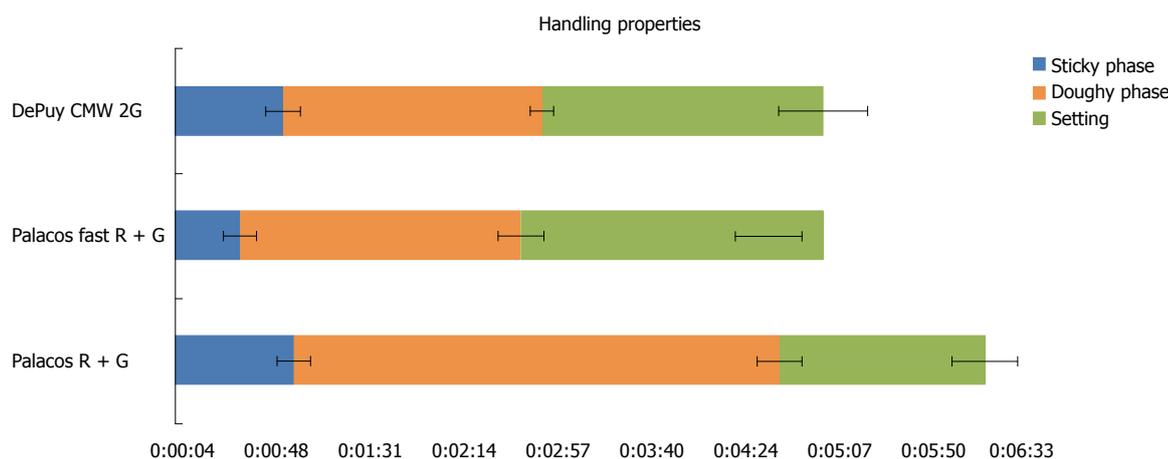


Figure 1 Graphical presentation of handling properties (sticky phase, doughy phase and setting) of tested fast setting cements and the reference material. Data is presented as mean ± SD.

Table 3 ISO mechanical properties of all tested cements

	ISO 5833:2002					
	Bending strength (MPa)		Flexural modulus (MPa)		Compressive strength (MPa)	
Limit	> 50		> 1800		> 70	
DePuy CMW [®] 2G	75.39	67.3 (-8.09) 81.8 (+6.41)	3002.75	2775 (-227.75) 3159 (+156.25)	91.53	80.94 (-10.59) 99.11 (+7.58)
Palacos [®] R + G	65.79	61.7 (-4.09) 68.7 (+2.91)	2552	2383 (-169) 2659 (+107)	87.46	81.92 (-5.54) 93.13 (+5.67)
Palacos [®] fast R + G	72.17	69.3 (-2.87) 76.2 (+4.03)	2995.18	2784 (-211.18) 3118 (+122.82)	106.25	100.26 (-5.99) 110.51 (+4.26)

Table 4 DIN mechanical properties of all tested cements

	DIN 53435			
	Bending strength (MPa)		Notched impact strength (kJ/m ²)	
Limit				
DePuy CMW [®] 2G	73.1	63.88 (-9.22) 82.81 (+9.71)	2.94	2.01 (-0.93) 3.98 (+1.04)
Palacos [®] R + G	71.21	65.06 (-7.15) 79.09 (+7.85)	3.2	2.39 (-0.81) 4.50 (+1.3)
Palacos [®] fast R + G	76.35	65.91 (-10.44) 88.3 (+11.95)	3.19	2.39 (-0.8) 3.98 (+0.79)

= 0.05, *n* = 12). The ISO compressive strength (MPa) of Palacos[®] fast R + G was significantly higher than CMW[®] 2G, ANOVA (*P* < 0.01) and *t*-test (*P* < 0.01) at 0.05 level of significance (*n* = 20). Dynstat bending strength (MPa) was comparable [ANOVA (*P* = 0.15) and *t*-test (*P* = 0.15) (*n* = 16)], as was the Dynstat notched impact strength (kJ/m²) [ANOVA (*P* = 0.196) and *t*-test (*P* = 0.200) (*n* = 16)] of both fast-setting cements (Tables 3 and 4).

Dynamic mechanical strength (fatigue)

CMW[®] 2G had a higher initial quasistatic ISO bending strength (62.3 ± 7.2 MPa) for fatigue according to ISO 16402 than Palacos[®] fast R + G (55.3 ± 1.1 MPa). Subsequently Palacos[®] fast R + G showed a higher fatigue strength of about 18% mean (ISO 16402) of

15.3 MPa instead of 13.0 MPa for CMW[®] 2G (*n* = 5 × 10⁶ cycles). All dynamic mechanical testing results showed no statistical significance (Figure 2).

BPO-content

Palacos[®] fast R + G and CMW[®] 2G differed only by 0.11% with the former having the higher content (Figure 3, mean values of all batches tested). The BPO-content of both cements were therefore comparable.

Powder/liquid-ratio

CMW[®] 2G had a powder/liquid ratio of 2:1, Palacos[®] fast R + G of 2.550:1 due to a higher powder content (Figure 4).

Elution profile

CMW[®] 2G contains 2.5% gentamicin sulphate in the powder, Palacos[®] fast R + G only 1.25% gentamicin. Both cements showed a typical biphasic antibiotic elution profile with high initial release of gentamicin within the first 24 h. Despite its higher gentamicin content, CMW[®] 2G however released only approximately half the amount gentamicin as compared to Palacos[®] fast R + G after the first 24 h. Further CMW[®] 2G showed a much lower antibiotic elution over time than Palacos[®] fast R + G. Additionally, after day 3, CMW[®] 2G had a significantly lower gentamicin release than Palacos[®] fast R + G (Figure 5).

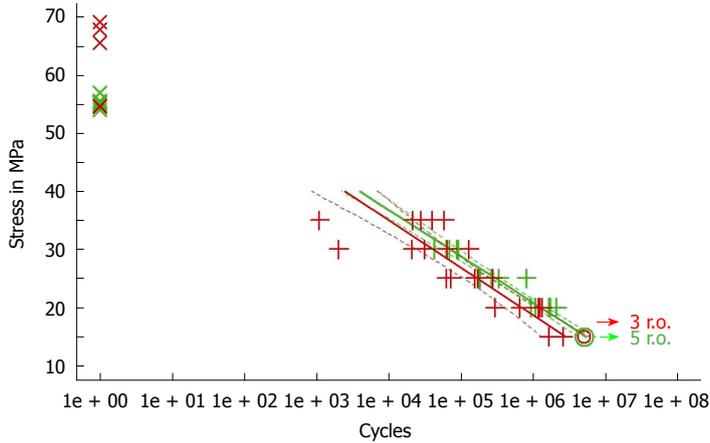


Figure 2 Fatigue strength ($n = 5 \times 10^5$ cycles) of both tested fast setting cements, CMW[®] 2G (in red) and Palacos[®] fast R + G (in green). Data is presented in a S/N curve. Lines: Result of the linear regression and the "narrow" confidence band at the 95% level; x: Quasi-static values; +: Failed under fatigue load; o: Run-outs, regression with + and o.

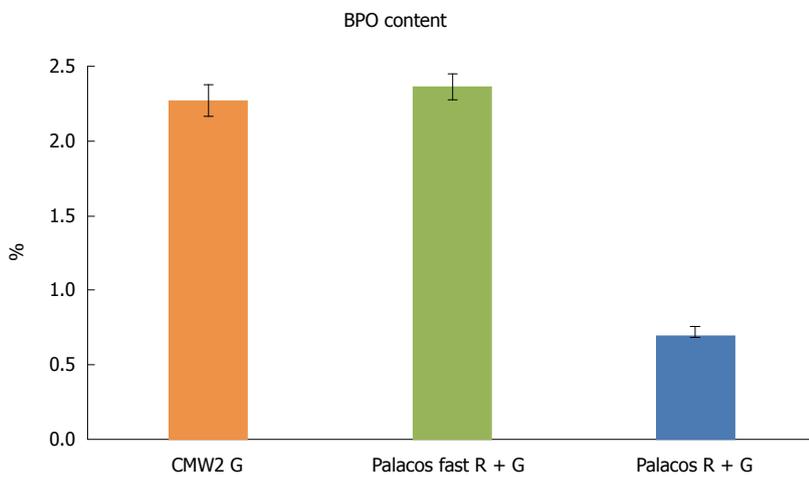


Figure 3 Graphical presentation of Benzoyl Peroxide-content of all tested cements. Data is presented as mean \pm SD. BPO: Benzoyl peroxide.

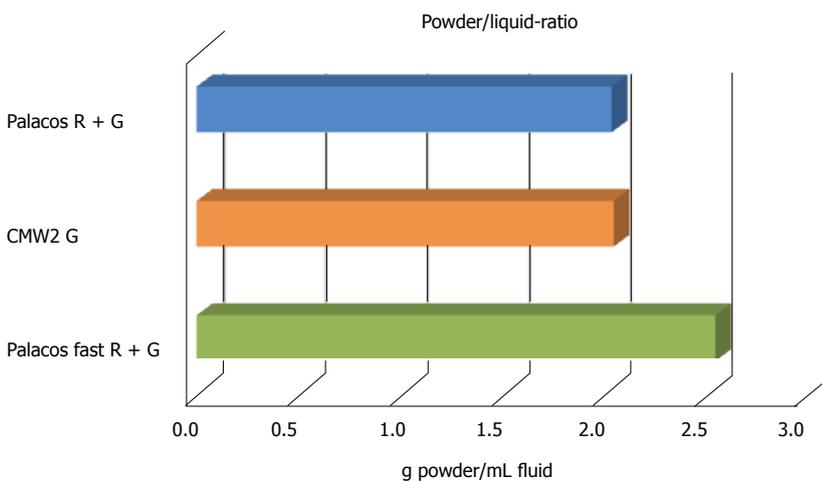


Figure 4 Graphical presentation of powder/liquid ratio of all tested cements. Data is presented as absolute.

DISCUSSION

Fast-setting high viscosity cements have gained popularity in clinical applications owing to their advan-

tageous handling properties and possible associated cost saving potential. Economically the rapid use immediately after mixing and the quick setting is of importance. In the United Kingdom and Australia such fast-setting cements

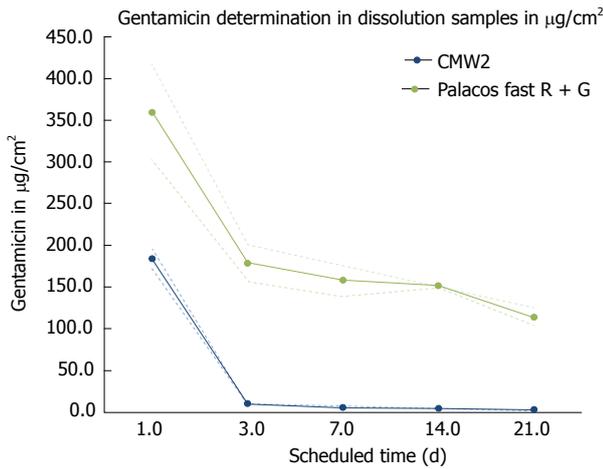


Figure 5 Graphical presentation of elution profile of CMW[®] 2G (in blue) and Palacos[®] fast R + G (in green) (specimen surface 3.1 cm²). Data is presented as mean ± SD.

are now widely used^[2,5].

Palacos[®] fast R + G and CMW[®] 2G were characterised by different mechanical and handling properties when compared to standard-setting high viscosity PMMA cements. The key question, is whether such fast-setting behaviour lends itself to use in all cement clinical applications for bone cement? The relatively short mixing, moderate working and setting phases when compared to standard-setting high viscosity may be less favourable in some scenarios such as femoral stem insertion when the downside of incomplete insertion would be detrimental to the outcome of the surgical procedure. None the less the fact that these cements will have set whilst standard versions are still in their working phase does offer some potential benefits to the surgeon, as detailed in the introduction.

The altered handling characteristics of CMW[®] 2G are the clinically corollary of the special PMMA bead formulation together with an increased content of BPO^[28]. In contrast, Palacos[®] fast R + G utilises an increased powder-liquid (polymer to monomer) ratio in combination with an increased BPO content to achieve the different handling properties.

Both tested fast setting cements are characterised by a short doughy/waiting phase with Palacos[®] fast R + G being ready to handle immediately after mixing. During THA these properties might be advantageous such as allowing better component position control during cup insertion with less extrusion and movement of the cement. The viscosity within the working or application phase is ideal for good cement penetration into the cancellous bone. Surgical technique must be altered to allow the use of fast-setting cements because the viscosity increases quickly and results in an earlier setting.

With regards to the handling properties of the two cements tested, Palacos[®] fast R + G may offer some benefits to surgeon over CMW[®] 2G. The latter is workable from about 60 s until 4 min after the start of mixing. The material sets at approx 5 min^[20]. The

viscosity at the end of the working phase is high and the cement becomes warmer quickly. Palacos[®] fast R + G is workable immediately after mixing at 35-40 s until 4 min after the start of mixing. This results in a slightly longer working phase at 23 °C. It is expected that these differences in the handling behaviour of the tested fast setting cements will be significantly higher at lower ambient temperatures.

Fast-setting cements can be used immediately after mixing during TKA in a sequential cementing technique. Before touching the cement users should be aware that CMW[®] 2G is sticky for slightly longer than Palacos[®] fast R + G. High viscosity fast-setting cements do not penetrate the cancellous bone as deeply as their standard-setting versions. The higher the monomer (liquid) content in a PMMA cement, the higher the temperature reached during setting^[29]. The higher powder-liquid ratio of Palacos[®] fast R + G results in a lower peak temperature in comparison to CMW[®] 2G. This might protect against thermal damage of the bone with use of the Palacos[®] fast R + G cement.

To our knowledge, only two fast-setting high viscosity cements are marketed today. Another cement is marketed as a fast setting cement - Simplex[®]P SpeedSet[®] (Stryker[®]). This is not a high viscosity fast-setting cement as studied in this paper, but rather represents a slightly faster-setting version of their medium viscosity Simplex P^[30].

The altered setting behavior of Simplex[®]P Speed Set[®] is achieved by using smaller copolymer particles which leads to an increased surface area of the powder beads. Such a change of the polymeric composition produces a more viscous material. Further, a higher BPO content is used to speed up the polymerisation reaction, leading to a faster setting time in comparison with the original Simplex[®]P cement^[31]. The handling properties of Simplex[®]P Speed Set[®] are markedly different from those of standard viscosity cements, such as Palacos[®] R + G. Simplex[®]P SpeedSet[®] is characterised by a doughing time of 2.53 min, a working time of approximately 4.8 min and a setting time of 8.2 min according to FDA510 (k) K 053198^[28]. The reference, the standard viscous Palacos[®] R + G showed a working time of approximately 4 min, a doughing of approximately 55 s and a setting of 6 to 7 min. Due to this, Simplex[®]P SpeedSet[®] is not a high viscosity fast-setting cement.

The clinical success of cemented arthroplasty relies upon the strength of the interfaces between the bone, the cement and the implants. Registry figures have confirmed the efficacy of combining implants and cements with optimal mechanical properties and design (NJR 2015). When assessing a new type of cement one must ensure that they will be able to withstand the varying loads they will encounter *in vivo*. The minimum requirements for mechanical properties on an acrylic cement to be used in human applications are described in ISO 5833 and DIN 53435^[23,24]. Both the fast-setting cements we tested in this study fulfilled these requirements. In addition, it was noted that Palacos[®] fast R + G had a statistically significant higher ISO compressive strength (MPa) than CMW[®] 2G.

Nevertheless, quasistatic tests on PMMA cements usually conveys similar strength values between brands.

Dynamic mechanical testing of cements probably offers more clinically relevant information relevant to the long-term survival of cemented implants. Such properties include visco-elastic properties and fatigue testing^[9]. Fatigue behaviour of PMMA cement was tested in this study because it is more sensitive to acrylic variation and can frequently distinguish between material differences in composition or preparation^[32]. Palacos® fast R + G showed higher fatigue strength according to ISO 16402. This may depend upon the different sterilisation techniques used in the preparation of the two cements tested explains these differences. CMW® 2G powder is sterilised by gamma irradiation, whereas Palacos® cements are sterilised by Ethylene oxide (ETO). Irradiation has been shown by other authors to reduce the molecular weight of the polymer beads by half, which results in lower fatigue strengths of the resultant cement^[33,34].

In revision surgery for prosthetic joint infection, local antibiotic delivery is a proven component of treatment in the form of hand-made antibiotic-loaded cement spacers and beads^[35,36]. Fast-setting cements may be preferable for this indication if they appropriate handling and elution characteristics? Firstly, the highly viscous dough of fast setting cements after mixing allows an easy manual application without the cement sticking to the gloves. Secondly, both cements tested showed standard bi-phasic elution of the antibiotic *in vitro*. Palacos® fast R + G showed superior gentamicin release at all stages, despite a lower antibiotic content in comparison to CMW® 2G. Palacos® fast R + G contains the same hydrophilic co-polymers that are present in Palacos® R + G. It is these co-polymers in combination with the special polymer/monomer ratios of Palacos® cements that accounts for the increased antibiotic release compared with other cement brands^[37]. This phenomenon has been described by numerous authors for the standard-setting Palacos® R + G and it would appear to hold true for the fast-setting version as well^[7,38].

The use of eligible, fast-setting high viscosity PMMA cements are already described in national joint registries for both knee and hip arthroplasty^[5,6]. Palacos® fast R + G and CMW® 2G are both highly suitable for their specified surgical indications as they afford a time-saving measure without detriment to the mechanical properties. Both are compliant with international standards and we have described in this study their relative handling and mechanical properties in order to inform surgeons so that they might apply them to their practice.

Due to Palacos® fast R + G's shorter doughy/waiting phase compared to CMW® 2G, it is ready to apply immediately after mixing. During surgeries Palacos® fast R + G allows better component position control during cup insertion with less extrusion and movement of the cement compared to CMW® 2G.

A higher powder-liquid ratio of Palacos® fast R + G

results in a lower peak temperature compared to CMW® 2G, which might protect against thermal damage of the bone with use of the Palacos® fast R + G cement.

Palacos® fast R + G had a statistically significant higher ISO compressive strength (MPa) than CMW® 2G, it also showed higher fatigue strength according to ISO 16402, likely due to different sterilisation techniques. Palacos® fast R + G also showed a much higher gentamicin release profile at all stages, despite a lower antibiotic content compared to CMW® 2G.

COMMENTS

Background

Polymethylmethacrylate (PMMA) cements provide reliable fixation of the implants in joint arthroplasty. Fast-setting high viscosity cements exist that have altered setting characteristics compared to standard setting cements.

Research frontiers

PMMA is widely used for implant fixation in orthopaedic and trauma surgery. Bone cements also act as space-filler and elastic buffer, distributing forces evenly between prosthesis and bone.

Innovations and breakthroughs

Fast-setting PMMA cements offer benefits to both surgeon and patient based on their handling properties. These benefits might include reduced operative time and therefore economic advantage and decreasing risk of infection, also due to better antibiotic release because of special polymer/monomer ratio.

Application

Fast-setting PMMA bone cements have gained popularity in knee arthroplasty and hip replacement surgery as described in the United Kingdom and Australian National Joint Registries over the last years.

Terminology

The chemical composition of PMMA cements accounts for its mechanical and handling properties. The polymerization reaction of PMMA is divided in to four phases: Mixing, waiting, working and setting. Bone cements are classified based upon the amount of time they spend in each of these phases. Fast-setting cements are characterised by a short mixing, moderate working and very short hardening phase.

Peer-review

The study is very well executed and presented.

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Basic Study

Augmented reality: The use of the PicoLinker smart glasses improves wire insertion under fluoroscopy

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Abstract**AIM**

To demonstrate the feasibility of the wearable smart glasses, PicoLinker, in guide wire insertion under fluoroscopic guidance.

METHODS

Under a fluoroscope, a surgeon inserted 3 mm guide wires into plastic femurs from the lateral cortex to the femoral head center while the surgeon did or did not wear PicoLinker, which are wearable smart glasses where the fluoroscopic video was displayed (10 guide wires each).

RESULTS

The tip apex distance, radiation exposure time and total insertion time were significantly shorter while wearing the PicoLinker smart glasses.

CONCLUSION

This study indicated that the PicoLinker smart glasses can improve accuracy, reduce radiation exposure time, and reduce total insertion time. This is due to the fact that the PicoLinker smart glasses enable surgeons to keep their eyes on the operation field.

Key words: Smart glasses; Imaging; Wearable devices; Fluoroscopy; Guide wire insertion

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Core tip: Smart glasses are a kind of wearable device that has a head-mounted monitor enabling augmented reality. The fluoroscopic video was displayed on the head-mounted monitor of the smart glasses, PicoLinker. A surgeon was asked to insert 3 mm guide wires into plastic femoral bones under fluoroscopic control while wearing the PicoLinker smart glasses or by viewing the conventional fluoroscope monitor. Total insertion time, radiation exposure time and tip apex distance were shorter while wearing the PicoLinker smart glasses than while viewing the conventional monitor. Smart glasses are an innovative device that enables surgeons to keep their eyes on the operation field during procedures carried out under fluoroscopic control.

Hiranaka T, Fujishiro T, Hida Y, Shibata Y, Tsubosaka M, Nakanishi Y, Okimura K, Uemoto H. Augmented reality: The use of the PicoLinker smart glasses improves wire insertion under fluoroscopy. *World J Orthop* 2017; 8(12): 891-894 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i12/891.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i12.891>

INTRODUCTION

Wearable technology has entered the medical field and will change surgery dramatically. Wearable smart glasses are a kind of computer that displays information on a head-mounted display. For procedures performed under fluoroscopic guidance, the head-mounted display enables surgeons to perform procedures under fluoroscopic control while keeping their eyes on the operative field. Google Glass® (Google Inc., Mountain View, CA, United States) is the most well-known wearable glasses and has been used for various medical purposes such as medical education^[1,2], surgery navigation^[3,4] and as vital sign monitors^[5]. However, it is not commercially available for general use. PicoLinker (Westunitis Co., Ltd., Osaka, Japan) (Figure 1) is a kind of wearable glasses that can display images or videos that are on existing monitor screens, on the head-mounted monitor. Unlike Google Glass, PicoLinker can capture video from various types of video sources *via* a transmission box that is connected to PicoLinker and contains various types of video connectors. We assumed that PicoLinker can be used as an alternative screen for fluoroscopic images. This technology is a kind of augmented reality (AR) where virtual images are added on real images. Virtual reality is where the wearer can see completely virtual or synthesized images in a completely shielded eyewear without viewing the real image. Through the AR, the wearer (operator) can obtain additional information (fluoroscopic video) simultaneously with the real image (operation field). Using this device, the operator can glance at the fluoroscope video on the PicoLinker smart glasses while keeping his/her eyes on the operation field. This would improve accuracy,

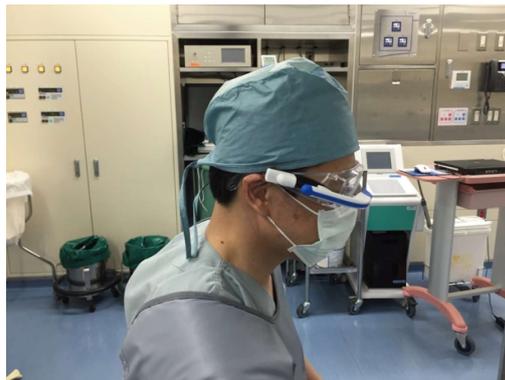


Figure 1 An operator wearing the PicoLinker (wearable smart glasses).

reduce radiation exposure, and reduce the procedure time. The aim of this pilot study was to evaluate the effectiveness of PicoLinker in guide wire insertion into an artificial femoral head under fluoroscopic control.

MATERIALS AND METHODS

Wearable device

The PicoLinker is a kind of wearable smart glasses and contains a prism monitor with resolution of 428 × 240 pixels. PicoLinker can be mounted on any type of normal glasses and is connected to a video box by a wire cable. The video box has six types of video-connectors: HDMI, USB, VGA, video composite, S-video composite, and encrypted and secured micro-SD slot. Various types of monitors such as a fluoroscope monitor can be connected to the video box, and can be viewed by the operator on the prism monitor of PicoLinker. Although most types of video lines can be connected, in the case where there is no available connector nor video signals, a video camera can be placed in front of the existing monitor so that the screen image can be transferred to the prism monitor *via* the video box. The prism screen is set on normal glasses. In the present study, a fluoroscope monitor was connected to the video box of PicoLinker so that the surgeon could view the fluoroscopic video through PicoLinker.

Evaluation of wire insertion

A surgeon performed guide wire insertion into five plastic femoral bones (Sawbone®, Sawbones Inc., Malmö, Sweden). The operator was instructed to introduce a Kirschner wire of 3.0 mm in diameter using an electric driver from the lateral cortex of the femur towards the femoral head, parallel to the femoral neck axis on anteroposterior view, under fluoroscopic control with the aim of minimizing the tip apex distance (TAD)^[6]. The driver was initially placed beside the operator. The operator was instructed to pick up the driver, pick up the wire with the driver, find the best insertion point, and advance the drill into the femoral head. The drill insertion was performed ten times with PicoLinker (Wearable group) (Figure 2) and another ten times without PicoLinker while viewing the conventional fluoroscope



Figure 2 The operator inserting a 3.0 mm Kirschner wire in a plastic femoral bone under a fluoroscope while viewing the fluoroscopic video on PicoLinker.



Figure 3 The operator inserting a 3.0 mm Kirschner wire in a plastic femoral bone under a fluoroscope without PicoLinker, while viewing a conventional fluoroscope monitor.

monitor (Conventional group) (Figure 3). The time from picking up the wire to completion of insertion, total radiation time and the TAD on anteroposterior view were measured and evaluated.

Statistical analysis

Results are expressed as the mean. The significance of differences between the groups was evaluated using unpaired *t*-test. A level of $P < 0.05$ was considered to be significant. Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, United States).

RESULTS

TAD, radiation exposure time and total insertion time were significantly shorter in the Wearable group than in the Conventional group [2.6 mm (mean) vs 4.1 mm, $P = 0.02$; 11.6 s vs 15.0 s, $P = 0.00001$; and 14.5 s vs 19.3 s, $P < 0.00001$, respectively].

DISCUSSION

Smart glasses are an innovative device for medical purposes that can be used in emergency surgery and surgical education including live streaming as well as remote instruction and monitoring. Although many papers on this device have been reported, evidence on the usefulness of the device has seldom been reported. Chimenti *et al.*^[7] reported a similar study using Google Glass in which an operator inserted Kirschner wires into cadaveric phalangeal and metacarpal bones. The results showed reductions in radiation time and operation time. Their results were similar to our results, which also showed reductions in radiation time and operation time. In addition, we found that the accuracy of pin insertion was significantly improved using PicoLinker. This is due to the fact that the operator can see both the operation field and fluoroscopic images without moving his/her eyes and head.

Numerous medical procedures are performed under images displayed on monitor screens. In most such

procedures, the operator needs to take his/her eyes off from the operation field to see the monitor (Figure 3). In addition to fluoroscopy, vital sign monitor, endoscope, and computer navigation as well as conventional images such as X-ray image, computed tomography and magnetic resonance imaging are images on monitors. Using the PicoLinker allows the operator to keep his/her eyes on the operative field while seeing the images (Figure 2).

Unlike Google Glass, PicoLinker has a video box that can be connected by various types of connectors. Furthermore, even if there is no available connector from a monitor, a video camera can be used to capture the monitor images and the images can be transferred to PicoLinker; consequently, the images on all types of monitors can be transferred to PicoLinker. In addition to connectivity, the simple structure is another advantage of PicoLinker over Google Glass. The PicoLinker contains no more than a prism monitor. It has no CPU, camera nor battery; therefore, it has a light weight and battery life is never a problem. As PicoLinker is connected to a video source *via* a wire cable, there is no image delay. On the other hand, Google Glass images are transferred *via* the internet, and therefore a certain degree of latency is inevitable. Commercial availability is another distinct advantage of PicoLinker over Google Glass.

Nearly all reports on the use of smart glasses for medical purposes have involved the use of Google Glass. However, some other devices are available for surgery. We reported another type of smart glasses, InfoLinker (Westunitis Inc., Osaka, Japan), which has both a head-mounted monitor and head-mounted video camera and can connect to the internet for surgical video streaming^[8]. This device is suitable for sending images in which the operator can see the same images through a head-mounted video camera. Although Google Glass has been used for this purpose, there are some advantages of the InfoLinker over Google Glass such as internet connection flexibility, battery durability and usability. Both PicoLinker and InfoLinker are currently available in Japan. They will soon become available in other countries.

Limitations of this study were that the trial was done by a single surgeon and the relatively small trial numbers. Nevertheless, the superiority of the use of PicoLinker smart glasses was demonstrated. The results on the usefulness of PicoLinker are encouraging. Further usage is expected.

COMMENTS

Background

There are few reports on head-mounted visualization of video from a fluoroscope monitor. Most operators have to see the fluoroscopic video on a fluoroscope monitor apart from the operation field. This may cause technical difficulties and inconvenience to the operator.

Research frontiers

Smart glasses are an innovative tool for visualization and image recording using a head-mounted monitor and head-mounted camera. Nearly all medical articles on smart glasses have involved the use of Google Glass. Although Google Glass can be utilized in various medical settings, head-mounted visualization of fluoroscopic video has rarely been reported.

Innovations and breakthroughs

The authors have presented a new type of smart glasses named PicoLinker. It is already commercially available in Japan and will soon be available in other countries. PicoLinker has some advantages over Google Glass with regard to direct image transfer *via* cable connection without image latency, its simple and light body, and unlimited battery life. The introduction of PicoLinker to the medical field will inspire new ideas to improve surgeries.

Peer-review

This is an interesting study testing a device "coming from the future".

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Case Control Study

Season of the year influences infection rates following total hip arthroplasty

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Abstract

AIM

To research the influence of season of the year on periprosthetic joint infections.

METHODS

We conducted a retrospective review of the entire Medicare files from 2005 to 2014. Seasons were classified as spring, summer, fall or winter. Regional variations were accounted for by dividing patients into four geographic regions as per the United States Census Bureau (Northeast, Midwest, West and South). Acute postoperative infection and deep periprosthetic infections within 90 d after surgery were tracked.

RESULTS

In all regions, winter had the highest incidence of

periprosthetic infections (mean 0.98%, SD 0.1%) and was significantly higher than other seasons in the Midwest, South and West ($P < 0.05$ for all) but not the Northeast ($P = 0.358$). Acute postoperative infection rates were more frequent in the summer and were significantly affected by season of the year in the West.

CONCLUSION

Season of the year is a risk factor for periprosthetic joint infection following total hip arthroplasty (THA). Understanding the influence of season on outcomes following THA is essential when risk-stratifying patients to optimize outcomes and reduce episode of care costs.

Key words: Hip arthroplasty; Healthcare; Infection; Outcomes; Season

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Core tip: Season of the year when a total hip arthroplasty is performed may affect 90-d post-operative outcomes in certain regions of the United States. Furthermore, there appears to be a difference of the effect of seasonal variation on the outcomes as superficial infections have different patterns compared to deep peri-prosthetic joint infection.

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INTRODUCTION

Total hip arthroplasty is one of the most common orthopaedic procedures in the United States, with over 600000 performed annually^[1,2]. Though this procedure has societal and personal benefits for patients, it is not without risks^[3]. Complications following THA range from increased length of stay to circulatory collapse and death. While minor and major complications are infrequent^[4,5] their impact on readmissions and post-discharge care represents a significant portion of the episode payment^[6]. Factors increasing the likelihood of complications are of great interest, as risk minimization strategies have been shown to reduce overall cost in THA^[7]. Hospital type, surgeon volume, comorbidities and other modifiable risk factors have recently been studied in great detail^[4,8-13]. However, non-modifiable risk factors have also been elucidated as important for pre-operative risk stratification^[14-17].

Recently, the influence of seasonality on outcomes in various surgical subspecialties has been investigated^[14,18-21]. How season or climate impacts outcomes following THA remains unknown, with the

only evidence originating from a single institution, retrospective study by Kane *et al*^[22] who demonstrated an association between summer and infection. In the United States, seasonality affects aspects of life in a variety of manners^[23]. Winter months encourage a sedentary lifestyle, changes eating patterns and results in fewer follow up visits^[24-27]. In contrast, the increased temperatures and humidity of summer months improves microbe survivorship, increases vitamin D levels, encourages being outdoors and overall activity levels^[28]. Given the impact of seasonality on such diverse aspects of life, this study sought to elucidate the influence of season of the year and geographic location on outcomes following THA at a national level. To improve the relevance of this study, we chose to compare differences in the incidence of postoperative infections within the 90-d period, simulating an episode of care period as put forth by the Comprehensive Care for Joint Replacement (CJR) Model.

MATERIALS AND METHODS

We conducted a retrospective case-control, level of evidence III study, evaluating the effects of season of the year on two types of infections following THA. This was achieved by analysis of the Medicare patient database. The query was performed through the PearlDiver Supercomputer (Warsaw, IN, United States). The supercomputer allows identification of patient records through international classification of disease (ICD) ninth revision codes. Patients were then stratified by season of surgery. The seasons were defined as follows: Spring (March, April and May), summer: (June, July and August), fall (September, October and November), winter (December, January and February). Demographical data including age, gender and region of the United States where the surgery was performed was gathered at baseline. Geographical region was classified according to the United States Census Bureau as follows: Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island and Vermont. South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia and West Virginia. West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming.

Patients and outcomes were tracked for 90 d. Using previously described methodology; ICD-9 codes were used to identify complications^[9-11,29,30]. The following outcomes were tracked: acute post-operative infection (998.5), osteomyelitis (730) and infection of orthopaedic device (996.66). Infections were then subdivided into acute postoperative infection (ICD-998.5) and deep infection (ICD-996.66 and 730). This methodology

Table 1 Study patient demographics

	NE	MW	WE	SO
Female	61.60%	61.10%	60.60%	61.40%
Male	38.40%	38.90%	39.40%	38.60%
Age (yr)	9%	9%	9%	12%
≤ 64	9%	9%	9%	12%
65-69	23%	24%	26%	24%
70-74	22%	22%	23%	22%
75-79	21%	21%	20%	20%
80-84	16%	15%	14%	14%
≥ 85	10%	9%	9%	8%

NE: North East; MW: Mid West; WE: West; SO: South.

Table 2 Incidence of acute postoperative infections at 90 d following total hip arthroplasty

Location	Spring	Summer	Fall	Winter	χ^2
North East	1.41%	1.35%	1.35%	1.47%	0.281
Mid West	1.54%	1.59%	1.51%	1.60%	0.39
South	1.60%	1.68%	1.58%	1.64%	0.277
West	1.25%	1.59%	1.31%	1.43%	< 0.001
Mean	1.45%	1.55%	1.44%	1.54%	
SD	0.16%	0.14%	0.13%	0.10%	

of separating infections has also been previously described^[9-11,29,30]. The incidence of complications was compared through Chi-squares with Yates corrections given the large sample size of the study. Statistical analysis was conducted through SPSS version 20 (IBM, Armonk, NY, United States). An alpha value less than 0.05 was deemed statistically significant.

RESULTS

A cohort representative of 1311672 patients who underwent THA between 2005 and 2014 was identified. The seasonal distribution of procedures was similar: 25% in the spring, 26.9% in the summer, 25% in the fall and 24% in the winter. Regional volume varied significantly ($P < 0.001$) with the south performing the majority of surgeries (35%) followed by the mid-west (28%), the northeast (19%) and the west (18%) (Table 1).

There was a significant difference in the incidence of acute postoperative infections by season in the West (Table 2). The greatest incidence in the West was following surgeries performed in the summer (1.59%), which was significantly greater than all other seasons ($P < 0.001$ for all) (Figure 1). There was no difference in acute postoperative infections when stratified by season in the other regions.

Our analysis demonstrated that season of the year had a significant effect on periprosthetic joint infections in two out of the four regions, Midwest and South (Table 3). The mean incidence in the Northeast and West was 0.85% (range 0.82% to 0.91%, $P = 0.358$) and 0.86% (range 0.84% to 0.89%, $P = 0.680$), respectively.

Table 3 Incidence of periprosthetic infections at 90 d following total hip arthroplasty

Location	Spring	Summer	Fall	Winter	χ^2
North East	0.82%	0.83%	0.84%	0.91%	0.358
Mid West	0.97%	0.97%	0.88%	1.04%	0.013
South	1.06%	1.06%	0.96%	1.10%	0.007
West	0.84%	0.84%	0.88%	0.89%	0.68
Mean	0.92%	0.92%	0.89%	0.98%	
SD	0.11%	0.11%	0.05%	0.10%	

The Midwest region had the highest incidence of periprosthetic infections in the winter 1.04%, which was significantly higher than the fall (0.88%, $P = 0.001$) but not higher than other seasons ($P = 0.175$ vs the summer and $P = 0.155$ vs the spring). There were no significant differences when comparing the remaining seasons. In the South, the highest incidence of periprosthetic infections was also seen in the winter (1.1%), which was significantly higher than the fall 0.96% ($P < 0.001$) but not than the summer or spring, both 1.06% ($P = 0.377$ and 0.344 respectively). In the South, the fall had a lower incidence, 0.96%, compared to the spring ($P = 0.018$) and to the summer ($P = 0.005$) (Figure 2).

DISCUSSION

This study sought to determine the effect of season of the year, a non-modifiable risk factor, on infections following THA. This was achieved by scrutinizing the entire Medicare population from 2005 to 2014 for the outcomes of interest during the 90-d post-operative period. Our analysis of over 1 million patients demonstrated that acute postoperative infections are significantly affected by season in certain geographical regions. These results are similar to the work of Kane *et al.*^[22], who reported infection rates during summer of 4.7%, fall 2.4%, winter 1.5% and spring 0.5%. Although the authors did not differentiate between deep and superficial infections, they highlight that humidity; colonization and the implementation of new house staff ("July effect") might be responsible for the reported findings. Similarly, various studies have demonstrated a seasonal variation in the rates of surgical site infections from *Staphylococcus aureus*, which is the main cause of superficial infections among orthopaedic patients^[14,19,31,32]. The seasonal influence of the microbes in conjunction with increased sweat gland output, skin hydration, and elevated temperatures may all contribute to the seasonal variation observed here^[20,28,32]. Conversely, the relative consistency of the weather in the South, with warmer year-round temperatures, may account for the lack of statistically significant variation in this region. Previous studies have found differences in infection rates are more pronounced in particular regions of the United States, which was also reported in the present study^[32].

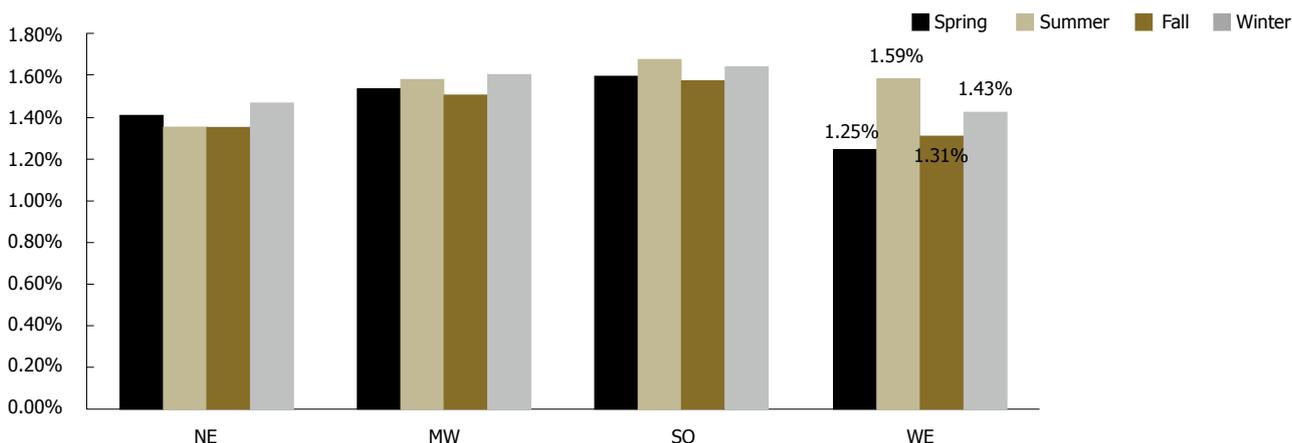


Figure 1 Incidence of acute post-operative infection following total hip arthroplasty by region of the United States. Values are shown for the region, which had a significant difference. There was a significant difference in the incidence of acute postoperative infections by season in the West ($P < 0.001$). NE: North East; MW: Mid West; WE: West; SO: South.

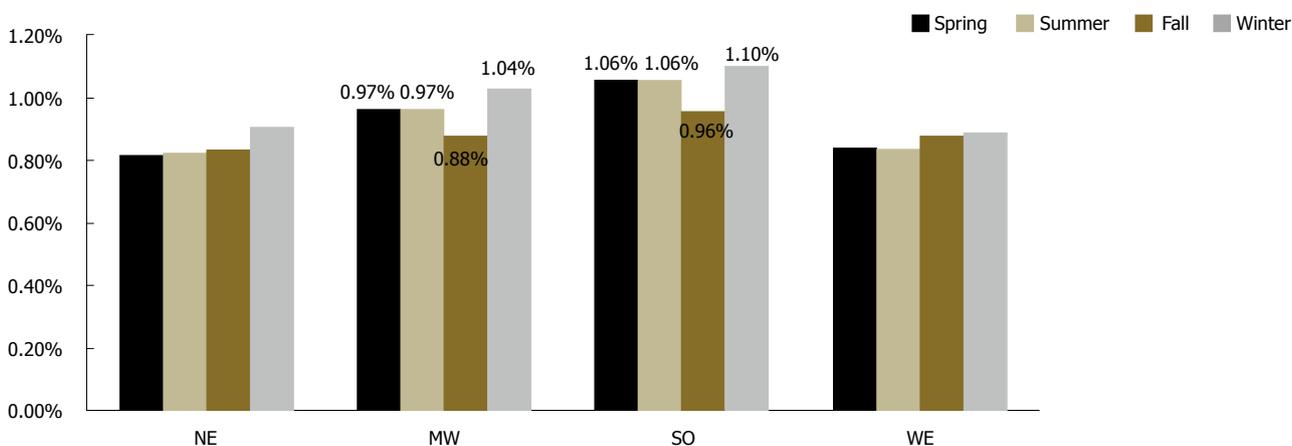


Figure 2 Incidence of periprosthetic infection following total hip arthroplasty by region of the United States. Values are shown for the regions, which had a significant difference. There was a significant difference in periprosthetic joint infections in two out of the four regions, Midwest and South ($P = 0.013$ and $P = 0.007$ respectively). NE: North East; MW: Mid West; WE: West; SO: South.

The overall incidence of periprosthetic joint infections reported in this study (0.89%-0.98%) is similar to epidemiological studies by Kurtz *et al.*^[33] who reported an overall incidence of 2% with variation by training center from 0.61% in rural hospitals to 0.73% at urban-teaching hospitals to 1.18% in Urban-non-teaching hospitals^[34]. This study also found a significant variation in the total number of procedures performed when stratified by geographic region, with the South performing the highest volume of cases. Thakore *et al.*^[35] reported similar results with the number of average discharges billed to Medicare at each hospital highest in the Midwest, followed by the South, Northeast and West. Similarly, this study demonstrated a seasonal variation in the incidence of infection in certain regions of the United States. The Midwest and the South were found to have higher rates of infection in the winter (1.04% and 1.1%, respectively). Previous studies in spine surgery have found a greater incidence of infectious complications in the summer (4.1%) followed by the fall (3.9%)^[31]. However, these authors did not differentiate between superficial and deep

infections and classified patients based on the surgical site infection classification. Similar findings were also reported by Kestle *et al.*^[36], who concluded that there is an increased risk of infections attributable to the "July effect," based on data from 737 patients treated in Canada. Nonetheless, these articles did not analyse a national sample stratified by region and potential reasons for the higher periprosthetic infection rate seen in the winter include longer length of stay because of travel/discharge difficulties, decreased patient compliance with post-operative care or difficulty making follow up appointments. The "July" effect which refers to incoming house staff lack of experience has been suggested as a cause of increased infections following surgical management of certain entities, but this has not held true in the arthroplasty literature^[31]. Although our study did not stratify by hospital type (teaching vs non-teaching), demonstration that periprosthetic joint infections are more common in the winter suggests incoming residents may not be at fault^[14,18].

Although our study demonstrates certain differences in infection rates by season of the year and by region,

we demonstrated that “superficial infections” have different variations that “deep infections” which although controversial, may be due to various reasons: first, the increased risk of superficial infections in the summer may be related to the increased in temperature as has been postulated by Anthony *et al.*^[37] in their large population-based study of the National Inpatient Sample. The authors conducted a comprehensive examination of the NIS and accounted for patient factors, hospital factors and weather variations with their models. Furthermore, the authors state that bacteria can colonize different skin areas at different concentration as temperature varies. Unfortunately, less is known about the seasonality of deep infections. Some authors have demonstrated a seasonal variation in bacteraemia in hospitalized patients, but bacteraemia does not always cause a joint infection and as such limited information can be extracted from this^[38]. Thus, with such little evidence available no definite conclusion can be made of why such variation exists.

This study is not without its limitations. Being a retrospective review, there is potential for selection bias due to the way patients were stratified. This bias was minimized, as the number of THAs in each group was similar. As a large database study, another source of selection bias might have been the coding of the procedures and/or the outcomes, which is beyond the author’s control. Although we relied on previously published literature regarding the identification of the outcomes, it is possible that coding errors may have influenced our results. However, the importance of coding on reimbursements, decreases this likelihood. Time-lead bias may also play a part in the significance of our results as the outcomes are tracked for 90 d following the procedures that occurred within a 3-mo period and thus we cannot account for whether a procedure was performed at the beginning or end of that 3-mo period that comprised a season of the year.

In conclusion, season of the year, which is a non-modifiable risk factor, influences the rate of postoperative infections following THA in some regions of the United States. Superficial, acute post-operative infections are more commonly seen after THAs performed in the summer and periprosthetic joint infections more frequently occur in THAs performed in the winter. Understanding that seasonality is a risk factor for periprosthetic joint infection following THA is essential when risk stratifying patients that are a part of a bundled payment reimbursement model.

ARTICLE HIGHLIGHTS

Research background

Limited information is available in regard to the correlation between season of the year when a surgery is performed to the outcomes of the surgery. Weather variations may account for different bacterial patterns that may lead to infection. Thus, we studied the effects of season of the year on the infectious outcomes after total hip arthroplasty in the United States Medicare patient population.

Research motivation

Due to the large effect on morbidity, mortality and cost that infections can cause, it is important to study modifiable and non-modifiable risk factors for adverse outcomes after surgery. By identifying a seasonal variation in post-operative outcomes, one may ultimately use this information to delay elective surgery.

Research objectives

The purpose of this study was to determine if season of the year when a total hip arthroplasty is performed had an effect on 90-d post-operative superficial and deep infections among Medicare beneficiaries in the United States. The study identified certain seasonal differences that should promote research on this subject through prospective studies.

Research methods

The authors conducted a retrospective review of the entire Medicare files and stratified patients by region and season when the surgery was performed. The authors evaluated the 90-d post-operative period after the procedure to determine the incidence of these complications. The authors analyzed the entire Medicare records from 2005 to 2014. Comparative statistical analysis was used to compare the 90-d incidences reported by international classification of disease 9th edition code tracked in the patient file.

Research results

There was a significant difference in the incidence of acute postoperative infections by season in the West. The greatest incidence in this region (West) was following surgeries performed in the summer (1.59%), which was significantly greater than all other seasons ($P < 0.001$ for all). Our analysis demonstrated that season of the year had a significant effect on periprosthetic joint infections in two out of the four regions, Midwest and South. These results help demonstrate that variation exists in certain regions of the United States by season of the year and that more research is needed on this non-modifiable risk factor.

Research conclusions

There were no previous articles in the literature describing seasonal variation of outcomes after lower extremity arthroplasty. The new findings of this study is: Season of the year may influence post-operative outcomes after total hip arthroplasty. This study proposes the new theories that seasonal variation of these outcomes varies and that the seasonal variability between superficial infection and peri-prosthetic infection exists. This study offered the original insights into the current knowledge by providing evidence that there is regional and seasonal variation in outcomes. This study proposed the new hypotheses that temperature and weather variations may lead to different infectious complications after hip arthroplasty. The authors proposed the new methods that prospective trials to investigate the effect of not only season of the year when the surgery is performed affect the outcomes but also weather. We found the new phenomena that certain regions of the United States have different post-operative complication rates of infectious outcomes after THA when stratified by season of the year when the surgery was performed. Through experiments in this study, the authors confirmed the hypotheses that seasonal variation exists in infectious outcomes after THA in certain regions of the United States. In the future, non-modifiable risk factors may play a role in the outcome of THA such as season of the year when the surgery is performed.

Research perspectives

Season of the year when surgery is performed may have an effect on complication rates after THA. Future studies should create models that account for weather and seasonal variations in the study of outcomes after arthroplasty procedures.

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Retrospective Cohort Study

Do Not Resuscitate status as an independent risk factor for patients undergoing surgery for hip fracture

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Abstract**AIM**

To determine morbidity and mortality in this specific patient group and also to assess for any independent associations between Do Not Resuscitate (DNR) status and increased post-operative morbidity and mortality.

METHODS

We conducted a propensity score matched retrospective analysis using de-identified data from the American College of Surgeons' National Surgical Quality Improvement Project (ACS NSQIP) for all patients undergoing hip fracture surgery over a 7 year period in hospitals across the United States enrolled in ACS NSQIP with and without Do Not Resuscitate Status. We measured patient demographics including DNR status, co-morbidities, frailty and functional baseline, surgical and anaesthetic

procedure data, post-operative morbidity/complications, length of stay, discharge destination and mortality.

RESULTS

Of 9218 patients meeting the inclusion criteria, 13.6% had a DNR status, 86.4% did not. Mortality was higher in the DNR status compared to the non-DNR group, at 15.3% *vs* 8.1% and propensity score matched multivariable analysis demonstrated that DNR status was independently associated with mortality (OR = 2.04, 95%CI: 1.46-2.86, $P < 0.001$). Additionally, analysis of the propensity score matched cohort demonstrated that DNR status was associated with a significant, but very small increased likelihood of post-operative complications (0.53 *vs* 0.43 complications per episode; OR = 1.21; 95%CI: 1.04-1.41, $P = 0.004$). Cardiopulmonary resuscitation and unplanned reintubation were significantly less likely in patients with DNR status.

CONCLUSION

Whilst DNR status patients had higher rates of post-operative complications and mortality, DNR status itself was not otherwise associated with increased morbidity. DNR status appears to increase 30-d mortality via ceilings of care in keeping with a DNR status, including withholding reintubation and cardiopulmonary resuscitation.

Key words: Do Not Resuscitate; Consent; Perioperative; Outcomes; Mortality; Hip fracture

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Core tip: We present a large, multi-institution retrospective cohort study which examines the independent association of Do Not Resuscitate (DNR) status with perioperative outcomes during hip fracture surgery. We find that DNR status independently predicts overall rates of complications and mortality at 30 d without other clear sources of morbidity. Our conclusions place this work in the context of other literature on the outcomes for patients with DNR status during the perioperative period, exploring the data among other surgical populations and hypotheses for this effect.

Brovman EY, Pisansky AJ, Beverly A, Bader AM, Urman RD. Do Not Resuscitate status as an independent risk factor for patients undergoing surgery for hip fracture. *World J Orthop* 2017; 8(12): 902-912 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i12/902.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i12.902>

INTRODUCTION

Do Not Resuscitate (DNR) status documents that a decision has been made to withhold certain resuscitative measures in the event of cardiorespiratory arrest. This

typically includes withholding chest compressions and endotracheal intubation. DNR status documents a patient's advance refusal of resuscitative procedures, due to expressed wishes or beliefs, or where cardiopulmonary resuscitation would fail to restore a quality of life compatible with the patient's goals of care^[1-3]. DNR status is most common when patients have multiple, severe co-morbidities, extreme frailty, or end stage diseases^[4-6].

DNR status does not prevent surgery, despite the potential need for endotracheal intubation or inotropic support during anesthesia. The American Society of Anaesthesiologists' Ethics Committee guidance of 2013 states: "an essential element of preoperative preparation and perioperative care for patients with DNR orders ... is communication among involved parties. ...The status of these directives should be clarified or modified based on the preferences of the patient"^[7]. Patients with DNR status can undergo a range of emergency, urgent or elective surgical procedures to prolong life or improve quality of life. However, as DNR status frequently coincides with narrowed goals of care, procedures tend to be life sustaining or palliative, rather than elective.

The true incidence and composition of surgery in patients with DNR status is unknown. One recent analysis identified 22% of all surgeries in patients with DNR status were lower limb orthopedic procedures^[8]. Hip fracture fixation is the most common indication for hip surgery at the older extreme of age, and orthogeriatric patient outcomes have been the focus of recent national quality improvement initiatives^[9-12]. However, outcomes after hip fracture surgery specifically in the DNR status population are unknown.

It is also unclear whether DNR status itself independently and negatively impacts major outcomes such as morbidity and length of stay^[13-16]. DNR status only directs actions in the event of cardiopulmonary arrest. The "failure to treat" hypothesis, describing inadequate (non-resuscitative) treatment of patients because of DNR status, has been suggested but with inconclusive evidence^[17]. The aim of this study is to describe the incidence and distribution of DNR status in patients undergoing hip fracture surgery and to determine whether DNR status is an independent risk factor for worse outcomes on 30 d follow up.

MATERIALS AND METHODS

Data source

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) is a data registry of cases reported from approximately 400 participating sites. ACS-NSQIP is a well-validated database and incorporates data from patients' medical charts, with data entry overseen by a designated Surgical Clinical Reviewer (SCR) at each site. Institutional Review Board (Brigham and Women's Hospital, Boston, MA, United States) approval was obtained for analysis of the data and was exempted from the

consent requirement due to the de-identified nature of the data.

Study sample

The 2007–2013 NSQIP was compiled into a single data file containing 306 variables across 2.8 million surgical cases. All cases recording patients under age 18, trauma cases, transplant surgeries, cases where the patient is American Society of Anesthesiologists (ASA) physical status class 6, representing a brain-dead organ donor are excluded from NSQIP. We isolated all admissions for hip fracture surgery using all listed ICD codes (Appendix 1) and Current Procedural Terminology (CPT) codes (included in Table 1 with case mix data). All cases failing to report the “do not resuscitate” variable or CPT code were excluded from the analysis. Patient demographic data were collected for age, ASA physical status (PS) class, sex, race, ethnicity, height, weight, and body mass index. Preoperative comorbidity data were collected for functional status prior to surgery, defined as ability to perform activities of daily living (ADL), baseline dyspnea, diabetes mellitus (insulin and non-insulin dependent); smoking status within one year prior to admission; presence of chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease (defined as a composite of a history of angina, myocardial infarction, percutaneous coronary interventions or previous cardiac surgery), hypertension, chronic kidney disease, cerebrovascular accidents, pre-operative weight loss of greater than 10% in the 6 mo prior to surgery, sepsis physiology and a previous operation within the past 30 d. Additional pre-operative laboratories, including the creatinine, albumin, hematocrit, platelet count and international normalized ratio (INR) were collected.

We calculated a frailty score for each patient undergoing hip fracture surgery to assess for presence of any baseline differences in pre-morbid status between the DNR and non-DNR status groups. We used a variation of the well-known Charlson Comorbidity Index^[18–21]. The Canadian Study of Health and Ageing (CSHA)^[22] Clinical Frailty Scale is a 7 point index, modified from the Charlson Comorbidity Index. It has been validated previously using NSQIP data, and has been modified for use with data collected within the NSQIP dataset^[23].

Data collection for the surgical procedure included the primary surgical CPT code, surgical wound classification, total anesthesia and surgical time and anesthesia type. To assess for independent association between preoperative patient demographic, comorbidity and frailty variables and DNR status, we conducted univariable and multivariable regression analysis. For the logistic regression, odds ratios (OR) were reported with their associated 95% CI. OR not including 1.00 in their 95%CI were considered statistically significant and were included in the multivariable regression analysis.

We collected binary outcomes data for the following postoperative events up to 30 d after surgery: Death, return to the operating room, superficial and deep space surgical site infections, post-operative pneumonia, unplanned intubation, failure to wean from the ventilator, progressive renal insufficiency and acute renal failure requiring dialysis, urinary tract infections, cerebrovascular accidents, myocardial infarction, post-operative bleeding requiring transfusion of packed red blood cells, deep venous thrombosis requiring therapy, pulmonary embolism and post-operative sepsis. Additional data on discharge destination (Home, Skilled Care, or Rehabilitation facility) and total length of stay were also collected. All outcomes were reported as percentages, with the numerator defined as the absolute count reporting a given outcome and the denominator defined as the total number of cases reporting any outcome for that variable. To assess for the associations between DNR status and post-operative outcomes, we developed a propensity score matched cohort in which patients were matched by propensity for DNR status. We performed univariable and multivariable regression analysis on the matched cohort and OR not including 1.00 in their 95%CI were considered statistically significant.

Statistical analysis

R Project for Statistical Computing (R version 3.2.3) was used to perform all statistical analysis. Differences between cohorts were assessed using the Pearson chi squared test for categorical variables and using the Student's *t*-test for continuous variables due to the assessment of normality. However, for the variable length of stay, assessment of the distribution of data was non-normal; thus a Wilcoxon rank sum test was performed on this variable. For all demographic, comorbidity, and operative characteristics, a univariable logistic regression model was fitted to assess the association of each variable with DNR status. Of note, the database does not report any postoperative outcomes (including death) occurring more than 30 d after surgery. Additionally, for variables with a large continuous range, the following assumptions were made; platelet count assumes a change of 100000, while the morbidity and mortality risk scores assume a change of 10%. For anesthesia and surgical operating time, the regression model assumes a time interval change of 10 min.

Multivariable logistic regression propensity score matched model

For our primary analysis, we applied a propensity score matched logistic regression model accounting for propensity for DNR status. The matched cohort was developed using a propensity scoring method in which we incorporated statistically significant variables from the unmatched model into a propensity score model. A 1:1 greedy, nearest neighbor matching strategy was employed utilizing the MatchIt library, producing successful matching of 725 patients who were DNR

Table 1 Surgical case mix of hip fracture surgery performed on Do Not Resuscitate and non Do Not Resuscitate status patients

Surgical specialty	Translation	DNR			Not DNR			P value
		num	denom	%	num	denom	%	
27236	Open treatment of femoral fracture, proximal end, neck, internal fixation or prosthetic replacement	210	725	28.966	223	725	30.759	0.994
27245	Treatment of intertrochanteric, per-trochanteric, or sub-trochanteric femoral fracture; with intramedullary implant	173	725	23.862	171	725	23.586	
27125	Hemiarthroplasty, hip, partial (e.g., femoral stem prosthesis, bipolar arthroplasty)	111	725	15.31	104	725	14.345	
27244	Treatment of intertrochanteric, per-trochanteric, or sub-trochanteric femoral fracture; with plate/screw type implant, with or without cerclage	91	725	12.552	99	725	13.655	
27235	Percutaneous skeletal fixation of femoral fracture, proximal end, neck	48	725	6.621	44	725	6.069	
27130	Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty)	20	725	2.759	19	725	2.621	
27248	Open treatment of greater trochanteric fracture, with or without internal or external fixation	9	725	1.241	5	725	0.69	
27506	Open treatment of femoral shaft fracture, with or without external fixation, with insertion of intramedullary implant, with or without cerclage and/or locking screws	8	725	1.103	12	725	1.655	
27187	Prophylactic treatment (nailing, pinning, plating or wiring) with or without methylmethacrylate, femoral neck and proximal femur	6	725	0.828	4	725	0.552	
27454	Osteotomy, multiple, with realignment on intramedullary rod, femoral shaft (e.g., Sofield type procedure)	5	725	0.69	4	725	0.552	
27507	Open treatment of femoral shaft fracture with plate/screws, with or without cerclage	5	725	0.69	8	725	1.103	
27511	Open treatment of femoral supracondylar or trans-condylar fracture without intercondylar extension, with or without internal or external fixation	5	725	0.69	6	725	0.828	
27228	Open treatment of acetabular fracture(s) involving anterior and posterior (two) columns, includes T-fracture and both column fracture with complete articular detachment, or single column or transverse fracture with associated acetabular wall fracture, with internal fixation	3	725	0.414	4	725	0.552	
27513	Open treatment of femoral supracondylar or trans-condylar fracture with intercondylar extension, with or without internal or external fixation	3	725	0.414	1	725	0.138	
27122	Acetabuloplasty; resection, femoral head (e.g., Girdlestone procedure)	2	725	0.276	2	725	0.276	
27138	Revision of total hip arthroplasty	2	725	0.276	2	725	0.276	
27165	Osteotomy, intertrochanteric or sub-trochanteric, including internal or external fixation and/or cast	2	725	0.276	0	725	0	
27509	Percutaneous skeletal fixation of femoral fracture, distal end, medial or lateral condyle, or supracondylar or trans-condylar, with or without intercondylar extension, or distal femoral epiphyseal	2	725	0.276	1	725	0.138	
27132	Conversion of previous hip surgery to total hip arthroplasty	1	725	0.138	1	725	0.138	
27134	Revision of total hip arthroplasty	1	725	0.138	0	725	0	
27254	Open treatment of hip dislocation, traumatic, with acetabular wall and femoral head fracture, with or without internal or external fixation	1	725	0.138	1	725	0.138	
27450	Osteotomy, femur, shaft or supracondylar; with fixation	1	725	0.138	3	725	0.414	
27514	Open treatment of femoral fracture, distal end, medial or lateral condyle, with or without internal or external fixation	1	725	0.138	1	725	0.138	

DNR: Do Not Resuscitate.

to 725 patients who were not DNR. Success of the matching process was evaluated using Student's *t*-test for continuous variables and Pearson's χ^2 test for categorical variables. We found only one statistically significant difference between the cohorts after matching, which suggested that the matched groups may have hematocrit values that differed by approximately 1.3% (OR = 0.87; $P = 0.017$; see Table 2).

For the logistic regression on the matched cohorts, odds ratios (OR) were reported with associated 95%CI. OR not including 1.00 in the 95%CI were considered statistically significant. To assess the association specifically between length of stay and DNR status, a Cox proportional hazard model was fitted, incorporating the demographic and comorbidity co-variables as described above to generate a hazard ratio (HR). The

model was right censored with death as a completing event.

RESULTS

Study population

The ICD codes included in the analysis are shown in Appendix 1. A total of 9218 cases met inclusion criteria (Figure 1). Of these, 1256 (13.6%) were patients with DNR status, and 7962 (86.4%) were patients without DNR status. Unmatched univariate and multivariable analysis demonstrated that patients undergoing hip fracture surgery with DNR status were more likely to be female, aged over > 80 years, unreported race/ethnicity, BMI < 18.5, dyspneic with moderate exertion or rest, ASA class III or IV, partially or totally dependent for

Table 2 Propensity score matched cohorts, matched by propensity for Do Not Resuscitate status

Surgical specialty	Translation	DNR			Not DNR			P value
		num	denom	%	num	denom	%	
27236	Open treatment of femoral fracture, proximal end, neck, internal fixation or prosthetic replacement	322	1252	25.719	1873	7758	24.143	< 0.001
27245	Treatment of intertrochanteric, pertrochanteric, or sub-trochanteric femoral fracture; with intramedullary implant	297	1252	23.722	1799	7758	23.189	
27125	Hemiarthroplasty, hip, partial (e.g., femoral stem prosthesis, bipolar arthroplasty)	233	1252	18.61	1178	7758	15.184	
27244	Treatment of intertrochanteric, pertrochanteric, or subtrochanteric femoral fracture; with plate/screw type implant, with or without cerclage	213	1252	17.013	914	7758	11.781	
27235	Percutaneous skeletal fixation of femoral fracture, proximal end, neck	66	1252	5.272	550	7758	7.089	
27130	Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty)	29	1252	2.316	377	7758	4.859	
27248	Open treatment of greater trochanteric fracture, with or without internal or external fixation	15	1252	1.198	132	7758	1.701	
27506		10	1252	0.799	197	7758	2.539	
27187		6	1252	0.479	71	7758	0.915	
27511		6	1252	0.479	102	7758	1.315	
22318		5	1252	0.399	23	7758	0.296	
27454		5	1252	0.399	7	7758	0.09	
27507		5	1252	0.399	68	7758	0.877	
27254	Open treatment of hip dislocation, traumatic, with acetabular wall and femoral head fracture, with or without internal or external fixation	4	1252	0.319	141	7758	1.817	
27509		4	1252	0.319	17	7758	0.219	
27513		4	1252	0.319	50	7758	0.644	
23615		3	1252	0.24	12	7758	0.155	
27122		3	1252	0.24	3	7758	0.039	
27165		3	1252	0.24	44	7758	0.567	
27228		3	1252	0.24	20	7758	0.258	
27514		3	1252	0.24	48	7758	0.619	
27138		2	1252	0.16	18	7758	0.232	
27759		2	1252	0.16	1	7758	0.013	
23470		1	1252	0.08	2	7758	0.026	
27132		1	1252	0.08	13	7758	0.168	
27134		1	1252	0.08	14	7758	0.18	
27177		1	1252	0.08	4	7758	0.052	

DNR: Do Not Resuscitate.

activities of daily living or diagnosed with hypertension, diabetes, COPD, CHF, PVD, prior stroke, weight loss, or sepsis (Table 3). Comparison between the groups in the unmatched cohort also suggested that patients with DNR status were more likely to have surgery booked as emergent, to receive a neuraxial or regional anesthetic, have a shorter anesthetic and operative time, and a higher modified Charlson score. These factors were used to construct the propensity score matched cohort as described above. The propensity matched groups are shown in Table 2.

Risk prediction

Using the ACS-NSQIP calculator, the average pre-operative risk prediction within the DNR status group was a mortality of 10% [Standard deviation (S.D) 10%] and morbidity of 15% (S.D 7%). In the non-DNR status group, using the ACS-NSQIP risk prediction calculator the average predicted mortality was 4% (S.D 6%) and morbidity of 11% (S.D 6%).

Surgical case mix for hip fracture surgery in DNR and non-DNR populations

Table 1 shows the commonest 23 CPT codes encountered for hip fracture surgery in the matched cohorts. Ninety-

seven point six percent of all DNR patients and 95% of all non-DNR patients had hip fracture surgery classed by one of these CPT codes. The remaining minority (2.4% of DNR and 5% of non-DNR) had other hip fracture surgery CPT codes not listed, and these patients were still included in the analysis. Table 3 also demonstrates the propensity score matched case mix of procedures and the distribution within DNR and non-DNR status groups. The numbers of patients per CPT code were too small to conduct regression analysis. However, ranking CPT codes by frequency demonstrated very similar surgical case mixes in terms of CPT codes between the DNR and non-DNR groups, with the same 10 CPT codes accounting for over 95% of cases and occurring in the same order of frequency, with several low volume exceptions. This suggests there were minimal differences and a high correlation between the surgical case mixes encountered across the two groups, however the degree or significance of differences beyond this were not analysed further. CPT codes were not included in multivariable regression modelling.

Operative and anesthetic comparisons in DNR and non-DNR populations undergoing hip fracture surgery

Table 2 demonstrates various surgical and anaesthetic

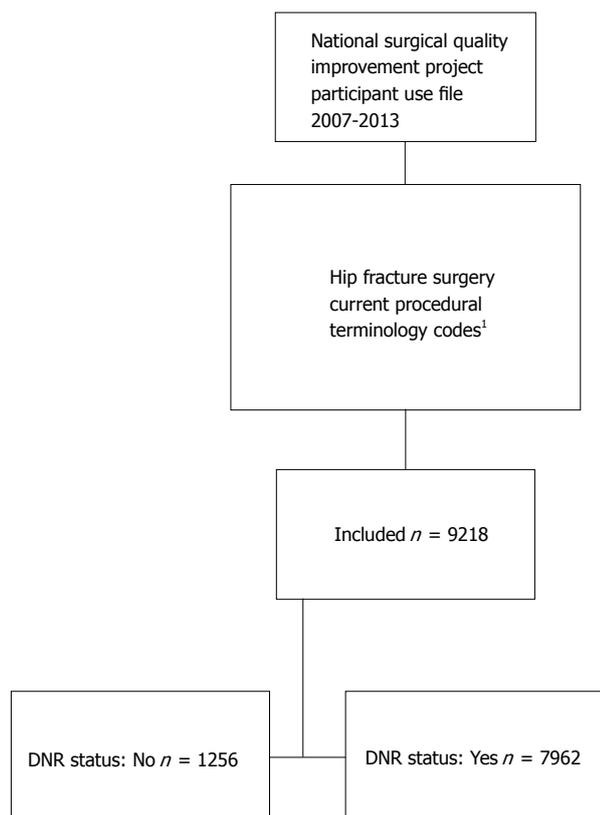


Figure 1 Study population. ¹See Appendix 1. DNR: Do Not Resuscitate.

factors between the matched groups. Multivariable regression demonstrated no increased likelihood for patients with DNR status to have a hip fracture surgery as an emergency procedure. DNR status was not independently associated with shorter surgical time (OR = 0.99, CI 0.99-1.00) or anesthetic time (OR = 0.99, 95%CI: 0.99-1.00). DNR status also did not appear to impact anesthesia modality: Compared to general anaesthesia, spinal anesthesia was not more likely in the DNR patient group compared to the non-DNR patient group in the propensity score matched analysis (OR = 0.96, 95%CI: 0.75-1.22).

Post-operative 30 d outcomes: Mortality

Table 4 presents outcomes up to 30 d postoperatively between the propensity matched cohorts. Mortality was higher in DNR status patients than in non-DNR status patients undergoing hip fracture surgery, at 15.3% vs 8.1% of patients. Multivariable regression demonstrated DNR status was independently associated with mortality (OR = 2.04, 95%CI: 1.46-2.85, $P < 0.001$). DNR status was not associated with return to the OR on multivariable regression.

Post-operative 30 d outcomes: Morbidity

Our analysis of the propensity score matched cohort found one difference with respect to post operative morbidity. Patients with DNR status had a slightly higher average number of complications per hospitalization (0.53 vs 0.43; OR = 1.213, 95%CI: 1.04-1.41).

Although DNR patients appeared more likely to experience superficial surgical site infections (OR = 21.3; 95%CI: 1.25-364), this was likely an artifact of no events for the non-DNR patients and was no difference was seen with deep surgical site infections or dehiscence rates. DNR patients were less likely to experience reintubation (OR = 0.253; 95%CI: 0.09-0.69), or cardiac arrest with CPR (OR = 0.115; 95%CI: 0.03-0.52). Mean length of stay in the DNR group was no different between the propensity score matched groups.

DISCUSSION

Our study aimed to examine post-operative mortality and morbidity in patients with DNR status undergoing hip fracture surgery. We also aimed to determine whether DNR status was independently associated with increased morbidity or whether DNR status purely decreased utilisation of CPR and reintubation, without affecting other postoperative outcomes. We found that mortality was over two times greater in the DNR status group, with DNR status independently predicting mortality after patient groups were matched for other underlying comorbidities using propensity scoring methods. However, relatively few sources of morbidity were independently associated with DNR status. Although overall complication rates were slightly higher, rates of reintubation and cardiac arrest with CPR were much lower among patients with a DNR order in place. This raises the question of how we reconcile the increased rate of mortality observed among the DNR cohort in the setting of an isolated, modest overall rate of complications but no clear source of morbidity.

Historically, some surgeons and anesthesiologists have considered perioperative DNR status controversial, given the interventional procedures and unique physiologic changes that occur during anesthesia and the way clinicians manage these events. In light of this, both the American College of Surgeons^[24] and American Society of Anesthesiologists^[7] have produced consensus statements to guide perioperative management of DNR status. These emphasize communication and individualized management plans, including suspending, then reinstating DNR status post-operatively, if in accordance with a patient's wishes.

The impact of DNR status on surgical outcomes has been examined previously in the wider surgical cohort and in specific specialty groups such as patients undergoing vascular surgery^[25,26]. Kazaure *et al.*^[25] demonstrated similar patient associations with having DNR status (white, female, > 85) and also demonstrated high mortality (nearly 1 in 4) in surgical patients with DNR status. However, in contrast to our findings, they demonstrated significantly higher morbidity rates in DNR vs non DNR patients. These higher rates of morbidity were not replicated in our hip fracture specific study, and therefore may imply that in our orthopedic cohort a DNR status did not negatively

Table 3 Demographics, co-morbidities and functional baseline of Do Not Resuscitate and non Do Not Resuscitate status patients undergoing hip fracture surgery

Categ.	DNR			Not DNR			OR (95%CI)	P values
	Num	Denom	%	Num	Denom	%		
Age, mean (SD)	85.1		6.7	77.55		12.3	1.098 (1.088-1.109)	< 0.001
(0, 65)	26	1256	2.1	1188	7962	14.9	Reference	< 0.001
(65,80)	169	1256	13.5	2384	7962	29.9	3.239 (2.131-4.923)	
(80,100)	1061	1256	84.5	4390	7962	55.1	11.043 (7.445-16.381)	
Sex								
Male	313	1254	25.0	2395	7950	30.1	Reference	< 0.001
Female	941	1254	75.0	5555	7950	69.9	1.296 (1.131-1.486)	
Demographics								
White	781	1215	64.3	6008	7544	79.6	Reference	< 0.001
Black	11	1215	0.9	371	7544	4.9	0.228 (0.125-0.417)	
Asian	3	1215	0.2	94	7544	1.2	0.246 (0.078-0.777)	
Other	4	1215	0.3	31	7544	0.4	0.993 (0.349-2.819)	
Not reported	416	1215	34.2	1040	7544	13.8	3.077 (2.686-3.525)	
Hispanic	18	824	2.2	314	6677	4.7	0.453 (0.28-0.732)	0.001
BMI								
Mean (SD)	24.1		5.5	25.3		6.5	0.966 (0.953-0.978)	< 0.001
(0, 18.5)	110	913	12.0	630	7076	8.9	1.261 (1.007-1.579)	< 0.001
(18.5, 25)	454	913	49.7	3279	7076	46.3	Reference	
(25, 30)	244	913	26.7	1976	7076	27.9	0.892 (0.756-1.052)	
(30, 100)	105	913	11.5	1191	7076	16.8	0.637 (0.51-0.795)	
Functional status								
No dyspnea	1098	1256	87.4	7136	7961	89.6	Reference	0.015
Dyspnea with moderate exertion	116	1256	9.2	652	7961	8.2	1.156 (0.94-1.423)	
Dyspnea at rest	42	1256	3.3	173	7961	2.2	1.578 (1.12-2.224)	
Independent	491	1251	39.2	4726	7917	59.7	Reference	< 0.001
Partially dependent	579	1251	46.3	2583	7917	32.6	2.158 (1.896-2.456)	
Totally dependent	181	1251	14.5	608	7917	7.7	2.865 (2.369-3.466)	
ASA class								
1-no disturb/2-mild disturb	108	1256	8.6	1739	7951	21.9	0.388 (0.315-0.478)	< 0.001
3-severe disturb	779	1256	62.0	4866	7951	61.2	Reference	
4-life threat/5-moribund	369	1256	29.4	1346	7951	16.9	1.712 (1.492-1.965)	
Comorbidities								
Hypertension	908	1256	72.3	5413	7962	68.0	1.229 (1.076-1.402)	0.002
Diabetes	184	1256	14.7	1468	7962	18.4	0.759 (0.643-0.897)	0.001
COPD	181	1256	14.4	899	7962	11.3	1.323 (1.114-1.571)	0.001
CHF	55	1256	4.4	234	7962	2.9	1.512 (1.12-2.041)	0.006
CAD	212	1256	16.9	1340	7962	16.8	1.004 (0.856-1.176)	0.966
PVD	25	1256	2.0	235	7962	3.0	0.668 (0.44-1.013)	0.056
CKD	29	1256	2.3	214	7962	2.7	0.856 (0.578-1.267)	0.436
Stroke	229	1256	18.2	1023	7962	12.8	1.512 (1.292-1.771)	< 0.001
Weight loss	31	1256	2.5	119	7962	1.5	1.668 (1.118-2.488)	0.011
Sepsis	204	1249	16.3	931	7892	11.8	1.46 (1.238-1.721)	< 0.001
Recent surgery	12	1256	1.0	114	7962	1.4	0.664 (0.365-1.207)	0.177
Labs								
Creatinine	1.09		0.8	1.08		0.9	1.015 (0.946-1.088)	0.664
Hematocrit	30.7			30.1			1.01 (0.986-1.034)	0.394
Platelets	212			208			1.04 (0.977-1.107)	0.196
Surgical urgency								
Emergent	428	1256	34.1	2194	7962	27.6	1.359 (1.197-1.542)	< 0.001
Surgical complexity								
Work RVU	17.45		2.0	17.46		2.7	0.998 (0.975-1.021)	0.841
Anesthesia								
General	796	1255	63.4	6028	7959	75.7	NA	< 0.001
Neuraxial/regional	446	1255	35.5	1876	7959	23.6	1.8 (1.586-2.044)	
Other	13	1255	1.0	55	7959	0.7	1.79 (0.974-3.291)	
Anesthesia time	117.9		48.1	128.8		58.5	0.996 (0.995-0.997)	< 0.001
Operation time	61.4		43.8	70.2		43.5	0.994 (0.992-0.996)	< 0.001
Modified charlson score	2.44		1.4	2.03		1.5	1.207 (1.16-1.255)	< 0.001

DNR: Do Not Resuscitate.

impact outcomes or morbidity to the degree described in the predominantly general surgery (63%) cohort which they analysed. Aziz *et al*^[26] investigated outcomes

of patients undergoing vascular surgery with DNR status and also demonstrated higher mortality in DNR patients, but found similarity in rates of complications between

Table 4 Thirty-days outcomes after hip fracture surgery in DNR and non-DNR status patients

Outcomes	DNR			Not DNR			OR (95%CI)	P values
	Num	Denom	%	Num	Denom	%		
Death	111	725	15.3	59	725	8.1	2.04 (1.459-2.851)	< 0.001
Reoperation/return OR	22	725	3.0	17	725	2.3	1.309 (0.689-2.487)	0.417
Failure to wean from vent	4	725	0.6	7	725	1.0	0.558 (0.161-1.934)	0.364
Reintubation	5	725	0.7	19	725	2.6	0.253 (0.093-0.688)	0.004
Superficial SSI	10	725	1.4	0	725	0.0	21.294 (1.245-364.078)	0.002
Deep incisional SSI	3	725	0.4	2	725	0.3	1.466 (0.242-8.901)	0.654
Organ/space SSI	2	725	0.3	2	725	0.3	1.011 (0.142-7.196)	1
Dehiscence	1	725	0.1	0	725	0.0	3.00 (0.122-73.870)	0.317
Pneumonia	25	725	3.4	34	725	4.7	0.725 (0.428-1.23)	0.232
Acute kidney injury	3	725	0.4	4	725	0.6	0.754 (0.168-3.383)	0.705
Renal failure requiring dialysis	3	725	0.4	2	725	0.3	1.5 (0.249-9.034)	0.654
CVA	4	725	0.6	5	725	0.7	0.798 (0.213-2.994)	0.738
Cardiac arrest with CPR	2	725	0.3	16	725	2.2	0.115 (0.025-0.523)	0.001
Acute MI	16	725	2.2	13	725	1.8	1.245 (0.594-2.608)	0.574
Transfusion	169	725	23.3	139	725	19.2	1.243 (0.964-1.603)	0.054
Venous thromboembolism	9	725	1.2	14	725	1.9	0.621 (0.265-1.457)	0.293
UTI	45	725	6.2	41	725	5.7	1.061 (0.683-1.649)	0.657
Sepsis	14	725	1.9	23	725	3.2	0.595 (0.303-1.17)	0.134
Number of complications	Mean		SD	Mean		SD	OR (95%CI)	P-values
	0.53		0.65	0.43		0.61	1.213 (1.043-1.409)	0.004
Length of stay	Mean		SD	Mean		SD	HR (95%CI)	P-values
	6.4		5.0	6.74		5.3	2.133 (0.469-0.871)	0.219

DNR: Do Not Resuscitate.

the two groups, except for graft failure, a procedure specific complication. This demonstrates the importance of procedure specific information in discussing risk with patients.

Other emerging literature supports our findings of relatively high mortality among patients with DNR orders who undergo surgery. A recent study by our group^[8] examined outcomes among DNR patients undergoing a variety of the most common procedures done for this patient population using NSQIP data. The most common procedures among DNR patients focused on symptom relief but were also associated with higher rates of 30 d mortality (but not morbidity) when compared to non-DNR matched controls^[8]. In another analysis focused on DNR patients undergoing hip surgery, the urgency of the procedure (emergent vs non-emergent) was found to cause no independent increase in 30-d morbidity, while DNR status itself again demonstrated high 30-d mortality rates in excess of those predicted by the NSQIP risk calculator^[27].

Patients undergoing hip fracture surgery comprise a diverse patient group, making risk stratification important^[28,29]. High quality perioperative care and subsequent recovery particularly in the most elderly and medically complex patients presents a growing challenge for an ageing population^[10-12]. Ours is among the emerging literature to measure hip fracture surgery outcomes in the presence of a DNR status and quantify the impact of this important risk factor in this common condition. Our analysis demonstrates that at present, 13.6% of all patients undergoing hip fracture surgery have DNR status. This incidence was previously unknown, despite the growing awareness of the higher risk orthogeriatric population. The burden

of mortality and morbidity in this population therefore may present a sizeable and specific opportunity for quality improvement^[30]. It may also identify a skills gap or systems gap in broaching discussions about end of life wishes in a pre-emptive, comprehensive, acceptable and sensitive fashion. Shared surgical decision making is an emerging topic in the literature, and there have been research and policy agendas proposed for improved perioperative code status discussion between providers involved in perioperative care and patients as well as their families^[31].

We report that patients with DNR status undergoing hip fracture surgery were more likely to be female, aged over > 80 years, dyspneic with moderate exertion or rest, ASA class III or IV, partially or totally dependent for activities of daily living or diagnosed with hypertension, diabetes, COPD, CHF, PVD, prior stroke, weight loss, or sepsis and this is in keeping with patterns described elsewhere^[4,25,32,33]. Similar to previous reports on DNR status, we also found patients with DNR status were less likely to report their race/ethnicity and more likely to be underweight (BMI < 18.5)^[33-35]. This could also reflect physician inconsistency in discussing end of life and resuscitation status as well as ethnic variations in fragility fractures or even of life expectancy^[36,37].

Concern has been expressed previously that DNR status may carry inadvertent care provider bias, or the so-called "failure to rescue" hypothesis. This could lead to inadequate or insufficient care, extending beyond withholding CPR or intubation and ventilation^[14]. Our study was not designed to evaluate this specifically, however propensity score matching and regression analysis created a model to compare outcomes in patients with and without DNR status, controlling for

age, gender, race, ethnicity, ASA class, functional status, albumin levels and presence of multiple independently significant comorbidities. Additionally, our model matched patients using a frailty index, which may have further eliminated differences between the matched groups based on physical status alone.

Our study found that patients with DNR status had slightly shorter mean anesthesia and surgery times in the unmatched analyses. This may reflect an effort to reduce operative or anesthetic time for higher risk patients, by selecting more senior or experienced staff, or less complex operative procedures^[38]. We found the rates of spinal anesthesia were higher for patients who were DNR. This may reflect ongoing debate as to whether spinal anesthesia out-performs general anesthesia in specific patient groups^[39,40]. Potential benefits from regional anesthesia, such as reduced respiratory and neurological complications, and reduced opiate consumption and side effects may be more pronounced in high risk patients. This finding was despite the fact that some contraindications to spinal anesthesia, such as anticoagulation, may be more prevalent^[39].

Limits of the study and summary

The primary limit to this study is fundamental to the retrospective data review design that we were obligated to by the dataset. We were not able to control selection of patients for the surgeries as a result, and therefore sought to address these limitations by our statistical methods, as described above.

The surgical case mix was similar for both groups, though due to a relatively small sample size this could not be analysed in detail. The 10 most common procedures appeared in approximately the same order for both groups, and no gross discrepancies were apparent to visual inspection of the relative proportions. Although our data was able to describe the case mix of procedures undertaken in this population, we were not able to discern sufficient level of detail to describe all aspects of the procedures performed. For instance, although we describe an approximately 15% incidence of total hip arthroplasty, the data set does not provide specific details on the techniques used to accomplish the surgery (*e.g.*, use of cementing agent type, specific screw or prosthesis hardware type). This must be recognized as one of the specific limitations of the study in addition to the general limitations of retrospective administrative and clinical datasets.

Although the emerging literature in this area suggests that shared decision making is a crucial aspect of care for patients with DNR status, our data sources did not allow us to investigate the surgical decision making that preceded the operations among DNR patients in this cohort. Thus, we cannot comment on the specific decision making process that was used in deciding to undergo surgery for hip fracture among these patients. However, this would be a valuable area of future investigation.

However, the mortality and morbidity demonstrated in this study provides a useful reference point for specific discussions about risks of hip fracture surgery, for informed consent, end of life discussions, and for planning perioperative care in this high risk demographic. Importantly, while mortality was higher in DNR status patients, morbidity, defined by post-operative complications, either individually or overall, was generally not higher in the DNR status patients. Indeed, the reduced rate of CPR and unplanned intubation is both expected and consistent with findings in general and other surgical specialities^[8]. It is unclear why a small number of patients with DNR status did undergo such resuscitative procedures, or what the events leading to this were. Taken together, it does not seem that an excess burden of post-operative adverse events cannot adequately explain the increased mortality and suggests the need for further research to understand what unmeasured variables account for these consistent differences in outcome. Our findings support the need for routine, systematic, perioperative discussion with hip fracture patients regarding their goals of care in the event of post-operative morbidity leading to cardiopulmonary arrest. Hip fracture surgery has high perioperative mortality, however this data suggests DNR status is effective in reducing specific interventions such as CPR and reintubation, without appearing to increase overall morbidity in the first 30 d after surgery.

ARTICLE HIGHLIGHTS

Research background

Relatively little is known about the exact mechanism through which Do Not Resuscitate (DNR) status affects patient outcomes during the perioperative period. The approach of surgical and anesthesia societies has been to treat DNR status as a component of the decision to undergo surgery or as a means of framing surgical goals and expectations with patients and their families. Depending on patients' goals, DNR status may even be reversed during the perioperative period. However, little is known about how preoperative DNR status affects morbidity and mortality during the perioperative period, if at all.

Research motivation

Patients in the orthogeriatric population who are undergoing hip fracture fixation surgery may be at increased risk for morbidity and/or mortality. Given that these patients have already made a premeditated decision to limit cardiopulmonary resuscitative aspects of their medical care, they may also benefit from additional counselling with regard to any additional risks that may apply to their surgical population.

Research objectives

This study seeks to describe the incidence and distribution of DNR status in patients undergoing hip fracture surgery and to determine whether DNR status is an independent risk factor for worse outcomes on 30-d follow up. The study's objective was realized by analysis of propensity matched groups of patients in a large retrospective cohort. The study seeks to support an emerging field of literature which describes the unique perioperative outcomes among patients with preoperative DNR/DNI status.

Research methods

A large, national, US-based retrospective cohort database was used to identify patients undergoing surgical fixation for hip fracture across a variety of geographic and hospital settings. Characteristics of this cohort were examined

for unmatched groups of patients with and without DNR/DNI orders, as well as for groups of matched on their propensity for having a DNR/DNI order.

Research results

This study demonstrates that when comparing groups of patients that have been matched on propensity for DNR/DNI status, having a DNR/DNI order was independently associated with mortality (OR = 2.04, 95%CI: 1.46-2.86, $P < 0.001$). Additionally, DNR/DNI status was associated with a very slight increased risk of perioperative complications without otherwise showing significantly different incidences of morbidity between the matched groups.

Research conclusion

New findings contributed by this study include insight in the role of DNR/DNI status as an independent predictor of perioperative mortality among patients undergoing hip fracture fixation surgeries. Notably, these matched groups did not demonstrate associations between DNR/DNI status and perioperative morbidity. Given that rates of CPR and reintubation were markedly lower in the DNR/DNI group, we demonstrate that there may be a “ceilings of care” effect in this context. The findings also raises a question as to whether a “failure to rescue” mechanism may be active among these patients in the perioperative period. Regardless, the results of this study raise questions for future research which will hopefully yield additional insight into the mechanisms driving increased mortality among patients with DNR/DNI status who are undergoing surgery for hip fracture. In the immediate term, these findings will assist clinicians in appropriately counseling patients who may have a DNR/DNI order and are undergoing surgery for hip fracture.

Research perspectives

Future research will hopefully yield additional insight into the mechanisms driving increased mortality among patients with DNR/DNI status who are undergoing surgery for hip fracture.

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Retrospective Cohort Study

Anterolateral rotatory instability *in vivo* correlates tunnel position after anterior cruciate ligament reconstruction using bone-patellar tendon-bone graft

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Abstract

AIM

To quantitatively assess rotatory and anterior-posterior instability *in vivo* after anterior cruciate ligament (ACL) reconstruction using bone-patellar tendon-bone (BTB) autografts, and to clarify the influence of tunnel positions on the knee stability.

METHODS

Single-bundle ACL reconstruction with BTB autograft was performed on 50 patients with a mean age of 28 years using the trans-tibial (TT) ($n = 20$) and trans-portal (TP) ($n = 30$) techniques. Femoral and tibial tunnel positions were identified from the high-resolution 3D-CT bone models two weeks after surgery. Anterolateral rotatory translation

was examined using a Slocum anterolateral rotatory instability test in open magnetic resonance imaging (MRI) 1.0-1.5 years after surgery, by measuring anterior tibial translation at the medial and lateral compartments on its sagittal images. Anterior-posterior stability was evaluated with a Kneelax3 arthrometer.

RESULTS

A total of 40 patients (80%) were finally followed up. Femoral tunnel positions were shallower ($P < 0.01$) and higher ($P < 0.001$), and tibial tunnel positions were more posterior ($P < 0.05$) in the TT group compared with the TP group. Anterolateral rotatory translations in reconstructed knees were significantly correlated with the shallow femoral tunnel positions ($R = 0.42$, $P < 0.01$), and the rotatory translations were greater in the TT group (3.2 ± 1.6 mm) than in the TP group (2.0 ± 1.8 mm) ($P < 0.05$). Side-to-side differences of Kneelax3 arthrometer were 1.5 ± 1.3 mm in the TT, and 1.7 ± 1.6 mm in the TP group (N.S.). Lysholm scores, KOOS subscales and re-injury rate showed no difference between the two groups.

CONCLUSION

Anterolateral rotatory instability significantly correlated shallow femoral tunnel positions after ACL reconstruction using BTB autografts. Clinical outcomes, rotatory and anterior-posterior stability were overall satisfactory in both techniques, but the TT technique located femoral tunnels in shallower and higher positions, and tibial tunnels in more posterior positions than the TP technique, thus increased the anterolateral rotation. Anatomic ACL reconstruction with BTB autografts may restore knee function and stability.

Key words: Anterior cruciate ligament; Patellar tendon; Bone-patellar tendon-bone; Rotatory instability; Magnetic resonance imaging; Tunnel position; Anatomic; Single-bundle

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Core tip: Anterolateral rotatory instability was quantitatively assessed in 40 anterior cruciate ligament-reconstructed knees with bone-patellar tendon-bone autografts using a Slocum anterolateral rotatory instability test in open magnetic resonance imaging 1-1.5 years after surgery, and correlated to tunnel positions evaluated by high resolution computed tomography scan 2 wk after surgery. Femoral tunnel positions were shallower ($P < 0.01$) and higher ($P < 0.001$), and tibial tunnel positions were more posterior ($P < 0.05$) in the trans-tibial (TT) group, compared with the trans-portal (TP) group. Anterolateral rotatory translations were significantly correlated with the shallow femoral tunnel positions, and they were greater in the TT group (3.2 ± 1.6 mm) than in the TP group (2.0 ± 1.8 mm) ($P < 0.05$).

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INTRODUCTION

It is the goal of anterior cruciate ligament (ACL) reconstruction to restore normal knee function and kinematics, finally achieving patient's return to sports and daily activities. Recently, anatomic ACL reconstruction which reproduces dimensions, fiber orientations and insertion sites of the native ACL has been reported to improve knee stability and clinical outcomes after surgery^[1-4]. Oblique fiber orientation based on anatomical location of bone tunnels is more favorable for controlling rotation, as well as resisting anterior tibial force, compared with a vertical graft orientation^[5,6]. ACL reconstruction creating femoral tunnels independently from tibial tunnels has been shown to locate femoral tunnels more closely to anatomical footprint than the trans-tibial (TT) technique^[7-9]. A double-bundle technique has been one of the popular methods to perform anatomic ACL reconstruction, principally using soft tissue grafts such as hamstring tendon^[10-13]. However, anatomic single-bundle technique has developed recently, showing comparable outcomes as double-bundle techniques^[14-17]. Therefore, it may be possible that single-bundle ACL reconstruction with bone-patellar tendon-bone (BTB) grafts, which is based on the modern concept of ACL anatomy^[18-21], could restore close to normal ACL function.

One of the great advantages of BTB autograft is its better graft-tunnel healing, as well as the stable initial fixation with bone block, compared with other soft tissue grafts^[22-25]. Although several original studies have reported kinematics after ACL reconstruction with BTB grafts, they were based on cadaveric specimens measured by testing machine or robotic system^[5,6,26-28], which could not reflect better graft-tunnel healing of BTB grafts. Recent *in vivo* studies using BTB grafts have introduced the anatomic single-bundle technique, which locates bone tunnels within the native insertion site, and have shown favorable clinical results after for ACL reconstruction, but the degree of rotatory instability was mainly assessed by manual pivot-shift test^[18,29-31], not quantitatively. Only a few studies from limited research groups so far have reported quantitative results of rotatory instability after anatomic ACL reconstruction using BTB grafts^[32-34]. Therefore, it would be clinically relevant to assess *in vivo* rotatory instability objectively after ACL reconstruction using BTB autografts.

For the surgical technique of creating femoral tunnels, we had used the TT technique until 2010, modifying the position and orientation of the graft more obliquely^[12,35,36]. But this technique sometimes made it difficult for us to place femoral tunnels within the

Table 1 Baseline data of the two groups

	TT group	TP group	Significance
<i>n</i>	20	30	
Period of surgery	Apr 2009- Dec 2010	Aug 2010-Mar 2013	
Age	29 ± 9	27 ± 9	NS
Height (cm)	171.3 ± 7.1	171.7 ± 6.0	NS
Weight (kg)	73.8 ± 6.9	75.5 ± 12.2	NS
Lysholm score	65 ± 11	63 ± 14	NS

Mean ± SD is shown. TT: Trans-tibial; TP: Trans-portal; NS: Not significantly.

anatomical footprint^[9,37-40], thus since the late 2010, we've shifted to the trans-portal (TP) technique, which enables femoral tunnel placement independently from tibial tunnels^[8,41,42]. In addition, we have utilized open MRI to assess anterolateral rotatory instability of ACL-deficient and ACL-reconstructed knees since 2005, and have shown its usefulness in quantification^[35,43-45].

The purpose of this study was to: (1) Compare the knee stability *in vivo* after ACL reconstruction using BTB autografts *via* TT and TP techniques; and (2) clarify the influence of tunnel position on the knee stability. We hypothesized that: (1) The TP technique would show less instability; and (2) tunnel positions may affect knee stability after single-bundle ACL reconstruction using BTB autografts.

MATERIALS AND METHODS

From April 2009 to March 2013, single-bundle primary ACL reconstruction was performed on 52 knees with a BTB autograft. Patients with any history of significant injury to other knee ligaments, articular cartilage and bilateral ACL cases (2 knees) were excluded. Consequently, 50 patients with a mean age of 28 years (range: 17-45) were enrolled. All patients were male. TT technique was used in 20 knees from April 2009 to 2010, and TP technique was used in 30 patients from August 2010 to March 2013 (Table 1). A computed tomography (CT) scan was performed with 1-2 mm slices in order to determine tunnel positions 2 wk after surgery. Anterolateral rotatory instability *in vivo* was assessed quantitatively in 40 patients (80%) using open MRI an average of 1.2 years (range: 1.0-1.5 years) after surgery. All aspects of this study was approved by the institutional review board (IRB) of our university (ID: 24-108), and all subjects gave their informed consent before they were included.

Surgical technique

The subjects underwent arthroscopic ACL reconstruction at a median of 6 wk after the injury. An arthroscopic leg holder was utilized to hold the affected knee in 90° of flexion. A 10-mm BTB autograft was harvested. The anterolateral portal was positioned as high as the inferior pole of the patella so that it gave an excellent arthroscopic view over the tibial footprint of the ACL.

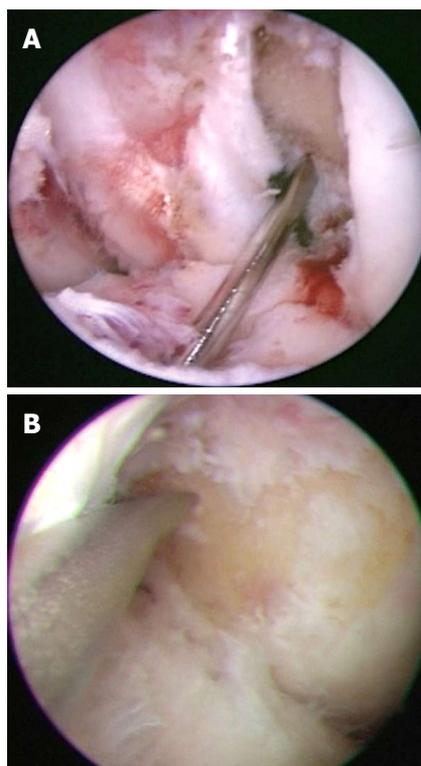


Figure 1 Arthroscopic techniques for creating the femoral tunnel. A: Arthroscopic view of trans-tibial technique in left knee is shown. The femoral guide wire was centered at the 1:30-2:00 o'clock position; B: Left knee. In trans-portal technique, the anteromedial portal was used to visualize the lateral wall of the intercondylar notch. The far medial accessory portal was used to directly access to the center of the anterior cruciate ligament femoral insertion site.

The tibial tunnel was targeted in the center of the native ACL insertion site, avoiding impingement during knee extension.

In the TT group, a femoral guide wire was inserted *via* the tibial tunnel, and then it was centered at the 1:30-2:00 o'clock position for the left knees (10:00-10:30 for right) (Figure 1A). The femoral tunnel was drilled trans-tibially with the knee in 90° of flexion. In the TP group, the anteromedial portal was used to allow optimal visualization of the lateral wall of the intercondylar notch, including the ACL femoral insertion site^[13,41]. In addition, the accessory medial portal was established far medially, just above the anterior horn of the medial meniscus, in a position allowing direct access to the center of the ACL femoral insertion site and avoiding damage to articular cartilage during femoral drilling (Figure 1B). A guide wire was introduced through the accessory medial portal and placed at the center of femoral insertion site. The femoral tunnel was drilled using a 2.4-mm straight guide pin and rigid drills, with the knee kept in maximal flexion.

In all cases, the BTB graft was fixed to the femur using extracortical fixation (EndoButton CL BTB, Smith and Nephew Endoscopy). Tibial side was fixed with interference screws (Softsilk 1.5 Fixation Screws, Smith and Nephew Endoscopy). A notch plasty was not performed in any of our patients. All of the patients underwent a standard rehabilitation program with early



Figure 2 Evaluation of tunnel positions in femur and tibia. A: 3D CT-based model of a femoral bone tunnel after an ACL reconstruction. Tunnel position was assessed according to the quadrant method^[46]. Depth = (distance from the posterior edge to tunnel center along Blumensaat's line/total length of the lateral condyle) × 100%. Height = (distance from Blumensaat's line to tunnel center/total height of the intercondylar roof) × 100%; B: For tibial side, Staubli's technique was used^[47]. Anterior-posterior position = (a/b) × 100%. a: Distance from anterior edge to tunnel center; b: Anteroposterior length of the tibia plateau. ACL: Anterior cruciate ligament.

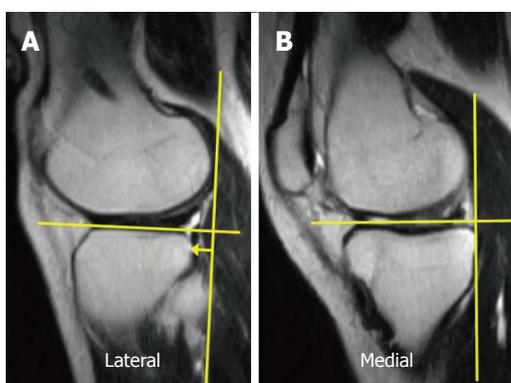


Figure 3 The anterior translation of the tibia with respect to the femoral condyle was measured on sagittal MR images of the (A) lateral compartment and (B) medial compartment, respectively. As a landmark for the center of the lateral compartment, slices that included the medial edge of the fibula were selected. For the center of the medial compartment, slices with the attachment of the medial head of the gastrocnemius were selected.

weight bearing and range of motion exercise. Sports activities were permitted 9 mo after the reconstruction, if the patients had regained functional strength and stability.

The locations of the femoral and tibial tunnel aperture centers were identified from 3D bone models generated from the high-resolution CT scan two weeks after surgery. Femoral tunnel positions were measured according to the quadrant method (Figure 2A)^[46]. For the tibial side, the technique of Staubli and Rauschnig was used for the measurement (Figure 2B)^[47]. A commercially available medical imaging software (Real INTAGE, Cybernet Systems Co, Ltd, Tokyo, Japan) was used in these analysis.

Evaluation of anterolateral rotatory instability

The assessment of *in vivo* anterolateral rotatory instability (ALRI) was performed by applying the Slocum ALRI test^[48] to stress the tibia rotating anteriorly and internally in a horizontal open MRI Scanner, as previously

described^[35,43-45]. The MRI system used in this study was an open MRI at 0.4 T (APERTO, Hitachi Medical Co, Tokyo, Japan). Briefly, the patient was kept in a semilateral recumbent position on the table. The hip and knee of the contra lateral side were flexed. The affected knee was placed in 10° of flexion and the medial side of the foot was rested on a pad so that the weight of the leg was borne on the heel and the knee sagged into valgus. The examiner placed his one hand on the distal femur and the other hand on the proximal tibia from the posterior side. He pushed the fibular head anteriorly with his thumb to increase the stress that makes the tibia rotate anteriorly and internally.

The anterior translation of the tibia with respect to the femoral condyle was measured on sagittal images scanned at each center of the medial and lateral compartments, respectively, in order to evaluate rotatory instability (Figure 3). The image plane scanned under stress was adjusted to the same sagittal plane scanned before stress, using the Interactive Scan Control (ISC) software program. The ISC program determines the image plane interactively on the basis of fluoroscopic images displayed on a user interface with an update time of 2 s, including the scan time. The MRI operator can change the image plane, oblique angle and phase encoding direction during the scan. It usually takes less than 3 min from applying stress to completing the scan, including the fine-tuning of the plane, when the ISC is used. The anterolateral rotatory translation, determined from anterolateral minus anteromedial tibial translation, was calculated to assess ALRI. Side-to-side differences of anterolateral tibial translation and anteromedial tibial translation were also analyzed, respectively. High intra- and inter-observer reproducibility (correlation coefficient = 0.98, 0.91, respectively) have been demonstrated between 2 successive examinations in our previous study, using this assessment technique^[43].

The subjective knee function was assessed with the Lysholm scores and Knee injury and Osteoarthritis Outcome Score (KOOS) scales^[49,50]. Anterior-posterior

Table 2 Tunnel positions of the femur and the tibia by postoperative computed tomography

		TT technique (%)	TP technique (%)	Significance
Femur	Depth	34.0 ± 4.9	29.7 ± 4.9	$P < 0.01$
	Height	30.3 ± 5.6	39.3 ± 7.3	$P < 0.001$
Tibia	Anterior-posterior	47.1 ± 7.5	42.0 ± 4.9	$P < 0.05$

Mean ± SD. TT: Trans-tibial; TP: Trans-portal.

Table 3 Clinical outcomes and knee stability parameters

	TT technique	TP technique	Significance
Lysholm score	94 ± 7	95 ± 7	NS
KOOS subscale			
Symptoms	89 ± 9	90 ± 12	NS
Pain	87 ± 7	89 ± 8	NS
ADL	92 ± 12	96 ± 10	NS
Sport/Rec	82 ± 14	84 ± 9	NS
QoL	78 ± 13	80 ± 11	NS
Re-injury (ipsilateral)	0	0	NS
Kneelax3			NS
Side-to-side diff. (mm)	1.5 ± 1.3	1.7 ± 1.6	
MRI analysis			
Anterolateral rotatory translation			
Affected side (mm)	3.2 ± 1.6	2.0 ± 1.8	$P < 0.05$
Contra-lateral side (mm)	2.4 ± 1.6	2.5 ± 2.7	NS
Side-to-side diff. (mm) of			
Anteromedial tibial translation	0.6 ± 0.8	1.4 ± 2.3	NS
Anterolateral tibial translation	1.4 ± 1.6	0.9 ± 1.9	NS

Mean ± SD is shown. TT: Trans-tibial; TP: Trans-portal; Anterolateral rotatory translation: Anterolateral minus anteromedial tibial translation; NS: Not significantly.

stability was evaluated with a Kneelax3 arthrometer (MR Systems, Haarlem, The Netherlands) at 134 N anterior force.

Statistical analysis

Femoral and tibial tunnel positions were compared between TT and TP groups using Student's *t*-test. The side-to-side differences of tibial translations, anterolateral rotatory translation and clinical outcomes were also compared between the 2 groups using Student's *t*-test. The relationships between tunnel positions and knee stability parameters were analyzed using Pearson's correlations. For those statistical analyses, the StatView 5.0 software (SAS Institute Inc., Cary, NC, United States) was used with a significance level of $P < 0.05$. All statistical analyses of this study were reviewed by a biomedical statistician.

RESULTS

Femoral tunnels were located significantly shallower ($P < 0.01$) and higher ($P < 0.001$) in the TT group, compared with the TP group. Tibial tunnel positions in the TT group were significantly posterior than those of the TP group ($P < 0.05$) (Table 2).

In open MRI analysis, the anterolateral rotatory

translation (= anterolateral minus anteromedial tibial translation) of the affected knees were 3.2 ± 1.6 mm in the TT group and 2.0 ± 1.8 mm in the TP group, and significantly larger in the TT group ($P < 0.05$). The side-to-side differences of anterolateral tibial translation were 1.4 ± 1.6 mm in the TT group and 0.9 ± 1.9 mm in the TP group (N.S.). There was no significant difference in the side-to-side difference of Kneelax3 arthrometer, Lysholm scores, KOOS and re-injury rate between the two groups (Table 3).

The anterolateral rotatory translation were significantly correlated with the shallow (distal and anterior in anatomy) femoral tunnel position ($R = 0.42$, $P < 0.01$), while the correlation between the side-to-side differences of Kneelax3 arthrometer and shallow femoral tunnel positions was weak and not statistically significant ($R = 0.27$, $P = 0.14$) (Table 4). Femoral and tibial tunnel positions are plotted in both groups, according to the quadrant method and Staubli's technique, together with the relationship with stability results of MRI and Kneelax3 arthrometer (Figure 4).

DISCUSSION

We aimed to clarify *in vivo* rotatory knee stability as well as the anterior-posterior stability after ACL reconstruction using BTB autografts, and correlate knee stability to tunnel positions. The most important findings of this study were that the anterolateral rotatory translations (= anterolateral minus anteromedial tibial translation) were significantly correlated with the shallow (distal and anterior in anatomy) femoral tunnel positions. A previous *in vivo* study has also reported that ACL reconstruction using BTB autografts with non-anatomic tunnel position resulted in significantly increased positive pivot-shift test cases, compared with those with anatomic tunnel positions at 1-year follow-up^[30]. Another robotic study using cadaveric knees has reported that anatomic ACL reconstruction with rectangular BTB grafts restored knee kinematics better than the one with oval femoral tunnels located in shallower and higher positions^[6], and these were consistent with our study.

Comparison between TT and TP groups showed shallower and higher femoral tunnel positions, more posterior tibial tunnel positions and increased anterolateral rotatory translation in the TT group. Previous studies have reported that it is more difficult for TT technique to locate femoral tunnels anatomically and restore normal kinematics, compared with TP technique^[7-9,37,41,42],

Table 4 Correlations between tunnel positions and knee stability

		Femur		Tibia
		Shallow (+)-Deep (-)	Low (+)-High (-)	Posterior (+)-Anterior (-)
Kneelax3	Corr (R)	0.27	-0.02	0.15
side-to-side differences	Significance	NS (P = 0.14)	NS	NS
MRI analysis				
Anterolateral	Corr (R)	0.42	-0.13	0.12
rotatory translation	Significance	P < 0.01	NS	NS

Anterolateral rotatory translation: Difference of anterior tibial translation between lateral minus medial compartment; NS: Not significantly.

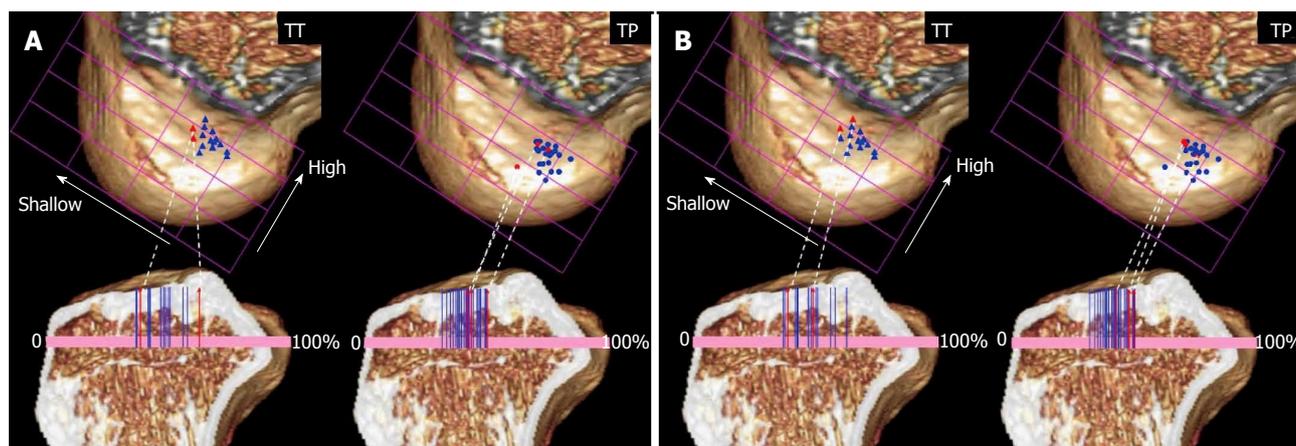


Figure 4 Tunnel positions in trans-tibial and trans-portal group are plotted for the femur and the tibia. A: Blue and red markers mean the side-to-side differences of Kneelax3 arthrometer of the case were under 3 mm (blue) and over 3 mm (red), respectively; B: Blue and red markers mean the side-to-side differences of anterolateral tibial translation were under 3 mm (blue) and over 3 mm (red), respectively. TT: Trans-tibial; TP: Trans-portal.

whereas no significant difference was found in side-to-side differences of Kneelax3 measurement, anterolateral and anteromedial tibial translation in MRI, or other clinical outcomes. The reasons why these stability parameters and clinical outcomes showed no difference between the two techniques may be that the TT-techniques we used did not locate femoral tunnels in “high-noon” isometric position, but located them in oblique positions which are mostly within the femoral footprint, as shown in Figure 4, thus the two groups resulted in less than 2 mm of mean side-to-side difference of anterolateral tibial translation and Kneelax3 measurement with small differences. A recent study using modified TT technique has reported similar anatomic femoral tunnel positions and good clinical results which are comparable to TP technique^[51], although TT technique still runs a risk of creating posterior tibial tunnels and resulting vertical graft orientation^[52,53]. A vertical graft orientation, created by shallow femoral tunnels and posterior tibial tunnels, may result in residual rotatory knee instability^[40,54].

It is well known that merits of using a BTB autograft are its stable initial fixation and good bone-graft healing^[23-25]. BTB cases in our cohort also showed sufficient stability within 2 mm of mean side-to-side difference of anterior tibial translation in rotatory and anterior-posterior evaluation and excellent clinical outcomes. To our knowledge, only a few studies so far have reported quantitative assessment of rotatory instability

in vivo after anatomic ACL reconstruction using BTB autografts^[32-34]. Most of the previous studies about BTB grafts were *in vitro* kinematic study using cadaveric specimens^[5,6,26-28], or *in vivo* study evaluated by manual testing of pivot-shift^[18,29-31]. We added the quantitatively assessed evidence of rotatory instability after anatomic ACL reconstruction using BTB autografts to the current knowledge. Our results suggest that anatomical placement of BTB autografts would restore knee stability and function after ACL reconstruction.

One of the limitations of this study was that all the subjects included were male patients, thus it might have affected the results^[55]. However, recent large cohort studies have reported gender is not a risk factor for knee instability or revision after ACL reconstruction^[56-58]. Secondly, our sample size was relatively small. It was because we usually used hamstring grafts for female patients and for those who had habits of frequent kneeling. The size might not be enough to detect small differences of anterolateral tibial translation between the two techniques.

Anterolateral rotatory instability *in vivo* significantly correlated shallow (distal and anterior in anatomy) femoral tunnel positions after ACL reconstruction using BTB autografts. TT technique located femoral tunnels in shallower and higher positions, and tibial tunnels in more posterior positions than the TP technique, thus increased the anterolateral rotation in reconstructed

knees. Clinical outcomes and knee stability in both techniques were overall satisfactory with less than 2 mm of side-to-side differences in rotatory and anterior-posterior instability. As for clinical relevance, anatomic reconstruction of the ACL using BTB autografts may restore knee function and stability.

COMMENTS

Background

Anatomic single-bundle anterior cruciate ligament (ACL) reconstruction using bone-patellar tendon-bone (BTB) autograft may restore close to normal ACL function. However, quantitative studies showing *in vivo* rotatory instability after anatomic ACL reconstruction using BTB graft are sparse.

Research frontiers

In vivo anterolateral rotatory instability (ALRI) can be assessed quantitatively by applying the Slocum ALRI test in a horizontal open MRI Scanner.

Innovations and breakthroughs

This study added the quantitatively assessed evidence of rotatory instability after anatomic ACL reconstruction using BTB autografts to the current knowledge.

Applications

It was suggested that anatomical placement of BTB autografts would restore knee stability and function after ACL reconstruction.

Terminology

ALRI: Anterolateral rotatory instability.

Peer-review

The manuscript is well-written.

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Retrospective Study

Evaluation of 1031 primary titanium nitride coated mobile bearing total knee arthroplasties in an orthopedic clinic

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Abstract

AIM

To evaluate the influence of the titanium nitride (TiN) coating on the results of a total knee arthroplasty (TKA).

METHODS

A total of 910 patients (338 men; 572 woman), with a mean age of 65 (range 36-94) undergoing 1031 primary TKAs were assessed. Clinical evaluation and patient-reported outcomes were gathered one year after surgery. The questionnaires included the Knee injury and Osteoarthritis Outcome Score (KOOS)-Dutch version, Visual Analogue Scale (VAS) pain scores in rest and during active knee movement, VAS-satisfaction scores, and EQ-5D-3L health scores. This was aimed to assess the overall knee function and patient satisfaction, and to enable us to make a gross comparison to other TKAs.

RESULTS

At a mean follow-up of 46 mo (range 1-92) the overall implant survival was 97.7% and 95.1% for any operative reason related to the implant. Twenty-three knees (2.2%) required revision surgery. Arthrofibrosis was the most common indication for a re-operation. The clinical evaluation and patient-reported outcomes revealed good to excellent patient satisfaction and function of the

arthroplasty. The median postoperative VAS-pain scores on a scale of 0-100, at one year after surgery were 1 in rest and 2 during movement.

CONCLUSION

The TiN coated, mobile bearing TKA results are excellent and similar to those of other widely used TKA designs. Residual pain of the knee remains a concern and the TiN coating in combination with the mobile bearing does not seem to be the simple solution to this problem. Future research will have to show that the coating gives a better survival than the cobalt chrome version.

Key words: Total knee arthroplasty; Titanium nitride coating; Mobile bearing; Pain; Satisfaction and survival

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Core tip: The titanium nitride coated, mobile bearing total knee arthroplasty (TKA) results are excellent and similar to those of other widely used TKA designs.

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INTRODUCTION

Total knee arthroplasty (TKA) is the golden standard treatment for treating patients with end stage Osteoarthritis, and although very successful, approximately 10% of patients experience residual pain^[1]. In the last 20-30 years much research have been done and many theories have been proposed to explain this residual pain. Today most TKA manufacturers use approximately the same design, but small differences in the used materials and coatings, make each arthroplasty unique. Each small change to a well renowned arthroplasty system needs to be evaluated.

Although fixed bearing designs have revealed a high degree of clinical success over the past decades, implant loosening and polyethylene wear were regularly causes for failure^[2,3]. In the 1970's, Buechel and Pappas introduced the (LCS-system) mobile bearing in TKAs, hereby trying to reduce polyethylene contact stress and therefore wear^[4]. Although the mobile bearing achieves excellent results, literature is not clear whether a mobile bearing is better than a fixed bearing TKA. Some studies show a difference, yet others show no significant differences between fixed- and mobile bearing TKAs^[5-9]. Today most femur and tibia components used, are made of cobalt-chromium-molybdenum (CoCrMo) alloy^[10].

Titanium nitride (TiN) is a ceramic, which is regularly

used as a coating to enhance other materials with the properties of TiN. This coating is administered to a wide variety of implants used in cardiac-, neurologic-, dental- and orthopaedic surgery^[11-13]. Beneficial properties of TiN include hardness, more scratch resistant, a smoother surface, less adhesion to polyethylene and a more wettable surface^[10,14-16]. The TiN coating is thought to reduce the wear of Polyethylene and the potential for wear debris induced osteolysis, which today is still a considerable cause for revision surgery^[2,3]. Furthermore *In vitro* studies have shown that Cobalt en Chrome ions can induce an inflammatory response, thus induce pain and swelling^[10]. Adding the TiN coating to the CoCrMo TKA system, is thought to reduce the release of Cobalt and Chrome ions^[10].

The primary goal is to report if the TiN coating in a mobile bearing TKA has any influence on the clinical outcome, patient satisfaction and the mid term implant survival of the TKA. This TiN TKA has been used in several clinics the last decade. Yet, little is published or reported about the clinical outcome and survival^[10,14,15].

MATERIALS AND METHODS

All patients that had received a primary ACS[®] (Implantcast, Buxtehude, Germany) TiN mobile bearing TKA, between February 2007 and April 2012 in our clinic, were included in this study. The data for all included patients was collected up until October 2014, by utilizing the clinics' database and by contacting patients if any necessary data was missing. No patients were excluded on the basis of the severity of their disease or deformity of the knee. Patient sex, age, BMI, ASA-class (American Society of Anaesthesiology), arthroplasty side, component sizing and use of posterior stabilised components were gathered as baseline patient characteristics. Informed consent was obtained from all individual participants included in this study.

The Primary endpoints were defined as true revisions, defined as exchange of the tibial and/or femoral component, and secondary resurfacing of the patella. Secondary endpoints were defined as "revision for any reason" and included also open and arthroscopic arthrolysis, exchange of the polyethylene liner, and realignment of the patella. All patients were asked to complete a questionnaire at 1 year following primary TKA. The questionnaire included the Knee injury and Osteoarthritis Outcome Score (KOOS)-Dutch version^[17], Visual Analogue Scale (VAS) pain scores in rest and during active knee movement, VAS-satisfaction scores, and EQ-5D-3L health scores. This was aimed to assess the overall knee function and patient satisfaction, and to enable us to make a gross comparison to other TKAs.

Operative technique

Three orthopaedic surgeons within the same orthopedic clinic performed all TKAs, with osteoarthritis being the most common indication for surgery. Patients underwent either a general- or spinal-anaesthetic and all patients

Table 1 Comparisons of clinical outcomes 1 year after primary total knee arthroplasty (medians with interquartile ranges)

	Arthroplasty <i>in situ</i> (<i>n</i> = 663)	Revised (<i>n</i> = 8)	<i>P</i> value
KOOS-pain	92 (72; 100)	64 (42; 72)	< 0.01
KOOS-sympt	86 (71; 93)	68 (56; 78)	< 0.01
KOOS-adl	89 (70; 97)	59 (51; 75)	< 0.01
KOOS-sport	40 (15; 70)	33 (6; 65)	0.56
KOOS-qol	69 (50; 88)	38 (38; 55)	< 0.01
VAS-pain (rest)	1 (0; 7)	8 (1; 61)	0.06
VAS-pain (activity)	2 (0; 13)	18 (3; 40)	0.03
VAS-satisfaction	91 (70; 100)	45 (14; 38)	< 0.01
EQ-5D	0.84 (0.78; 1.0)	0.76 (0.35; 0.78)	< 0.01
EQ-5D-VAS	80 (70; 90)	71 (50; 89)	0.26

KOOS: Knee injury and osteoarthritis outcome score; VAS: Visual analogue scale.

received a locally infiltrated anaesthetic (LIA) at the end of surgery. All patients received perioperative antibiotic prophylaxis for 24 h. A straight longitudinal incision was made to expose the knee joint. A surgical tourniquet was used during all TKAs. All prostheses were fixed using bone cement. Postoperative thrombo-prophylaxis was administered in the form of daily subcutaneous injections with Low Molecular Weight Heparin (LMWH) and use of a Trombo Embolism Deterrent (TED) stocking during 4 wk after surgery. Physical therapy was prescribed generally starting two weeks after surgery.

Statistical analysis

Survival analyses were performed using the Kaplan-Meier methods and cumulative survival rates were calculated with 95%CI for both true revision and revision for any reason as endpoints. Patients who died with the implant intact or who were lost to follow up were identified from patient files, and the follow-up time for these patients was censored at the date of death or last clinical or telephone based contact. Multivariate Cox regression analysis was performed to assess the association between potential risk factors (age, BMI, ASA, component sizing and indication) and revision. The KOOS, VAS-pain and satisfaction, and EQ-5D scores are described as medians with accompanying interquartile ranges (IRQ). Comparisons between the revision and non-revision group were performed by use of Mann Whitney *U*-tests. Statistical analysis was performed with the use of SPSS 24.0 (Armonk, NY: IBM Corp). A *P*-value < 0.05 was considered statistically significant.

RESULTS

A total of 910 patients with 1031 Primary ACS arthroplasties, performed by 3 orthopaedic surgeons, were identified from the database. This included 338 male (37.1%) and 572 female (62.9%) patients, with a mean age of 65.4 years (range 36-94) at time of surgery.

The arthroplasties were performed in 52.7% (*n* = 543) on the right side, and in 47.3% (*n* = 488) on the left. A total of 121 patients had received bilateral

arthroplasty between 2007 and 2012. Mean BMI was 28.7 (range 20.4-47.3). 26.3% of patients had an ASA-score of 1, 67.8% had an ASA-score of 2 and 5.9% had an ASA-score of 3.

Clinical outcomes at 1 year after surgery

A total of 671 patients (65%) had filled out the questionnaires at one year after primary TKA (Table 1). The KOOS measured at 1 year after surgery showed generally good levels of function during activities of daily life (ADL), pain, and symptoms with a median scores of 89 (IQR: 70-97), 92 (IQR: 72-100), 86 (IQR: 71-93), respectively. The domains "sport/rec" and "QoL" had median values of 40 (IQR: 15-70) and 69 (IQR: 50-88), respectively. In all but the "sports and recreational function" subscale of the KOOS, patients without required revision surgery scored significant higher scores (*P*-value < 0.01) than the revision group (Table 1).

The median postoperative VAS-pain scores on a scale of 0-100, at one year after surgery were 1 in rest and 2 during movement of the joint in the non-revision group. The patients that required a revision operation scored significantly higher VAS scores during activity (*P* = 0.03).

Overall patient satisfaction levels were good, revealing a median VAS-satisfaction score of 91 (IQR: 70-100) out of 100 in the non-revised, vs 45 (IQR: 14-38) out of 100 in the revision group at one year following primary surgery. This difference was statistically significant (*P* < 0.01).

At one year after surgery patients reported high levels of health-related quality of life. There was a significant difference (*P* < 0.01) in the EQ-5D scores between the revised and non-revised TKA scores, with the revision group showing lower scores corresponding with a lower quality of life (Table 1).

Component sizing

Table 2 shows the overall use of arthroplasty sizes utilised in this study. Size 4 femoral and tibial components were the most frequently implanted (both 38%) with a 10 mm thick liner (53%). Twelve female knee replacements were done using a Gender-specific, also known as a Slim-variety, arthroplasty. In 18 cases, use of a Posterior Stabilised (PS) femoral component with matching PS-liner was deemed necessary to acquire a peri-operative stable knee joint. All but two TKAs were primarily implanted without a patellar component. In these two cases peri-operative patellar tracking was suboptimal due to heavy wear and severe deformation of the patella and/or trochlea. The size of the components was not significantly associated with revision rates for component exchange as well as revisions for any reason (0.22 < *P* < 0.72).

Survival analysis

The mean follow-up period of all 1031 patients was 46 mo, ranging from 1 to 92 mo. Overall arthroplasty

Table 2 Implant component sizing (*n* = 1031)

Component size femur	<i>n</i> (%)	Component size tibia	<i>n</i> (%)	Size liner	<i>n</i> (%)
2	5 (0.5)	3	57 (5.6)	10	545 (53)
3	257 (25.0)	4	386 (37.6)	12.5	394 (38.2)
4	390 (37.9)	5	287 (27.9)	15	80 (7.8)
5	280 (27.2)	6	221 (21.5)	17.5	8 (0.8)
6	97 (7.4)	7	76 (7.4)	20	2 (0.2)
Missing	2	Missing	4	Missing	2

survival for component exchange was 97.7% (95%CI: 97.2-98.2) and 95.1% (95%CI: 94.4-95.8) for revision for any reason. Seventeen patients (18 TKAs) had died due to causes unrelated to knee surgery after a mean follow-up of 30.1 mo (range: 9 to 56) (Figure 1).

A total of 23 (2.2%) TKAs required revision surgery of at least one component of the TKA or addition of a patellar button. All revisions were performed within the first three years postoperatively. Mean time to revision was 21 mo (range: 3 to 36). Revision of six tibial components was performed due to malpositioning at primary surgery, two of which also required addition of a patellar button. In five cases revision was required following a traumatic event, resulting in periprosthetic bone fractures, and muscle-/ligament tears. One of which, revision of the femoral component was necessary at 27 mo, after a fracture of the femur was caused during manipulation under narcosis, at five months after primary TKA. Revision surgery was performed on 2 patients due to infection of the TKA. Revision surgery of the total joint was performed in two stages with addition of antibiotic treatment. These treatments proved successful as the revised TKAs are still implanted.

Isolated Patellofemoral (PF) pain occurred in four patients after TKA and required addition of a patellar component. Two patients had PF pain accompanied by non-traumatic instability and required polyethylene exchange along with the addition of a patellar component. One patient reported PF pain and instability after a traumatic event for which PE exchange and addition of a patellar component was performed. Arthrofibrosis combined with PF pain was seen in four patients. In these cases addition of a patellar component was done along with an arthrolysis and in three cases removal of the liner was necessary to release the posterior capsule. An implantation of a patellar component was necessary to improve patellar tracking along the trochlea.

Revision for other reasons in terms open and arthroscopic arthrolysis, exchange of the polyethylene liner, and realignment of the patella, was performed in an additional 27 patients (2.6%), resulting in a total amount of 50 revisions for any reason (4.8%) with a mean time to revision of 18 mo (range 1 to 36). Of these 27 procedures, seventeen knees (34% of all revisions for any reason) required an open release for which the PE needed to be removed, eight knees (16%) required an open arthrolysis without PE exchange, one knee (2%) was arthroscopically released and in one

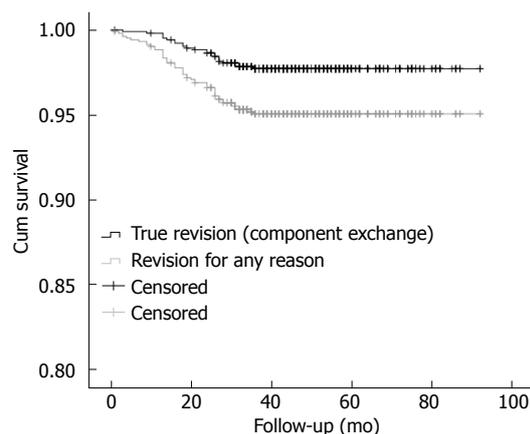


Figure 1 Kaplan-Meier survival curves of the ACS total knee arthroplasty for both True revision (component exchange and revision for any reason).

knee (2%) an arthroscopic lavage was done, followed by antibiotic treatment due to an infection of the knee.

Five patients required open arthrolysis with exchange of the polyethylene liner. In three of these cases no clear improvement of the ROM was achieved by a manipulation under anaesthesia (MUA). One patient suffered from periarticular ossifications (PAO's), which were excised at 13 mo after surgery and therefore required polyethylene exchange. In one case, the patient had complaints of a large fabella for which removal of the PE was needed to gain access for excision. Five patients suffered from joint instability after a traumatic event, and four patients had complaints of instability following primary surgery without any clear trauma. One early infection (within 1 mo) was treated with arthroscopic lavage followed by an additional treatment. Of the eight TKAs that received an open procedure without PE exchange, seven patients underwent arthrolysis for arthrofibrosis, of which two cases required additional realignment of the patella without implantation of a patellar button. One patient had complaints of a Corpus Liberum (CL) that required removal. On inspection, there was no visible damage caused by the CL.

In one case amputation of the lower limb was necessary within the first month after surgery, due to a rupture of a pseudo-aneurysm. This led to a compartment syndrome, which was detected too late due to an epidural anaesthesia.

MUA was performed in 33 knees (3.2%) at a mean follow up time of 4.1 (range 1-8) mo. In three cases MUA was followed by an open release, for which PE exchange was also necessary and in one case by component exchange. All TKAs that required MUA suffered from arthrofibrosis that limited the functional Range of Motion (ROM) of 90 degrees of flexion or full extension. Patient age, gender, BMI and ASA-class were not significantly associated with true revision as well as revision for any reason ($0.38 < P < 0.99$).

DISCUSSION

In this large retrospective review of a TiN coated mobile

bearing TKA, good to excellent scores were achieved and a very low pain scores. A median postoperative VAS pain scores in a scale of 0-100, at one year after surgery were 1 in rest and 2 during movement of the joint. The median reported KOOS-pain scores were 92. These reported pain scores seem to be comparable with the reported VAS-pain scores reported by Moon *et al.*^[18] of 1.4 (in de "Buechel and Pappas" total knee group) and 1.8 (in the "NexGen-LPS" total knee group). Therefore the results of the TiN coated mobile bearing TKA concur with the results of the CoCrMo mobile bearing TKA, and are not superior or inferior to the CoCrMo mobile bearing TKA^[18,19].

It was suggested in the literature, that the TiN coating could protect the synovium of the knee for the release of Co and Cr ions^[10]. *In vitro* studies have shown that Co en Cr ions can induce an inflammatory response, thus induce pain and swelling^[10]. Van Hove *et al.*^[10] compared the TiN coating to a CoCrMo mobile bearing TKA and found no difference in postoperative pain scores or inflammation between the two groups. So the hypothesis that the TiN coating could make a difference in the direct post operative period, does not seem to be the case, our results are comparable to the CoCrMo mobile bearing TKA.

Another reason for our group to use the mobile bearing TKA is the low number of patients with anterior knee pain or PF pain after a TKA. Resurfacing or not resurfacing the patella during primary TKA still remains controversial^[1,20]. Anterior knee pain after TKA could have multiple causes and is not solely caused by not resurfacing the patella during primary surgery. In our series all but two TKAs in this study were implanted without the use of a patellar component. Later 10 Patients (1.0%) suffered from PF pain and required a secondary resurfacing of the patella. Thus in our series, more than 1000 knees were not resurfaced with a patella, this may further support the theory that resurfacing of the patella is not strictly necessary in primary mobile bearing TKA^[20-22]. There are some limitations in this study with regard to this dilemma. We did not specifically ask questions regarding PF pain or quantify that amount of pain. Although the completed questionnaires can give some insight in the overall knee function and pain scores, they do not isolate PF pain. We only have data on PF pain if this resulted in the secondary resurfacing of the patella.

Patient satisfaction were good, revealing a median VAS-satisfaction score of 91 (IQR 70-100) out of 100 in the non-revised, vs 45 (IQR: 14-38) out of 100 in the revision group at one year following primary surgery. This difference was statistically significant ($P < 0.01$). At one year after surgery patients reported high levels of health-related quality of life. There was a significant difference ($P < 0.01$) in the EQ-5D scores between the revised and non-revised TKA scores, with the revision group showing lower scores corresponding with a lower quality of life. The impact of a revision or secondary operation can be revealed in this way.

The TiN coating of the CoCrMo TKA could be beneficial to patients with a metal allergy, especially those with a known nickel sensitivity^[23]. This precludes them from receiving a CoCrMo alloyed arthroplasty. Due to the increase in the number of TKAs performed annually; the amount of patients with a painful well-implanted TKA is also thought to increase. If a patient is known with a metal allergy, it is advised to perform an anallergic implant, like the TiN coated implants.

MUA was performed in 33 (3.2%) cases, and this is in unison with the widely reported prevalence of 1.3%-12%^[8]. For all but 3 patients in our study, a single MUA followed by intensive physical therapy was sufficient to improve ROM to a functional level of > 90 degrees of flexion and full extension. An additional open release was necessary in the above-mentioned three patients following MUA to regain a functional ROM.

The TiN coating is thought to reduce the wear of Polyethylene and the potential for wear debris induced osteolysis, which today is still a considerable cause for revision surgery^[2,3]. This is thought to be due to the beneficial properties of TiN coating, they include: The hardness, more scratch resistant, a smoother surface, less adhesion to polyethylene and a more wettable surface^[10,14-16]. In this series a survival of 97.7% at a mean follow-up period of 46 mo was found. This is comparable to the survivorship of other TKAs. The survival of conventional knee arthroplasties, using fixed bearing implants, ranges from 90%-95% of > 10 years^[18]. Beuchel *et al.*^[19] reported a 20 year survival of the LCS cemented rotating platform TKA of 97.7%. Jordan *et al.*^[24] reported survivorship of 94.8% at 8 years of the meniscal-bearing TKA. All retrieved polyethylene liners were inspected for wear during revision surgery. There were no reports of significant wear of the retrieved liners. The mean revision period of 21 mo is however, arguably too short to reveal high levels, if any, of polyethylene wear. Whether or not the addition of a TiN coating of a mobile bearing TKA reduces polyethylene wear and thus enhance the survival of the arthroplasty needs to be further investigated in the upcoming years.

Results of this study should be interpreted taking into account the limitations inherent to retrospective studies. Additionally, the response rate of completed questionnaires was 65%. This percentage might be susceptible to selection bias. A limitation of our study is due to lack of pre-operative pain scores, it is however not possible to quantify the improvement of patient reported pain after TKA.

In conclusion the ACS TiN mobile bearing TKA is a reliable arthroplasty yielding good to excellent clinical results, with a high level of function and low revision rates at a mean follow-up of 46 mo after surgery. Based on the outcomes of this study, the use of the ACS TiN coated, mobile bearing TKA appears to be justified and will be used as our primary TKA. Further research is necessary to investigate long-term survival of the arthroplasty and whether or not the addition of the TiN

coating is beneficial for polyethylene wear.

ARTICLE HIGHLIGHTS

Research background

Evaluate the influence of the titanium nitride (TiN) coating on the results of a total knee arthroplasty (TKA).

Research motivation

Very little is known about the influence of the TiN coating on the results of a TKA.

Research objectives

Evaluate the overall clinical outcome, evaluating pain and patient satisfaction and the mid-term implant survival.

Research methods

A total of 910 patients (338 men; 572 woman), with a mean age of 65 (range 36-94) undergoing 1031 primary TKAs were assessed. Clinical evaluation and patient-reported outcomes were gathered one year after surgery. The questionnaires included the Knee injury and Osteoarthritis Outcome Score (KOOS)-Dutch version, Visual Analogue Scale (VAS) pain scores in rest and during active knee movement, VAS-satisfaction scores, and EQ-5D-3L health scores. This was aimed to assess the overall knee function and patient satisfaction, and to enable us to make a gross comparison to other TKAs.

Research results

At a mean follow-up of 46 mo (range 1-92) the overall implant survival was 97.7% and 95.1% for any operative reason related to the implant. Twenty-three knees (2.2%) required revision surgery. Arthrofibrosis was the most common indication for a re-operation. The clinical evaluation and patient-reported outcomes revealed good to excellent patient satisfaction and function of the arthroplasty. The median postoperative VAS-pain scores on a scale of 0-100, at one year after surgery were 1 in rest and 2 during movement.

Research conclusion

The TiN coated, mobile bearing TKA results are excellent and similar to those of other widely used TKA designs. Residual pain of the knee remains a concern and the TiN coating in combination with the mobile bearing does not seem to be the simple solution to this problem. Future research will have to show that the coating gives a better survival than the cobalt chrome version.

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Retrospective Study

Acetabular cup version modelling and its clinical applying on plain radiograms

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Author contributions: Kovalenko A designed the study and analyzed data; Bilyk S performed three-dimensional modeling part; Denisov A revised the manuscript for important intellectual content and in couple with expert-doctor from United States made the translation in English.

Institutional review board statement: The study “Acetabular cup version modelling and its clinical applying on plain radiograms” was approved by the Institutional Review Board (IRB) of the Vreden Scientific Orthopedic Institute, Saint-Petersburg, Russian Federation.

Informed consent statement: Patients were not required to give informed consent to the study because in retrospective analysis were used anonymous data that were obtained after each patient agreed to treatment by written consent.

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Abstract**AIM**

To measure the sensitivity and specificity of the cup version assessment by using only anteroposterior hip and pelvis views, evaluate the incidence of inadequate cup version in patients with repeated dislocations after total hip arthroplasty (THA).

METHODS

Radiographic retrospective analysis of 2 groups of patients, with follow up of 6-60 mo, after undergoing primary THA. First group of 32 patients (20 female, 12 male) with unilateral THA (32 hips) required early revision arthroplasty for reasons of dislocation. The mean age and mode were 59 (from 38 to 83) and 66 ages respectively. The average body mass index (BMI) was 24.2 (from 17.7 to 36.3), mode 23.9. Second group was consisted of 164 patients (101 female, 63 male) without dislocations during the follow-up period (170 hips). Among them 6 patients required bilateral THA. The mean age was 60 (from 38 to 84) and mode 59. BMI was 24.8 (17.2-36.8), mode 25.2. Clinical significance of the cup anteversion sign was estimated with cross tabulation 2×2 .

RESULTS

The value of the χ^2 yates was 10.668 ($P < 0.01$).

Sensitivity of SAI (sign of anteversion insufficiency) was 29% (95%CI: 9%-46%), and specificity was 92% (95%CI: 88%-96%). Relative risk of dislocation in patients with SAI was 3.4 (95%CI: 1.8-6.3).

CONCLUSION

This method provides the surgeons with the ability to perform a reliable and simple qualitative assessment of the acetabular component version. It can be useful during patient examination with early loosening of the implant, dislocations, and impingement. Additionally, it can provide necessary information during planning of revision surgery, especially when considering question about cup replacement, although final assessment of the cup position should be done with a computed tomography scan.

Key words: Hip arthroplasty; Acetabular component; Retroversion; Dislocation

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Core tip: The acetabular cup position is a crucial factor of normal function and implant survival. Several methods to determine cup anteversion are described. Among them are mathematical methods based on a standard anteroposterior (AP) view, modifications of a cross-table lateral views, and computed tomography-scan. Latter two methods are not always available or practical in outpatient setting. The purpose of our study was to estimate sensitivity, specificity of the cup version assessment by using only AP hip and pelvis views. Our findings suggest that inadequate anteversion sign appears when the anteversion angle is less than half the angle between X-ray beams in the AP hip and pelvis views.

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INTRODUCTION

Compared to most other orthopedic interventions, total hip arthroplasty (THA) is only a first step in a lengthy journey. Successful patient outcome relies heavily on the implant, which requires regular observation to assess the prosthesis and surrounding tissues. It is well known that bearing surface wear rate and prosthesis stability are dependent upon proper component positioning^[1-3]. Thus, timely recognition of component malposition is a major goal in the postoperative period. Early awareness may allow for a timely correction of acetabular cup position and expedited return to daily activities without undesirable effects of improper component alignment. Two main parameters that must be taken into account

while assessing acetabular component position are inclination and anteversion. Inclination is a measure of the angle between longitudinal axis (line drawn between the teardrops) and acetabular axis (cup tilt). Cup version measurement, on the other hand, poses a greater challenge.

Calculation of this angle can be achieved via several techniques. These methods are based on the evaluation of a visible ellipse on anteroposterior (AP) view as a result of cup rotation. Previously described techniques by Pradhan, Acland, Lewinnek are often used^[4], as well as specialized software which can provide calculation of cup version^[5], and even orthopedic grid calipers which approximate this calculation^[6]. However, none of these techniques can differentiate cup ellipse appearance in patients with same degree of anteversion vs retroversion. This issue can be resolved by using a cross-table lateral view or computed tomography (CT) scan^[7], both of which are seldom used due to challenge with patient position in the early postoperative period and concerns for radiation exposure.

To measure the sensitivity and specificity of the cup version assessment by using only AP hip and pelvis views and evaluate the incidence of inadequate cup version in patients with repeated dislocations after THA.

MATERIALS AND METHODS

Cup shadows in retroversion and anteversion were reproduced on AP hip and pelvis views using Autodesk 3ds Max software (Autodesk, Inc., San Rafael, CA, United States) (Figure 1). Difference in angles of cup version, which may be seen as a result of difference between X-ray beams centered on AP hip and pelvis views, were subsequently analyzed. The distance from the beam source to the screen was 100 cm, the distance from the cup model to the screen was 15 cm, and the cup diameter was 50 mm. Cup version angles ranged from -20 to 20 degrees in one degree intervals. The shift of the source beam between AP pelvis and AP hip views was 12 cm. Acquired data was used for radiographic retrospective analysis of 2 groups of patients, with follow up of 6-60 mo, after undergoing primary THA.

First group of 32 patients (20 female, 12 male) with unilateral THA (32 hips) required early revision arthroplasty for reasons of dislocation. The mean age and mode were 59 years (38-83) and 66 years respectively. Average BMI was 24.2 (17.7-36.3), mode 23.9.

Second group consisted of 164 patients (101 female, 63 male) without dislocations during the follow-up period (170 hips). Among them 6 patients required bilateral THA. The average age was 60 years (38-84) and mode 59 years. BMI was 25.1 (17.2-36.8), mode 25.2. Clinical significance of cup anteversion sign was estimated with cross tabulation 2 × 2.

RESULTS

Three-dimension modelling revealed that the widths

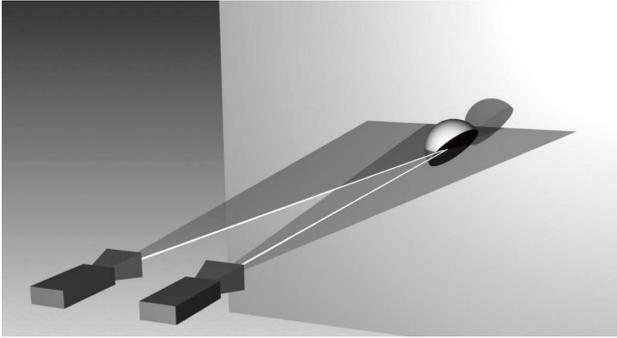


Figure 1 The scheme of model of anteroposterior pelvis view (X-ray source on the left) and anteroposterior hip view (X-ray source on the right) for acetabular cup of left hip.

of the ellipse-shaped shadow formed by the projection of the cup base to the screen are distinct in different views (Figure 2). The shadow ellipse width appears less pronounced in AP pelvis view as compared to AP hip view when the cup is anteverted (Figure 3). On the other hand, the observed shadow profile is greater in AP pelvis view as compared to AP hip view when cup is retroverted (Figure 4). A sign of retroversion was also noted when true anteversion angle did not exceed 1/2 of the angle between X-ray beam in different views (AP hip and AP pelvis). Ellipse width profiles were equal between 2 projections at the point where true anteversion was 3.5 degrees (Figure 5).

Doubling the distance of medialization of the source beam (12 to 24 cm) from the AP hip to AP pelvis position, this threshold increased in a linear manner from 3.5 degrees to 7 degrees. Retro- or anteversion angle was confirmed with a CT scan among patients having indications for revision arthroplasty (Figure 6). For discrete X-rays assessment, we assigned expression of sign shown on Figure 2 to the sign of anteversion (SA), and all others options (Figures 3 and 4) to sign of anteversion insufficiency (SAI). Thus, two options were available in assessment of cup position on X-rays-SA and SAI. Findings are presented in Table 1.

The value of the χ^2 Yates was 10.668 ($P < 0.01$). Sensitivity of SAI was 29% (95%CI: 9%-46%), and specificity was 92% (95%CI: 88%-96%). Relative risk of dislocation in patients with SAI was 3.4 (95%CI: 1.8-6.3).

Predictiveness (positive predictive value) of SAI (predictive probability dislocation appearance) was 0.20 (95%CI: 0.09-0.38). Counter-predictiveness (Counter-negative predictive value) of SA (predictive probability dislocation absence) was only 0.046 (95%CI: 0.026-0.081) (Figure 7).

DISCUSSION

The method of this investigation was described by Markel *et al.*^[8] in 2007. However, the authors only described the technique and recommended its use as a screening tool without reporting its sensitivity and

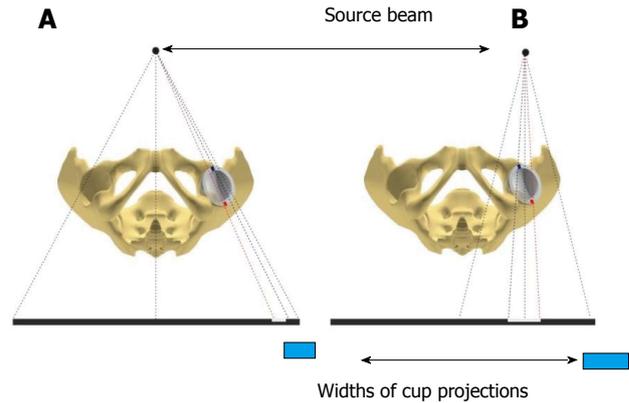


Figure 2 Different width of cup projections in pelvic and hip anteroposterior views. A: Pelvic anteroposterior views; B: Hip anteroposterior views.

specificity.

Threshold value for the sign inversion corresponds to the cup anteversion value that is equal to 1/2 of the X-ray beam angle penetrating the acetabular component in AP hip and AP pelvis views. The threshold value was only 3.5° in baseline conditions of our experiment. The version sign can appear retroverted in the cases when true cup anteversion is less than the threshold values. Thus, the sign can point to retroversion while the cup is, in fact, anteverted. However, in such cases, anteversion value will be out of Lewinnek's safety zone of 10°-20°^[9] and further imaging would be encouraged. For these cases, we recommend the use of special views or a CT-scan to refine implant position.

In clinical practice threshold value, will depend on the patient anthropometric parameters which affect cup distance to the X-ray detector and the distance between centers of pelvis and hip joint. Nevertheless, two-fold shift in the beam source, compared to our model baseline condition, leads to increase in sign of inversion threshold up to 7°. This either corresponds to patient with a pelvis twice as wide than average^[10] or, to a beam centered in front of a contralateral joint instead of symphysis pubis, which is unlikely. In addition, method accuracy can be affected by improper beam centering during radiography.

Low sensitivity (29%) and predictiveness (positive predictive value) of SAI (20%) can be explained by multifactorial causes of dislocation such as stem position, offset, muscle insufficiency and comorbidities. On other hand, specificity of SA (92%) points to a high probability to find SA in a patient without dislocation. Furthermore, counter-predictiveness (counter-negative predictive value) of SA points to the probability that dislocation can occur with frequency of only 4.6%. This data leads us to believe that these radiographic signs have a strong clinical relevance and can be useful in orthopedic practice.

X-ray assessment immediately after surgery or during outpatient follow-up, when lateral view is not available, can be limited to evaluation of cup inclination and ellipse presence that suggests about probable

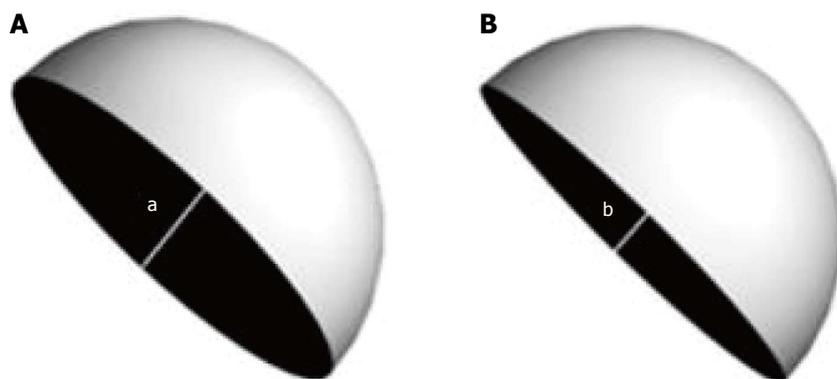


Figure 3 Acetabular component with anteversion angle of 20 degrees. A: Acetabular component image for hip AP view; B: Acetabular component image for pelvic AP view, $a > b$. AP: Anteroposterior.

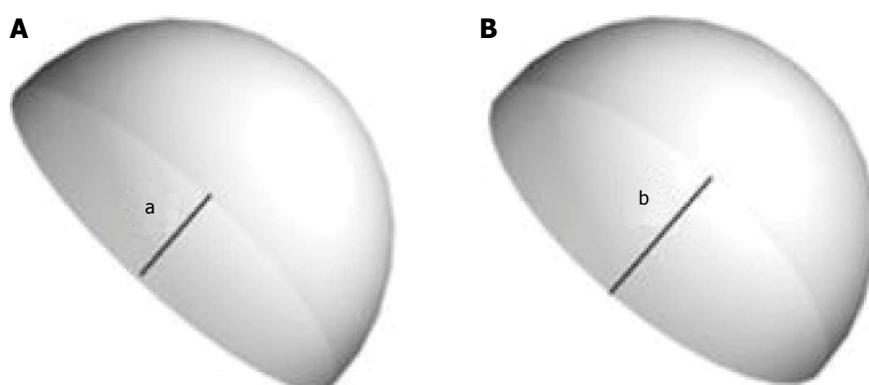


Figure 4 Acetabular component with retroversion angle of 20 degrees. A: Acetabular component image for AP hip view; B: Acetabular component image for AP pelvic view, $a < b$. AP: Anteroposterior.

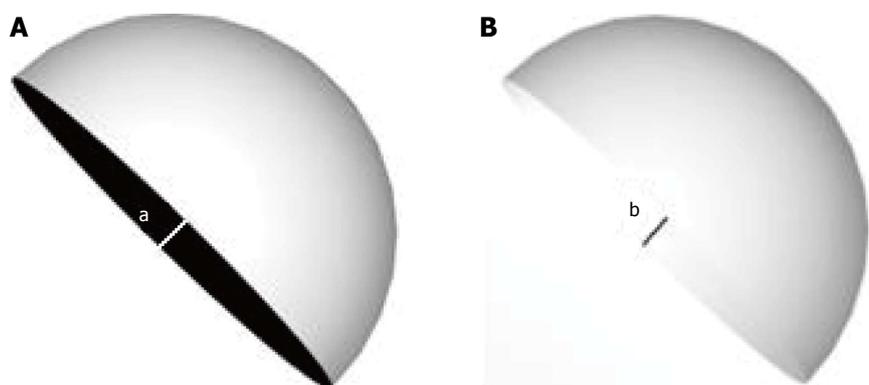


Figure 5 Acetabular component views with anteversion angle equal to half angle between rays of the beam. A: Acetabular component image for hip AP view; B: Acetabular component image for pelvic AP view. Equal width of ellipse in both views, $a = b$. AP: Anteroposterior.

cup version. However, a bias exists because of a two-dimensional nature of conventional X-ray views. Additional comparison of cup position on AP hip and AP pelvis views allows to avoid this bias. This simple method is useful as a screening assessment of post-op cup position and, in outpatient and remote follow-up. Furthermore, it can be used for X-ray assessment in patients with early components loosening, dislocations, impingement and preoperative revision planning, especially when there is a possibility of avoiding an

acetabular cup revision. In the last example provided, we recommend performing a CT-scan for additional analysis.

On the other hand, high incidence of retroversion sign confirms clinical relevance of this method in the group of patients who required early revision surgery for the reason of hip dislocations. Postoperative radiographic evaluation is usually limited to measuring of inclination and cup ellipse, may be indirect evidence of anteversion. Such assessment methodology can

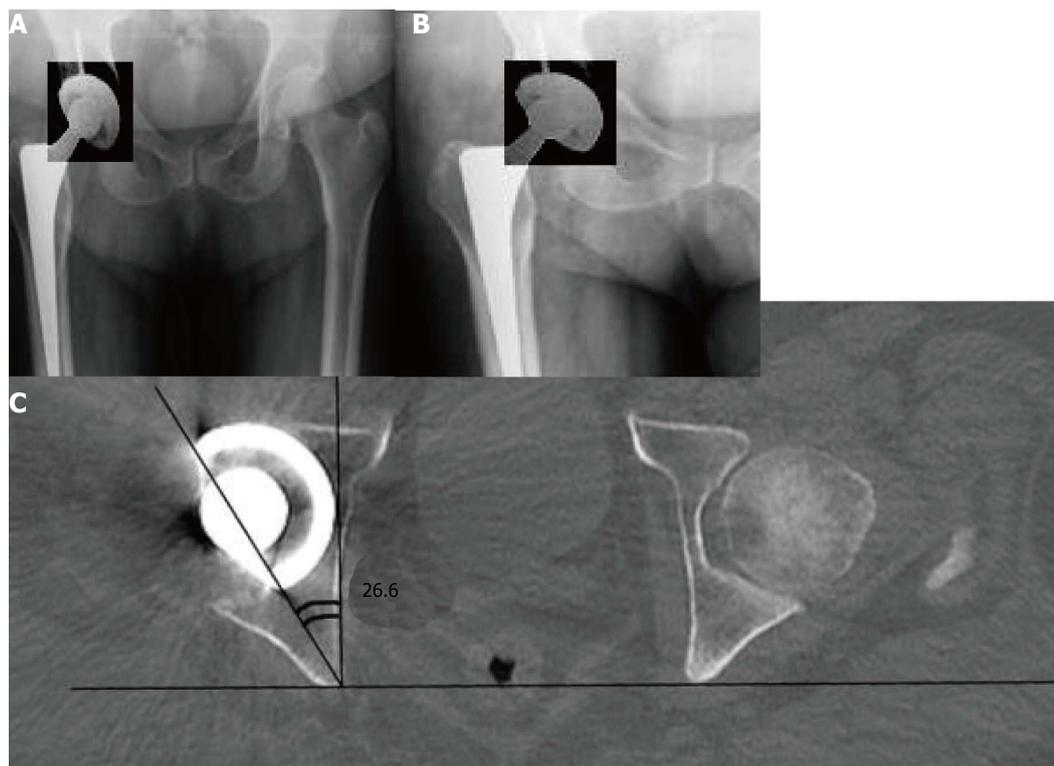


Figure 6 Retroversion sign in a patient with recurrent hip dislocations (enhanced contrasting applied to provide better recognition of acetabular cup ellipse). A: AP Pelvic view; B: AP hip views; C: CT-scan of the same patient confirming acetabular component retroversion. AP: Anteroposterior.

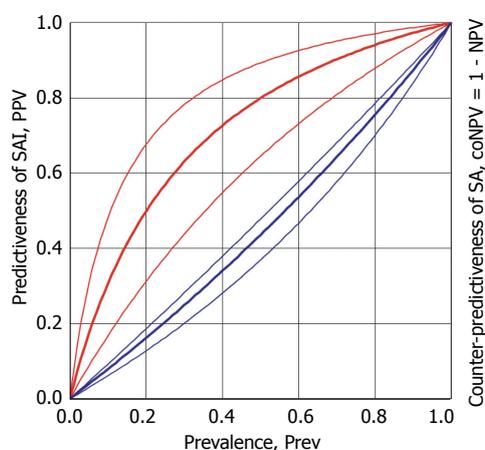


Figure 7 Predictiveness of sign of anteversion insufficiency appearance and counter-predictiveness of sign of anteversion appearance. SAI: Sign of anteversion insufficiency; SA: Sign of anteversion.

have an error due to plain radiography imaging features described above. Additional comparison of pelvic AP and hip AP view allows the possibility to eliminate this error during radiographic evaluation and decreases the probability of early hip joint instability. This simple radiographic test can be used both for screening assessment of acetabular cup version on postoperative images and in outpatient setting.

This method provides surgeons with ability to use it as a screening examination because of the simplicity of the acetabular component version qualitative assessment. It can be useful during patient examination

Table 1 Prevalence of sign of anteversion insufficiency and sign of anteversion in patients with absence and recurrence of dislocations after primary total hip arthroplasty

X-ray diagnostic conclusion	Dislocation		Total
	Yes	No	
SAI	9	12	21
SA	23	158	181
Total	32	170	202

SAI: Sign of anteversion insufficiency; SA: Sign of anteversion.

with suspicion of the implant malposition, early implant loosening, dislocations and impingement to provide with the argument for obtaining CT scan. Additionally, it can provide necessary information during planning of revision surgery, especially when considering question about cup replacement, although final assessment of the cup position should be done with a CT scan.

ARTICLE HIGHLIGHTS

Research background

Correct cup positioning is one of the crucial factors of preventing hip luxation after total hip arthroplasty (THA). It can be estimated using simple radiographic views (AP of pelvis and hip) and calculating of the cup inclination angle.

Research motivation

Some techniques can provide calculation of cup version, however none of these techniques can differentiate cup ellipse appearance in patients with same degree of anteversion vs retroversion. It can be resolved by using a cross-table

lateral view or CT scan, both of which are seldom used due to challenge with patient position in the early postoperative period and concerns for radiation exposure and sometimes not available in orthopedic practice.

Research objectives

The authors measured the sensitivity and specificity of the cup version assessment by using AP hip and pelvis views, evaluated the incidence of inadequate version in patients with repeated dislocations after THA. The authors believe that estimation of simple radiographic anteversion sign can be used for screening assessment for further obtaining of additional examinations in case of cup malposition and repeated dislocations (as one of the provoking factor).

Research methods

Cup shadows in retroversion and anteversion were reproduced on AP hip and pelvis views using Autodesk 3ds Max software (Autodesk, Inc., San Rafael, CA, United States). Difference in angles of cup version, which may be seen as a result of difference between X-ray beams centered on AP hip and pelvis views, were subsequently analyzed. Acquired data was used for analysis of 2 groups of patients, with follow up of 6-60 mo, after undergoing primary THA.

Research results

The value of the χ^2 yates was 10.668 ($P < 0.01$). A sign of retroversion was also noted when true anteversion angle did not exceed 1/2 of the angle between X-ray beam in different views (AP hip and AP pelvis). Sensitivity of SAI was 29% (95%CI: 9%-46%), and specificity was 92% (95%CI: 88%-96%). Relative risk of dislocation in patients with SAI was 3.4 (95%CI: 1.8-6.3).

Research conclusions

Results of our study showed high specificity of the sign of anteversion inclination 92% and low sensitivity (29%) due to other risk factors of hip dislocation.

Research perspectives

In this article were not studied other factors provoking hip dislocation. That is way for future perspectives, the authors want to determine the current role of the cup malposition in comparison with other factors of hip luxation.

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Observational Study

Deepening trochleoplasty combined with balanced medial patellofemoral ligament reconstruction for an adequate graft tensioning

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Institutional review board statement: The study was reviewed and approved by the Ethical Committee of the University of Witten/Herdecke (Study No. 108/2015).

Informed consent statement: All persons involved in this study gave their informed consent prior to study inclusion.

Conflict-of-interest statement: All authors have no interests, commercial or otherwise, which represent a conflict of interest in relation to this study.

Data sharing statement: No additional data are available.

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Abstract

AIM

To evaluate our modified deepening trochleoplasty combined with a balanced medial patellofemoral ligament (MPFL) reconstruction for soft tissue alignment.

METHODS

Thirty-three knees with recurrent patellar dislocations and a trochlear dysplasia in 30 patients (m/f = 12/21, mean age 24 ± 9 years) underwent a combination of a modified deepening trochleoplasty and a balanced MPFL reconstruction for a medial soft tissue alignment. After a mean follow-up period of 29 ± 23 mo, patients' return to sports, possible complications as well as the clinical outcomes using the Kujala, International Knee Documentation Committee (IKDC) and Lysholm scoring were evaluated. Moreover, patients' satisfaction with the general outcome, the cosmetic outcome, the pre- and postoperative pain and a potential avoidance behaviour were assessed with additional standardized questionnaires

which also included different visual analog scales.

RESULTS

There were no signs of a persistent instability. The Kujala score improved from a mean of 64 ± 16 points to 94 ± 9 points, the Lysholm score improved from a mean of 63 ± 17 to 95 ± 6 points and the IKDC score from 58 ± 11 to 85 ± 12 points, $P < 0.0001$, respectively. The assessment of pain using a visual analog scale showed a significant pain reduction from a mean of 4.8 ± 2.0 to 1.3 ± 3.4 points ($P < 0.0001$). Two of 26 cases (92%) who were engaged in regular physical activity before surgery did not return to full sporting activities. One patient felt that his sport was too risky for his knee and reported an ongoing avoidance behaviour. The other patient preferred to wait for surgery of her contralateral knee. Of the eight patients who were not engaged in sporting activities before surgery, three started regular sporting activities after surgery. In 31 of the 33 cases (94%), the patients were very satisfied with the clinical outcome of the surgery. Regarding the cosmetic results, no patients felt impaired in their self-confidence and in their clothing decisions.

CONCLUSION

Our technique shows a good clinical outcome in terms of the common scorings as well as in terms of pain, return to sports and patient satisfaction.

Key words: Trochlea dysplasia; Medial-patellofemoral ligament; Patellofemoral instability; Patella dislocation; Trochleoplasty

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Core tip: Patients with recurrent patella dislocations typically have an insufficiency of the medial patellofemoral ligament (MPFL), which is an additional instability factor in a symptomatic trochlear dysplasia. Following a trochleoplasty, the articulation of the patella is changed to a more medial and dorsal mechanical position. As a consequence, a balanced alignment of the medial soft tissue restraints during a trochleoplasty is very reasonable to achieve an adequate stabilization. The combination of a modified Bereiter trochleoplasty and our MPFL reconstruction technique allowing a simple intra-operative tensioning shows encouraging results.

von Engelhardt LV, Weskamp P, Lahner M, Spahn G, Jerosch J. Deepening trochleoplasty combined with balanced medial patellofemoral ligament reconstruction for an adequate graft tensioning. *World J Orthop* 2017; 8(12): 935-945 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i12/935.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i12.935>

INTRODUCTION

In flexion angles of more than 30° , the patella is

predominantly guided by the trochlear groove. Between 30° of flexion and the full extension, both the medial patellofemoral ligament (MPFL) and the trochlear groove stabilize the patella^[1,2]. In trochlear dysplasia, the trochlea is shallow, flat, or dome shaped, leading to an inadequate resistance to lateral patellar dislocations. Therefore, it has been described to be a major risk factor for patellofemoral instability^[3]. Trochlear dysplasia is described in less than 2% of the population, whereas it occurs in up to 85% of patients with patellar instability^[4]. An isolated MPFL reattachment or reconstruction in the presence of a severe dysplasia of the trochlea shows a relatively poor clinical outcome and leads to an increased risk for a recurrent instability with persistent apprehension and/or dislocations^[5-10]. Therefore, a severe dysplasia of the trochlea should be addressed when corresponding clinical findings are present.

Following an acute patellar dislocation, the MPFL is ruptured with a frequency of more than 90%, which can cause recurrent dislocations and/or a significant instability^[1,11,12]. During a trochleoplasty, the intra-operative impression that the patella is moved to a more medial and dorsal mechanical position has been proven by a computed tomography (CT) study on corrective postoperative changes^[13]. As a logical consequence, a MPFL plastic surgery seems advisable, not only to address a torn, insufficient ligament, but also because a balancing and alignment of the medial soft tissue restraints is necessary (Figure 1). Therefore, our technique of a MPFL reconstruction allowing a simple intra-operative testing and adjustment of the graft tension^[14], might be convenient especially in cases with a combined trochleoplasty. This might help in minimizing common complications of MPFL reconstructions, such as an overtensioning with anterior knee pain and/or motion deficits, patellar fractures, *etc.* or an undertensioning with an ongoing instability^[6,15,16]. This study was necessary to explore our combination of a deepening trochleoplasty and our technique of a balanced MPFL reconstruction for a medial soft tissue alignment. Our hypothesis is that this technique provides reasonable advantages.

MATERIALS AND METHODS

Ethical considerations

This study has been approved by the Ethical Committee of the University of Witten/Herdecke (Study No. 108/2015) and was carried out in accordance with the ethical standards laid down in the Declaration of Helsinki. The participation was voluntary and all patients gave their informed consent to this study.

Population

This study includes 33 knees with a severe trochlear dysplasia in 30 patients (m/f = 12/21, mean age 24 ± 9 years) who underwent surgery with a combination of trochleoplasty and MPFL reconstruction as described

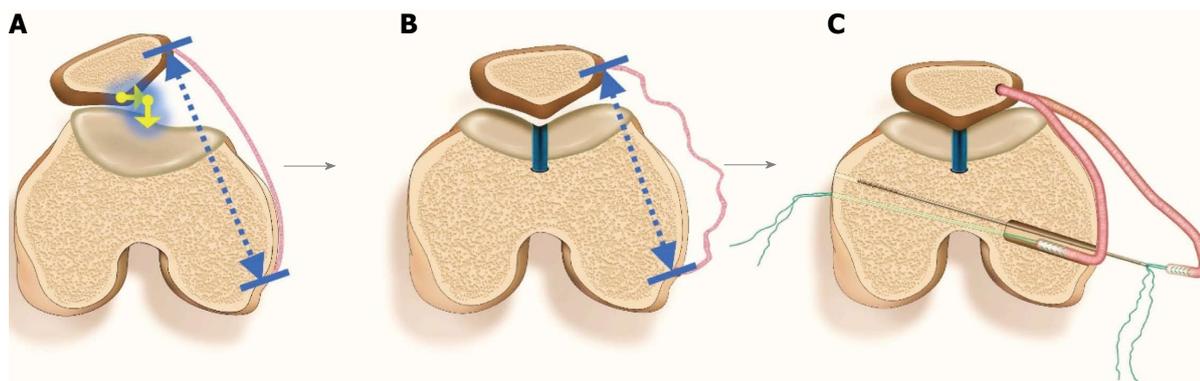


Figure 1 Drawings of the preoperative situation and the biomechanical changes during surgery. A: Drawing of a type C dysplasia showing a too high lateral facet with a bump in the superolateral aspect and a trochlear facet asymmetry with hypoplastic medial facet. This trochlea is not effective in constraining a patellar displacement; B: After mobilization of a thin osteochondral flap off the medial and lateral trochlea, the trochlear bone is deepened. The lateral edge of the trochlea is not lowered to obtain a raised lateral inclination. This way, a recentralized groove is created. The flexible osteochondral flap is fixed into the new formed groove with a transosseous resorbable 3 mm Vicryl band. As depicted, a trochleoplasty leads to a more medial and dorsal biomechanical position of the patella with a reduced distance between the femoral and patellar insertions of the medial soft tissue restraints. As a consequence, a preexisting insufficiency of the medial patellofemoral ligament (MPFL) might be aggravated by these biomechanical changes; C: Hardware-free MPFL reconstruction technique for the alignment of the medial soft tissue restraints during a trochleoplasty.

below. The estimated mean number of dislocations before surgery was 35 ± 24 (range: 1-250). Before surgery, all patients had a clear positive patella apprehension sign. Exclusion criteria were additional surgeries such as corrections of the knee rotation and/or axis, tibial tuberosity transfers, etc. Moreover, patients with advanced osteoarthritic changes or previous fractures of the knee were not included in this study. Factors of patellar instability were measured on preoperative radiographs and magnetic resonance imagings (MRIs) or CT scans^[4]. In our series, the mean Caton-Deschamps index was 1.09 ± 0.09 and the tibial tubercle-trochlear groove distance was $16 \text{ mm} \pm 3 \text{ mm}$. The lateral trochlea inclination (LTI) angle was measured on the most superior MRI slice depicting the cartilage of the trochlear surface using the method described by Carrillon *et al.*^[17]. In our patients, the mean angle between the posterior contours of the condyles and the lateral facet of the trochlear groove was $-9^\circ \pm 6^\circ$. Trochlear dysplasia was graded using the Dejour classification. Nine knees showed a type B, ten a type C and 14 a type D trochlear dysplasia.

Assessment and evaluation

The mean follow-up period was 29 ± 23 mo. Possible complications such as recurrent dislocations, fractures, knee stiffness, etc. were registered. In addition to a routinely performed clinical examination, the knee function was assessed with different scoring scales. In this study, the Kujala anterior knee pain scoring, the knee-specific outcome measure of the International Knee Documentation Committee (IKDC) and the Lysholm knee scale was used. Moreover, additional questionnaires and different visual analog scales were used to assess the general satisfaction of the patients, the satisfaction with the cosmetic outcome, the return to sports, a potential avoidance behaviour, different sports activities as well as a potential anterior knee

pain.

Surgical technique

The gracilis tendon is harvested through a minimal invasive posterior or anterior harvest over the pes anserinus. After whip-stitching the armed graft has been given in a Vancomycin solution for presoaking in most cases. In contrast to the Bereiter technique, which describes a lateral parapatellar approach, we prefer a short medial parapatellar access to expose the trochlea. A seven to 10 cm long skin incision running from the medial part of the patella to the distal part of the quadriceps tendon is made (Figure 2A). The medial patellar retinaculum is divided by leaving enough tissue near the patella for later reattachment. The proximal joint capsule is incised between the superomedial pole of the patella and the vastus medialis obliquus muscle. Finally, the distal quadriceps tendon is split. Using this distally shortened medial parapatellar approach, the saphenous nerve with its infrapatellar branch is usually not affected. With this simple arthrotomy and a dislocation of the patella towards lateral, the trochlea can be completely exposed (Figure 2B). A soft tissue tunnel between both layers and running down from medial patella to the femoral MPFL insertion can be created easily by using this approach. After exposure of the trochlea, the articular cartilage is separated from the synovium. Using a curved osteotome, a thin osteochondral flap, leaving 2 mm of subchondral bone, is very carefully chiselled off the medial and lateral trochlea (Figure 2B). The flap is extended down to the intercondylar notch. The trochlear bone is then deepened using chisels and a high-speed diamond burr (Figure 2C). The lateral edge of the trochlea is not lowered to obtain a raised lateral inclination angle with an effective bony stabilization. This way, a recentralized groove is created. In cases with an increased TT-TG distance, the groove can also

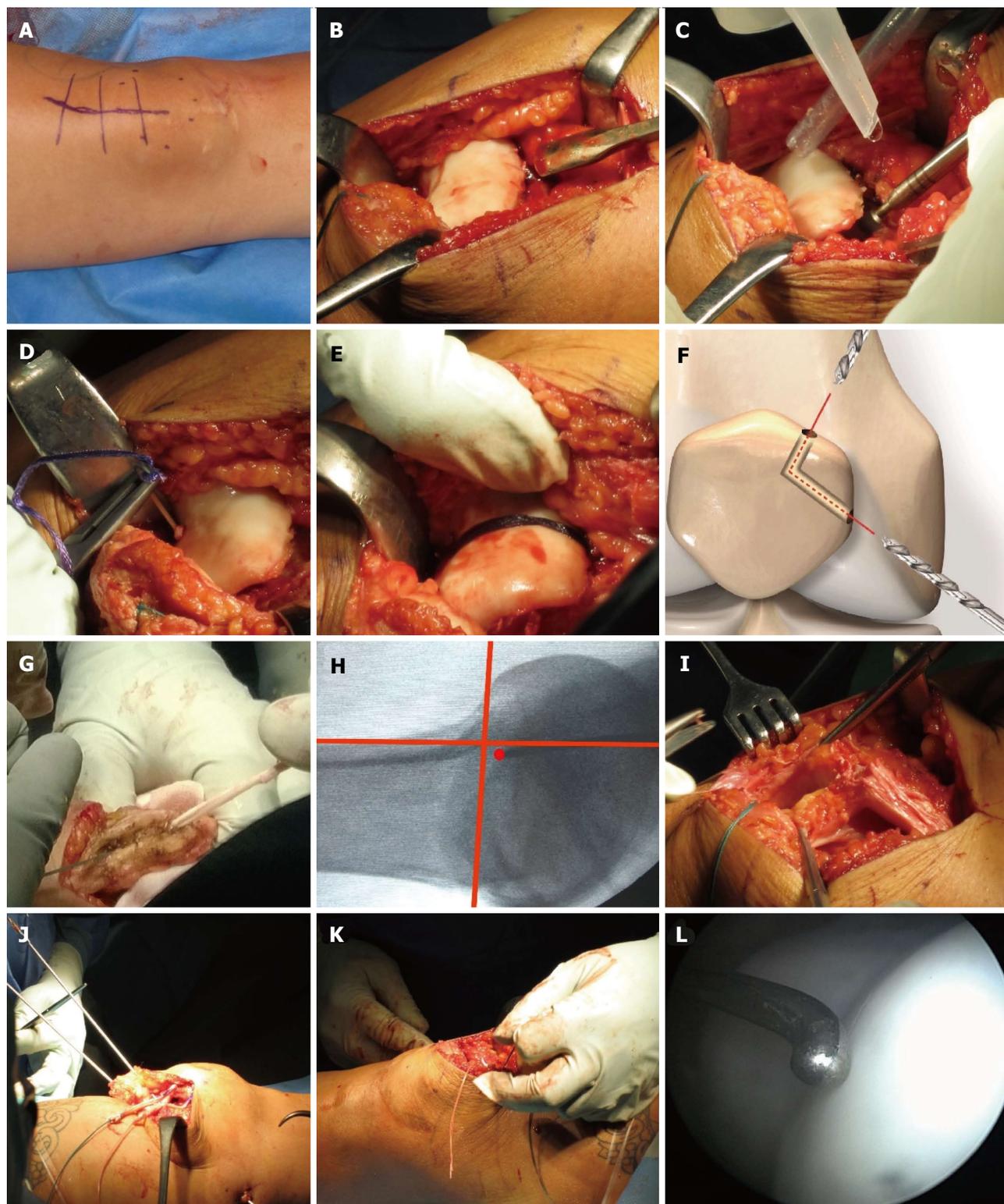


Figure 2 Step-by-step description of the combined surgical procedure. A: Short skin incision running from the medial part of the patella to the distal part of the quadriceps tendon; B: Using a curved osteotome, a thin osteochondral flap is chiselled off the trochlea; C: Trochlear bone is deepened using chisels and a high-speed burr; D: Vicryl band is passed from the distal beginning of the formed groove through the condyle using a curved needle; E: Starting at the junction between the trochlear cartilage and the anterior femoral bone, the other end of the band is passed through the femur. After pressing the flap onto the bone, the band is fastened; F: Drilling of a V-shaped tunnel coming from the superomedial pole and from the middle of the medial facet of the patella; G: Gracilis tendon is passed through the drill holes; H: Femoral medial patellofemoral ligament (MPFL) insertion side is marked with a K wire under fluoroscopic guidance; I: Prepared soft tissue tunnel between both layers of the medial retinaculum is running down to the femoral MPFL insertion; J: Two divergent beath pins are passed from the blind ending tunnel through the lateral femoral cortex; K: After passing the strands to the lateral femur, a temporary knot is tied down in approximately 30° knee flexion; L: Arthroscopy of the trochlear groove after trochleoplasty.

be deepened in a lateralized position. Then, the thin and flexible osteochondral flap is pressed into the newly formed groove. When the flap is not flexible enough, it should be thinned with the high-speed burr. The osteochondral flap is fixed into the new formed groove with a transosseous resorbable 3 mm Vicryl band (Ethicon Products, Norderstedt, Germany). For this step, the Vicryl band is passed from the distal start of the formed groove, which is usually a couple of millimeters above the intercondylar notch, through the femoral condyle using a big and eyed curved needle (Figure 2D). A second, proximal transosseous passage through the femoral condyle is performed starting exactly at the proximal end of the new groove. After pressing the flap onto the femoral bone, the Vicryl band is tightened and fastened (Figure 2E). If needed, a second Vicryl band, running from the distal part of the sulcus to the cranio-lateral edge of the trochlea, can be used to press the flap more firmly to the bone. After preparation of the medial patella facet and a debridement of the bone between both layers, two guide wires, coming from the middle of the medial edge of the patella and the superomedial pole, are advanced into the bone. Using a 4.5 mm cannulated drill bit, a V-shaped tunnel with an angulation of around 120° is created. The drillings should run as vertically as possible and leave a bone bridge between both ends of at least 15 mm (Figure 2F). The starting points of both patellar tunnels may correspond to a recent anatomic study on the MPFL, where the attachment spreads out along the upper and middle third of the medial patella edge^[18]. Using a curved needle, the graft is passed through the tunnel (Figure 2G). After palpation of the bony femoral MPFL insertion, the origin is marked with a K wire under fluoroscopic guidance. As described by Schöttle *et al.*^[19], the radiographic landmark of the femoral attachment is located 2.5 mm distal to the posterior origin of the femoral condyle and 1.3 mm anterior to a line at the posterior cortical bone of the femur (Figure 2H). After a stab incision, the guide wire is advanced to the opposite cortical bone of the femur and overreamed to a depth of at least 4 cm. Then the medial capsule is exposed and a soft tissue tunnel between both layers of the capsule is extended down to the femoral insertion of the MPFL graft (Figure 2I). Two beath pins are introduced into the femoral bone tunnel. From the end of this blind-ending tunnel, both pins are advanced in divergent directions and passed through the lateral cortical bone of the femur (Figure 2J). Using the prepared soft tissue tunnel between both layers of the medial capsule, both armed ends of the graft loop are shuttled from the patella down to the femoral bone tunnel. Each strand of the whipstitch sutures at both ends of the graft is passed through the eyelets of the beath pins. By passing the pins through the femur, the ends of the whipstitch sutures are passed through the lateral femoral cortex. By pulling on each suture pair, both armed ends of graft are introduced into the tunnel (Figure 2K). On the lateral femur, a temporary knot is

tied down to the lateral femoral cortex in approximately 30° knee flexion. This knot is temporarily fastened with a needle driver or by hand. The tension of the MPFL graft and the achieved motion of the patella is assessed by knee flexion and lateral translation of the patella. If necessary, the tension of the double limbed graft can be adjusted and functionally tested again. Finally, the knot is permanently tied up by using a series of half hitches. The inner layer of the capsule underneath the graft and the thicker superior layer which lies above the graft are closed separately and right up to both layers at the patellar margin (Figure 2G and I). The tendon of the vastus medialis obliquus muscle can be tightened medially to the patella if needed. Finally, the longitudinal incision within the distal part of the quadriceps tendon is closed up.

Rehabilitation

In the first two post-operative weeks, a partial load was recommended. In the first six weeks, an adjustable knee brace was prescribed. During the first two weeks, the motion was restricted to a knee flexion between 0° and 30°. During the third and fourth weeks, the flexion was limited to 60° and to 90° within the fifth and sixth weeks. In this context, we have to amend that we do not recommend these limitations any more (please see discussion). A rehabilitation of 12 wk was recommended before starting with sporting activities.

Statistical analysis

The statistical analyses in this study were done by using the SPSS statistics 22.0 software (SPSS Inc, Chicago, IL, United States). A statistical review of the study was performed by a biomedical statistician. The Wilcoxon signed-rank test was used to compare the pre- and postoperative clinical scores. For the comparison of the scoring between different groups within this study we used the Mann-Whitney-*U* test.

RESULTS

Stabilization of the patellofemoral joint

No patients showed signs of a persistent instability. Thus, persistent postoperative instabilities from subtle instability with anamnestic subluxations to frank dislocations were not reported. The apprehension tests were negative in all patients. Two patients reported a persistent avoidance behavior. Even if they had already mastered typical stress situations with experienced luxations in the past, they continued a slight avoidance behavior. Both patients reported that this behaviour was caused psychologically and not instability- and/or pain-related. All other patients reported being able to fully load their knee without anxiety.

Patient satisfaction with the clinical results

In 31 of the 33 cases (94%) the patients were very satisfied with the clinical outcome of the surgery. All of them would again decide for the same procedure.

Two patients (6%) were dissatisfied. Both patients had a flexion deficit between 20° and 30°. One of these patients also reported an anterior knee pain. However, the main reason for her disappointment was that she was not able to play and to crawl an all fours with her toddler.

Patient satisfaction with the cosmetic results

Regarding the cosmetic outcome, all patients were satisfied with the outcome. Thus, no patients felt impaired in their self-confidence and/or in their clothing choices such as skirts or trousers. Two patients were only partially satisfied because they would have preferred a shorter and narrower scar. On the other hand, they would not decide for an aesthetic correction operation assuming that this would be most likely successful.

Pain

Four patients (12%) reported no changes of their pain symptoms, which could be described in all of these cases as a slight anterior knee pain occurring occasional during exercise and/or longer runs. A further four patients (12%) reported an increase of pain at the last follow-up. Further six patients (18%) reported a severe knee pain before surgery which improved almost completely at the last follow-up. Further 14 patients (42%), who mainly showed severe pain symptoms before surgery, became completely pain-free. Further five patients (15%) had no knee pain before surgery as well as at the last follow-up. Taken together, in 29 of 33 cases (89%), the patients either remained unchanged with mild symptoms or no pain, or showed a notable improvement to an almost or completely pain-free situation. The assessment of pain using a visual analog scale showed a significant pain reduction from a mean of 4.8 ± 2.0 to 1.3 ± 3.4 points ($P < 0.0001$).

Return to sports

In 25 of the 33 cases, patients were engaged in regular physical activity before surgery. After surgery, two of these did not return to full sporting activities. Both did not have any complaints. One patient reported an anxiety or avoidance behaviour for typical stress situations as a reason for not returning to his full sporting activities. He played soccer and he felt that this sport is too strenuous or risky for his knee. The other patient preferred to wait for the surgery of her contralateral knee. Of the eight patients who were not engaged in sporting activities before surgery, three moved to the group of patients engaging in regular physical activity. The remaining five patients were very satisfied with their knee function during daily activities and none of them reported any complaints or recurrent luxations. Nevertheless, four of them still had no interest in sporting activities. One of the five patients who remained uninvolved in sports reported a continuing avoidance behavior in her daily activities.

Although she had already mastered typical stress situations with previously experienced dislocations, she reported persistent avoidance behavior.

Complications

No deep infection or wound infection occurred. Recurrent dislocations, patella fractures, breakages of the osteochondral flap during surgery *etc.*, were not registered. The re-operation rate in our study was 6% (2/33). In both cases, an early postoperative motion deficit with a markedly reduced flexion between 70° and 90° was treated. After the hospital stay, both patients did not attend the recommended physiotherapy. In both cases, arthroscopy with an arthrolysis and a mobilization was performed around three months after the initial surgery. During arthroscopy, adhesions within the joint were removed. Arthroscopy of the trochlear groove and the cartilage of the patellofemoral joint showed regular findings, the vicryl fiber was fully resorbed (Figure 2L). Subsequently, both patients had better motion and decreased pain during motion. At the final follow-up, they showed an unlimited motion and no anterior knee pain. Furthermore, we have to report three patients with a slight flexion deficit at the last follow-up. Two showed a deficit of around 20°. Both patients reported a slight anterior knee pain occurring after prolonged load during physical exercise such as longer runs, *etc.* A persistent and/or severe anterior knee pain was denied. The third patient showed a flexion deficit of 35° compared to the contralateral side. He was pain-free.

Functional outcome at the scoring

As depicted in Figure 4, the Kujala score improved significantly from a mean of 64 ± 16 points preoperatively to 94 ± 9 points postoperatively ($P < 0.0001$). The Lysholm score improved significantly from a mean of 63 ± 17 to 95 ± 6 points and the IKDC score from 58 ± 11 to 85 ± 12 points, $P < 0.0001$, respectively. There were no significant differences regarding age, sex, BMI and affected side of the knee ($P > 0.05$).

DISCUSSION

Different deepening trochleoplasty techniques are currently performed in a symptomatic dysplasia^[20]. Dejour *et al.*^[21] describes an osteotomy and bone removal at both femoral condyles to create a V-shaped trochlear groove. Both trochlear fragments are refixed with metallic staples. Goutallier *et al.*^[22,23] described the recession trochleoplasty, where the trochlear bump is settled into a deeper position after the removal of a wedge at the lateral femoral condyle. The Bereiter *et al.*^[24]'s technique describes a lateral parapatellar approach to raise an osteochondral flap from the anterior aspect of the femur. After remodeling the trochlear groove, the flap is seated and pressed into the deepened trochlea. A histological follow-up study reported no further cartilaginous damage or degeneration for this "thin flap technique"

[25]. This corresponds to our findings of an intact and stable cartilage in two patients who underwent an arthroscopic arthrolysis (Figure 2L). All authors who use the Bereiter trochleoplasty describe a lateral parapatellar approach^[26-32]. In contrast, the Dejours' Lyons' procedure uses a modified midvastus approach with a dissection of the vastus medialis muscle fibers extending around 4 cm into the muscle belly^[21]. As described above, we routinely use a shortened medial parapatellar approach (Figure 2A). This approach provides a good exposure of the medial edge of the patella to create our bony tunnel for the graft loop (Figure 2G). Furthermore, it provides a good access to the medial capsule for the preparation of a soft tissue tunnel between both layers going down to the femoral insertion of the MPFL graft (Figure 2I). An extensive skin mobilization or a further skin incision to expose the medial edge of the patella is not needed for the MPFL reconstruction. Moreover, we feel that this approach provides a much easier access to the trochlear groove (Figure 2B). After the closure of both capsular layers, the tendon of the vastus medialis obliquus muscle can be tightened medially to the patella if needed. Taken together, this medial parapatellar approach might have several advantages.

Even if MPFL reconstruction is a proven method, an optimized tensioning of the graft should not be taken for granted. Regarding the literature, an excessive graft tension is one of the most common complications during MPFL reconstruction^[10,33]. This might lead to stiffness, pain, cartilage degradation, arthrosis and patella fractures^[10,33,34]. Thus, techniques which provide an adequate tensioning might help to achieve a sufficient stabilization with a minimized risk of an overtightened graft. Regarding the literature, a variety of techniques are described to get an appropriate amount of graft tension. Thauinat and Erasmus^[35] recommend a full extension and the use of a hook to pull the patella proximal to avoid an overtensioning. Feller *et al.*^[36] tension the graft with one quadrant of lateral translation in knee extension, then the knee is flexed to 20° for permanent fixation. Other authors prefer techniques with the use of 30° of knee flexion for graft fixation^[8,26,28] and some prefer a position between 60° and 90° of flexion because this might allow a more precise settling of the patella within the deeper, more inferior parts of the trochlear groove^[37]. Therefore, finding the most appropriate technique for graft fixation seems quite confusing. Furthermore, there is currently no consensus on the question of how many degrees the knee should be flexed when the graft is secured to its insertion points. Therefore, our technique to simply test and balance the tension during knee motion before permanent fixation might be a feasible and satisfying solution. Considering that 30° of knee flexion seems to be recommended most frequently in the literature^[8,26,28], we begin with a temporary graft fixation at 30° of flexion. Only after testing and balancing the tension is the graft permanently fastened^[14]. Because our technique uses nearly the entire length of the gracilis tendon with a loop through the patella, this construct appears less rigid

(Figure 1C). This might additionally reduce the risk of an overloading. Besides the advantage to reach a balanced and less rigid construct, the avoidance of hardware such as screws and/or anchors might be another benefit of our technique. This does not only save money, it also reduces possible implant specific complications such as an implant loosening and/or discomfort with the anchoring material^[6,16,28].

An important finding of the present study is that the combination of a modified Bereiter trochleoplasty and our hardware-free, balanced MPFL reconstruction technique, provides a sufficient and reliable stabilization of the patellofemoral joint. Thus, the apprehension tests were negative in all cases and no subluxations or recurrent dislocations were reported at the last follow-up. This is in accordance to a recent systematic review, where the overall rate of recurrent dislocations after different trochleoplasty techniques was 2%^[20]. The highest rate for recurrent dislocations was reported for the recession type trochleoplasty (10.5%), followed by the Dejour (3.2%) and Bereiter (0.8%) techniques^[20]. Interestingly, all studies on the combination of a Bereiter trochleoplasty and a MPFL reconstruction describe a 0% rate for recurrent dislocations^[26,28,38]. Regarding a residual apprehensiveness, studies on a Bereiter or Dejour trochleoplasty without a routinely added MPFL reconstruction might be of interest. These studies reported a residual apprehensiveness in 16%^[39], 20%^[31], 21%^[32] and 47%^[40] of cases. In contrast, in studies where a MPFL reconstruction was routinely performed in combination with a trochleoplasty, the apprehension sign was eliminated in all patients^[26,28,38]. These data imply that a MPFL reconstruction seems to be a useful addition to a trochleoplasty. Regarding the clinical outcome, studies on trochleoplasties which were routinely combined with a MPFL reconstruction demonstrate similar postoperative Kujala scores of 96^[26], 88^[28] and 95^[38] points, respectively. In comparison, studies on trochleoplasties which were not routinely combined with a MPFL reconstruction showed Kujala scores of 76^[31], 80^[32], 75^[40] and 71 points^[27], respectively. At this point, we would like to mention that we did not consider all studies with different types of trochleoplasty techniques, soft tissue procedures, additional procedures, *etc.* Rather, we aim to highlight possible tendencies. Thus, differences that are apparent at first sight might not be substantial or at least statistically significant. However, the superior results of a combined surgery in terms of a persisting apprehensiveness, recurrent dislocations, as well as in terms of the clinical outcome scoring can also be explained by the pathophysiology of the patient cohort. Thus, in more than 90% of cases, a dislocation of the patella results in a traumatic disruption and insufficiency of the MPFL^[1,11,12]. Moreover, a trochleoplasty changes the articulation of the patella to a more medial and dorsal biomechanical position (Figure 1A). These changes, measuring at least 5 mm in each direction, have been nicely shown in this series with pre- and postoperative CT scans after a Bereiter trochleoplasty^[13]. This might lead

to a reduced distance between the femoral and patellar insertions of the medial soft tissue restraints (Figure 1B). Thus, a preexisting insufficiency of the MPFL might be aggravated by the biomechanical changes following a trochleoplasty. As a consequence, a balanced alignment of the medial soft tissue restraints, such as an adequately tensioned MPFL reconstruction (Figure 1C), seems very reasonable during a trochleoplasty.

Another additional surgery, which is not so rarely combined with a trochleoplasty, is a tibial tuberosity transfer to reduce an elevated TT-TG as a further instability factor^[27,40-42]. During a trochleoplasty we normally prefer to deepen and set the created trochlear groove more laterally to tendentially correct an asymmetry of the trochlear facets (Figure 1A and B). This possibility to address an elevated TT-TG distance has already been described by several authors for both the Dejour and the Bereiter technique^[29,41,42]. Fucentese *et al.*^[13] demonstrated a case series with pre- and postoperative CT scans showing a successful lateralized trochlear groove after trochleoplasty. This possibility might influence the decision to perform an additional medialization osteotomy of the tuberosity. Considering this, we perform this additional procedure only in cases with an excessive TT-TG distance.

Showing an overall rate of 6.7%, a significant motion deficit is the second most common complication in trochleoplasty procedures^[20]. In our series, at the last follow-up, three patients (9.1%) showed a slight flexion deficit compared to the contralateral side. Two had a deficit of 20° and one patient had a deficit of 30°. In regard to these data, we reconsidered our rehabilitation protocol, which limited the flexion to 30° for the first two weeks, to 60° in the third and fourth weeks and to 90° in the fifth and sixth weeks. The rationale behind these limitations was to avoid a shearing of the osteochondral flap. Reviewing the literature, we had to recognize that the majority of authors are much more progressive. Thus, most of them use protocols without a postoperative flexion limitation^[26,27,30,31,38,40]. Other authors limit the flexion to 100°^[21], 90°^[28] or 60°^[23,29]. Interestingly, some authors recommend a 20° or 30° block to full extension^[30,31,38]. The idea of this protocol is to centralize the patella within the remodeled groove and to facilitate a healing of the trochlear osteotomy^[30]. However, considering our results we do not use or recommend the protocol previously described in the methods section any more. Currently, we do not limit the flexion after trochleoplasty. Moreover, the two patients who needed an early arthroscopic arthrolysis as a result of a failed physiotherapy emphasize the importance of motion exercises. Therefore, physiotherapy including a continuous passive motion (CPM) is performed immediately after surgery. Moreover, each patient receives a knee CPM machine as a loan for at least four weeks after surgery. Regarding the return to sports rates, we had two patients who did not return to full sporting activities. One of these was in the group which was engaged in sports before surgery, the other

patient did not participate in regular physical activity before surgery. Neither patient had complaints or an ongoing instability. However, even if they had already mastered situations with experienced luxations in the past, both reported an ongoing anxiety for typical stress situations. Both reported that this behavior was psychologically caused and not instability- and/or pain-related. Thus, despite a sufficient stabilization, an unlearning process of such an acquired avoidance behavior should not be taken for granted. This study result is important to us because it highlights the need for a prolonged postoperative physiotherapy according to the individual need of the patient. This might minimize the reported avoidance behaviour.

The major limitations of this study are the short mean follow-up of 29 mo and the lack of a direct comparison to other surgical techniques. A larger clinical outcome study is needed to ensure the efficacy of our method. Therefore, the outcome results should be regarded cautiously. Being able to present only short-term results, data on the prevention of a secondary arthritis are lacking. However, the study presented here was a necessary first step in exploring our modified method, which seems to provide reasonable advantages. The preliminary clinical results demonstrate a good efficiency in relieving the symptoms and improving the function of the affected knee.

Our modified technique shows encouraging results in terms of a sufficient stabilization of the patellofemoral joint, a low incidence of complications and a good outcome in terms of pain, cosmetic results and return to sports. In accordance to these results, a significant improvement in all evaluated scores was achieved and a high patient satisfaction was demonstrated. These findings correlate with the literature on similar techniques, which combine a trochleoplasty with an alignment of the medial soft tissue restraints. Nevertheless, the good outcome in our case series and in previous studies should not be taken for granted. The need for an individual postoperative physio- and sports therapy is also outlined in this study.

ARTICLE HIGHLIGHTS

Research background

Trochlear dysplasia is an important and frequent instability factor in patients with recurrent patella dislocations. These patients typically have an insufficiency of the medial patellofemoral ligament (MPFL), which is an additional instability factor. During a trochleoplasty, the articulation of the patella is changed to a more dorsomedial position, which might worsen the insufficiency of the medial soft tissue restraints. All these patho-biomechanical conditions are relevant for a symptomatic instability and should therefore be addressed during surgery. Despite its relevance, studies on combined concepts to address all pathological conditions are rare.

Research motivation

Regardless of whether a MPFL reconstruction is performed as an isolated surgery or as in combination with a trochleoplasty, an adequate tensioning of the graft is a key problem during these surgical procedures. Thus, an overtensioning might lead to stiffness, pain, cartilage degradation, arthrosis and patella fractures, whereas an undertensioning leads to persistent instability

complaints. Authors' technique, which provides an adequate graft tensioning, appears to be helpful to solve these problems. Thus, the study presented here was a necessary first step in exploring authors' method, which seems to provide reasonable advantages.

Research objectives

To realize a combination of authors' technique of a balanced MPFL reconstruction to the bony alignment procedure, authors modified both, the technique and especially the approach of the Bereiter trochleoplasty as well as authors' recently published technique of a balanced MPFL reconstruction. To evaluate authors' method, 33 knees with recurrent patellar dislocations and a trochlear dysplasia were evaluated after a mean follow-up of 29 mo.

Research methods

To assess the outcome of authors' modified technique, the Kujala, IKDC and Lysholm scoring were evaluated. Moreover, patients' satisfaction with the general outcome, the return to sports, the cosmetic outcome, the pre- and postoperative pain and a potential avoidance behaviour were assessed.

Research results

The preliminary clinical results of this technique demonstrate a good efficiency in relieving the symptoms and improving the function of the affected knee. There were no signs of a persistent instability. A significant pain reduction and a significant improvement at the Kujala, Lysholm and IKDC scoring is demonstrated. 94% of the patients were very satisfied with the clinical and cosmetic outcome of the surgery. 92% of the patients who were engaged in regular physical activity before surgery returned to full sporting activities. In regard to three patients showing a slight flexion deficit compared to the contralateral side at the last follow-up, authors changed the postoperative treatment protocol. Thus, authors do not limit the flexion any more post-operatively and authors try to ensure intensive motion exercises. One patient did not return to sports and another patient, who was not active in sports before surgery, still did not participate in regular physical activity after surgery. Both reported that this was related to a persistent avoidance behavior and not instability- and/or pain-related. This specific problem, which reduced authors' return to sports rate, might highlight the need for an intensive individual sports therapy.

Research conclusions

In patients with a symptomatic patellar instability, both a trochlear dysplasia and an insufficiency of the MPFL should be addressed during surgery. Regarding the literature, an inadequate graft tensioning is one of the most important reasons for complications during MPFL reconstruction such as stiffness, pain, cartilage degradation, arthrosis, patella fractures, *etc.* Therefore, authors' balanced MPFL reconstruction technique might optimize the alignment of the medial soft tissue restraints with a correspondingly low incidence of complications. The authors technique is a practicable solution to achieve a feasible correction of the bony dysplasia combined with a balanced alignment of the medial soft tissue restraints. Thus, authors' technique shows a reliable stabilization of the patellofemoral joint and a low incidence of complications. The results in common clinical outcome scorings as well as in terms of pain, return to sports and patient satisfaction are encouraging. To realize a simple combination of authors' recently published techniques of a balanced MPFL reconstruction with sulcus deepening trochleoplasty, authors modified both techniques. Especially the described approach to the medial margin of the patella, the medial retinaculum and to the trochlear groove appears very feasible. On the one hand, the study presented here was a necessary first step in exploring authors' modified method, which seems to provide reasonable advantages. On the other hand, this study gives an original insight to the patients' outcome. Besides the assessment of the commonly used scorings and the incidence of complications, this investigation gives a deeper insight to understand the outcome in terms of pain, cosmetic results, patient satisfaction and the return to sports. This might give us a better understanding of the patients' expectations and the role of physio- as well as an individual sports therapy. Because both trochlear dysplasia and an insufficiency of the medial soft tissue restraints are relevant for a symptomatic patellar instability, a method which addresses both patho-biomechanical conditions might be a good solution. A balanced medial soft tissue reconstruction might optimize the procedure. To combine authors' technique of a balanced MPFL reconstruction

to the bony alignment procedure, authors modified both the technique and especially the approach of the Bereiter trochleoplasty as well as authors' MPFL reconstruction technique. Authors' balanced MPFL reconstruction technique might help to get an adequate alignment of the medial soft tissue restraints. Besides the assessment of the commonly used outcome scorings, this study gives a better understanding of the outcome in terms of pain, cosmetic results, patient satisfaction and the return to sports. A new phenomenon author noticed in two patients was a persistent avoidance behaviour for typical stress situations during sports. Even if both patients reported that this was not instability- and/or pain-related, this behaviour interfered with their return to sports. Even if this phenomenon was seldom, these findings might highlight the need for an intensive physiotherapy as well as the need of an individual sports therapy. The modified technique shows encouraging results in terms of a sufficient stabilization of the patellofemoral joint, a low incidence of complications and a good outcome in terms of pain, cosmetic results and return to sports. The preliminary clinical results of authors' technique demonstrate a good efficiency in relieving the symptoms and improving the function of the affected knee. Therefore, authors will continue this method in the future when indicated. In three patients, authors noticed a slight flexion deficit at the last follow-up. Considering this phenomenon, authors changed the postoperative treatment schedule to a protocol without any postoperative limitations of flexion. Furthermore, authors will try to ensure intensive postoperative motion exercises by using continuous passive motion devices, *etc.*

Research perspectives

The comparatively good outcome presented in authors' study should not be taken for granted. The need for an individual postoperative physio- and sports therapy is also outlined in this study. A larger clinical outcome study with longer follow-up periods is needed to investigate long-term outcome results of authors' methods. This will assess the durability of the clinical results. Furthermore, data on the prevention of a secondary arthritis are of interest in this patient group, which normally shows high rates of osteoarthritis development. Besides further improvements of the surgical technique, the questions of how to optimize and individualize the postoperative physio- and sports therapy will be of interest. A larger long-term clinical outcome study on the clinical results and the prevention of secondary arthritis will be a useful method for the future research.

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Antibiotic bone cement's effect on infection rates in primary and revision total knee arthroplasties

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Abstract

AIM

To compare infection rates in primary and revision total knee arthroplasty (TKA) procedures using antibiotic impregnated bone cement (AIBC) to those rates in procedures not using AIBC.

METHODS

A systematic review and meta-analysis was conducted in search for randomized controlled trials/studies (RCTs) pertaining to the field of antibiotic AIBC *vs* non-AIBC groups in both primary and revision TKA procedures. The primary literature search performed was to identify all RCTs that assessed AIBC in primary and revision TKA procedures. This search was done strictly through the PubMed database using the article "filters" setting that identified and separated all RCTs from the overall search. The original search was "Primary/revision total knee arthroplasty using AIBC". Other key terms and phrases were included in the search as well. Eligible articles that were used in the "results" of this review met the following criteria: (1) Involved primary or revision TKA procedures (for any reason); (2) included TKA outcome infection rate information; (3) analyzed an AIBC group *vs* a non-AIBC control group; (4) were found through the RCT filter or hand search in PubMed; and (5) published 1985-2017. Exclusion criteria was as follows: (1) Patients that were not undergoing primary or revision TKA procedures; (2) articles that did not separate total hip arthroplasty (THA) *vs* TKA results if both hip and knee revisions were evaluated; (3) papers that did not follow up on clinical outcomes of the procedure; (4) extrapolation of data was not possible given published results; (5) knee revisions not done on human patients; (6) studies that were strictly done on THAs; (7) articles that were not found through the RCT filter or through hand search in PubMed; (8) articles that did not evaluate AIBC used in a prosthesis or a spacer during revision; (9) articles that did not compare an AIBC group *vs* a non-AIBC control group; and (10) articles that were published before 1985.

RESULTS

In total, 11 articles were deemed eligible for this analysis. Nine of the 11 studies dealt with primary TKA procedures comparing AIBC to non-AIBC treatment. The other two studies dealt with revision TKA procedures that compared such groups. From these papers, 4092 TKA procedures were found. 3903 of these were primary TKAs, while 189 were revision TKAs. Of the 3903 primary TKAs, 1979 of these used some form of AIBC while 1924 were part of a non-AIBC control group. Of the 189 revision TKAs, 96 of these used some form of AIBC while 93 were part of a non-AIBC control group. Average follow-up times of 47.2 mo and 62.5 mo were found in primary and revision groups respectively. A two-tailed Fisher's exact test was done to check if infection rates differed significantly between the groups. In the primary TKA group, a statistically significant difference between AIBC and non-AIBC groups was not found (AIBC infection rate = 23/1979, non-AIBC infection rate = 35/1924, $P = 0.1132$). In the revision TKA group, a statistically significant difference between the groups was found (AIBC infection rate = 0/96, non-AIBC infection rate = 7/93, $P = 0.0062$). No statistically significant differences existed in Knee Society Scores, Hospital for Special Surgery Scores, or Loosening Rates.

CONCLUSION

AIBC did not have a significant effect on primary TKA infection rates. AIBC did have a significant effect on revision TKA infection rates.

Key words: Total knee arthroplasty; Knee revision; Antibiotic impregnated/laden/infused bone cement; Bone cement; Knee arthroplasty; Primary/revision total knee arthroplasties infection

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Core tip: A systematic review and meta-analysis of randomized controlled trials/studies on primary and revision total knee arthroplasties (TKA) using antibiotic impregnated bone cement (AIBC). AIBC was found to lower infection rates in revision TKA procedures, but not in primary TKA procedures.

Kleppel D, Stirton J, Liu J, Ebraheim NA. Antibiotic bone cement's effect on infection rates in primary and revision total knee arthroplasties. *World J Orthop* 2017; 8(12): 946-955 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i12/946.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i12.946>

INTRODUCTION

The use of antibiotic impregnated bone cement (AIBC) was first described by Buchholz and Englebrecht^[1] in 1970. Throughout the years since, AIBC's mechanical properties and use in a clinical setting have been expounded upon greatly. In as early as 1981, Buchholz

et al^[2] reported up to a 77% success rate using AIBC, many times without systemic antibiotics, in primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures. More recently, antibiotic infused spacers have also been described in two stage joint knee revision procedures to reduce the rate of infection during and after revision.

Since AIBC was first introduced into the field of orthopedics there has been controversy over its safety and how antibiotics affect the bone cement. In addition to the problem of organism specific antibiotic resistance, mechanical loosening may also result from antibiotic combination. One study^[3] found that in low doses (≤ 2 g of antibiotic powder per 40 g cement) AIBC does not lead to an increased rate of mechanical loosening. However, other studies^[3-5] have indicated that in much higher doses (> 4.5 g of antibiotic powder per 40 g cement) or with usage of liquefied antibiotics in bone cement, mechanical problems such as loosening in the prosthesis can occur more frequently. Adalberth *et al*^[6] performed a study demonstrating that antibiotics added to bone cements had similar fixation, extent of radiolucent lines, and clinical outcomes as compared to plain bone cement (PBC). Moreover, in a recent systematic review and meta-analysis published in 2013 inspecting eight randomized controlled trials/studies (RCTs) comparing AIBC and non-AIBC primary TKA and THA procedures, there was shown to be no difference in rate of aseptic loosening when antibiotics were added to the cement as compared to the control^[7].

Much of the information published and reviewed on antibiotic and antiseptic usage thus far has focused on primary total joint arthroplasty (TJA) procedures. Nevertheless, promise has been shown using AIBC in revision procedures. Clinically, AIBC is widely accepted to cure surgical site infections during revision procedures^[8,9]. Peersman *et al*^[10] noted that rates of infection following revisions are approximately 2-3 times higher than rates following primary procedures. In 2015, Bini *et al*^[11] published that AIBC used in revision TKA procedures nearly halved the risk of re-revision suggesting AIBC's potentially crucial role in infection prevention during revision procedures. Furthermore, the planet is experiencing a large increase in elderly populations, which will most likely increase the need for TKA procedures in the near future. Kurtz *et al*^[12] demonstrated that with this increase in age, there will also be an increase in deep infection rates following primary TKA. These rates are expected to rise up to 6.8% within the next 15 years. These statistics portray how important AIBC will be in the future of both primary and revision TKA procedures.

In recent years, the use of prophylactic antibiotics and antiseptics in both primary and revision TJA have been explored through systematic reviews found on PubMed^[7,13-15]. Although interest in the area of antibiotics and antiseptics on infection rates in both primary and revision TKA and THA procedures has increased, there has been a lack of high quality information published in systematic reviews to draw relevant conclusions

from^[13].

Not only has there been a shortage of studies that have explored this field, but many of the studies done have shown variable and inconclusive data. In a more detailed look at these studies, there was one systematic review that analyzed over 6300 primary TKAs and THAs that showed no statistically significant differences in the rates of deep infection or superficial infection between the group that used AIBC and the group that used PBC^[7]. Similar results were found in two other systematic reviews published in 2015 and 2016 as well^[14,15]. However, these studies did not include the most up-to-date articles on primary and revision TKA procedures. These reviews were not limited to RCTs and therefore did not consider the most credible sources for data collection in the field. Past reviews have not included information on TKA revisions, which is an overly unexplored field that will be considered in this systematic review.

The inconsistencies in search criteria and evaluations reported in most of these studies reveal the importance of a systematic review and meta-analysis on this topic. As shown from the search conducted on this topic in PubMed, there has not been an up-to-date systematic review evaluating both primary and revision TKA procedures with AIBC vs non-AIBC control groups strictly in randomized controlled trials/studies in the current literature. As agreed upon in multiple studies^[16,17], periprosthetic joint infections are some of the most devastating complications of TKA procedures and the importance of their prevention is of great value to the field of orthopedics. It is hypothesized that AIBC will result in lower infection rates amongst primary and revision TKA procedures. Therefore, the purpose of this review and analysis was to combine the most up-to-date and relevant data from RCTs focusing on primary and revision TKA procedures using AIBC vs not using AIBC. This study aimed to primarily analyze and compare infection rates in primary and revision AIBC procedures to those rates in procedures not using AIBC. A secondary aim was to examine other clinically significant differences between groups using and not using AIBC during primary and revision TKAs.

MATERIALS AND METHODS

Study design

A systematic review and meta-analysis was conducted in search for randomized controlled trials/studies (RCTs) pertaining to the field of AIBC vs non-AIBC groups in both primary and revision total knee arthroplasty procedures.

Literature search

The primary literature search performed was to identify all randomized controlled trials/studies that assessed antibiotic impregnated bone cement in primary and revision TKA procedures. This search was done strictly through the PubMed database using the article "filters" setting that identified and separated all RCTs from the

overall search. The original search was "Primary/revision total knee arthroplasty using AIBC".

Other key terms and phrases in the search included "primary TKA infection", "primary knee infection", "knee revision infection", "knee revision failure", "revision TKA infection", "antibiotic impregnated/ laden/ infused bone cement", "2 stage knee revision", and "1 stage knee revision". In addition, search terms such as "gentamicin", "tobramycin", "cefuroxime", "cefazolin", and "vancomycin" were used in conjunction with the phrases above. After the primary literature search was conducted, articles that met relevant criteria were further scanned in their titles and abstracts for inclusion. Once articles' titles and abstracts were scanned, the articles were hand-searched for other sources that could be of relevance to the topic. PubMed articles that did not initially show full text access were searched in Ovid, MEDLINE database as well as in the Journal of Bone and Joint Surgery (American volume), and Clinical Orthopedics and Related Research. During the screening process all titles and abstracts were inspected for the key search terms mentioned. This search was conducted up until July 2017.

Inclusion and exclusion criteria

Eligible articles that were used in the "results" of this review met the following criteria: (1) Involved primary or revision TKA procedures (for any reason); (2) included TKA outcome infection rate information; (3) analyzed an AIBC group vs a non-AIBC control group (4) were found through the RCT filter or hand search in PubMed; and (5) published 1985-2017.

Exclusion criteria was as follows: (1) Patients that were not undergoing primary or revision TKA procedures; (2) articles that did not separate THA vs TKA results if both hip and knee revisions were evaluated; (3) papers that did not follow up on clinical outcomes of the procedure; (4) extrapolation of data was not possible given published results; (5) knee revisions not done on human patients; (6) studies that were strictly done on THAs; (7) articles that were not found through the RCT filter or through hand search in PubMed; (8) articles that did not evaluate AIBC used in a prosthesis or a spacer during revision; (9) articles that did not compare an AIBC group vs a non-AIBC control group; and (10) articles that were published before 1985.

Exclusion criteria were limited to studies evaluated in the results of this paper. Multiple studies were used as references in this paper that did not meet the inclusion criteria or that did meet the exclusion criteria. However, these articles were used only in the introduction and discussion sections of this review to bring other relevant data on this topic into light. It is important to note that data from these articles may still be relevant to the topic, but do not meet inclusion criteria for analysis in this paper. Inclusion criteria were selected in order to set a standard for comparison amongst the RCTs discovered upon the systematic search. If study information was unclear, authors were contacted requesting the relevant

Table 1 Data from primary total knee arthroplasty randomized controlled trials

Paper	AIBC group number of TKAs infected	Infection rate of AIBC group	Non-AIBC number of TKAs infected	Infection rate of non-AIBC group	Reason for procedure	Follow-up (mo)
Chiu <i>et al</i> ^[18] , 2001	0/41	0	5/37	0.13514	Osteoarthritis	50
Vrabec <i>et al</i> ^[23] , 2016	0/10	0	0/5	0	N/A	12
Chiu <i>et al</i> ^[19] , 2002	0/178	0	5/162	0.03086	N/A	49
Lizaur-Utrilla <i>et al</i> ^[24] , 2014	1/48	0.020833	0/45	0	Non-inflammatory arthritis	76.8
Nilsson <i>et al</i> ^[25] , 1999	0/28	0	2/29	0.068966	Osteoarthritis and Rheumatoid arthritis	60
Bercovy <i>et al</i> ^[26] , 2012	2/164	0.012195	1/157	0.006369	N/A	91.2
Hinarejos <i>et al</i> ^[20] , 2013	20/1483	0.013486	20/1465	0.013652	N/A	38
McQueen <i>et al</i> ^[22] , 1987	0/13	0	1/13	0.076923	Osteoarthritis and rheumatoid arthritis	24
McQueen <i>et al</i> ^[21] , 1990	0/14	0	1/11	0.090909	Osteoarthritis	24
	Total: 23/1979 (1.16%)		Total: 35/1924 (1.82%)			Average: 47.2

AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty.

information to check eligibility of the article.

Outcome measures

The chief outcome evaluated in this analysis was infection rate following primary or revision TKA. Other factors were assessed and quantified including follow-up times, record of previous infection, whether or not systemic antibiotics were used to supplement AIBC, and publication year. Variables reported in more than one paper that were noted in this analysis included whether or not there was a statistically significant difference in deep infection rates, loosening rates, Knee Society Scores (KSS), and Hospital for Special Surgery Scores (HSS).

Article quality

Only randomized controlled trials were assessed. Articles were published in reputable journals including the Journal of Bone and Joint Surgery, Journal of Arthroplasty, Journal of Clinical Orthopaedics and Related Research, Journal of International Orthopaedics, and the Journal of Knee Surgery, Sports Traumatology, and Arthroscopy. All articles were deemed of high quality based on these factors.

Literature search results

After searching all key terms and phrases, a total of 176 RCTs were shown on the PubMed database. After initial screening of titles and abstracts, 148 articles were eliminated because they were deemed irrelevant to this study for various reasons (Figure 1). The 28 remaining articles were full-text hand searched in order to identify if they were appropriate for this study. Of the 28 articles, six were found to fit inclusion criteria. Five more articles were also found to fit inclusion criteria through the full-text hand search of the 28 articles. Therefore, 11 articles in total were found in the initial screening and secondary hand search. Further details of this search and screening procedure using inclusion and exclusion criteria were found in a flow chart (Figure 1). Further information from the articles including first author, year published, number of TKAs studied, infection rates, follow-up times, and reason for the TKA

procedures was noted in Tables 1 and 2. RCTs' individual comparisons were shown in Tables 3 and 4. Information on loosening rates, statistically significant differences in deep infection found in individual articles, and KSS and HSS knee scores were described in Table 5.

Statistical analysis

From the studies searched, important statistics were extracted and compiled into Excel documents for analysis. Averages and totals were calculated for relevant data sets as mentioned in the "outcome measures" section above. A two-tailed Fisher's exact test was used to calculate statistically significant differences in infection rates between groups. Differences in loosening rates were calculated using a two-tailed Fisher's exact test as well. Differences in KSS/HSS knee scores were calculated using a two-tailed, type-3 *t*-test (95%CI).

RESULTS

General study characteristics

In total, 11 articles were deemed eligible for this analysis. Nine of the 11 studies dealt with primary TKA procedures comparing AIBC to non-AIBC treatment^[18-26]. The other two studies dealt with revision TKA procedures that compared such groups^[17,27]. From these papers, 4092 TKA procedures were found. 3903 of these were primary TKAs, while 189 were revision TKAs. Of the 3903 primary TKAs, 1979 of these used some form of AIBC while 1924 were part of a non-AIBC control group. Of the 189 revision TKAs, 96 of these used some form of AIBC while 93 were part of a non-AIBC control group. Average follow-up times of 47.2 mo and 62.5 mo were found in primary and revision groups respectively. In six of the studies, the TKA procedures were conducted after a diagnosis of some form of arthritis^[17,18,21,22,24,25]. In one study^[27], the revision TKAs were done because of previous infection. Four of the studies did not report such data on the patient population used^[19,20,23,26]. In all of the studies, systemic antibiotics were used in conjunction with AIBC to facilitate recovery and prevent reinfection.

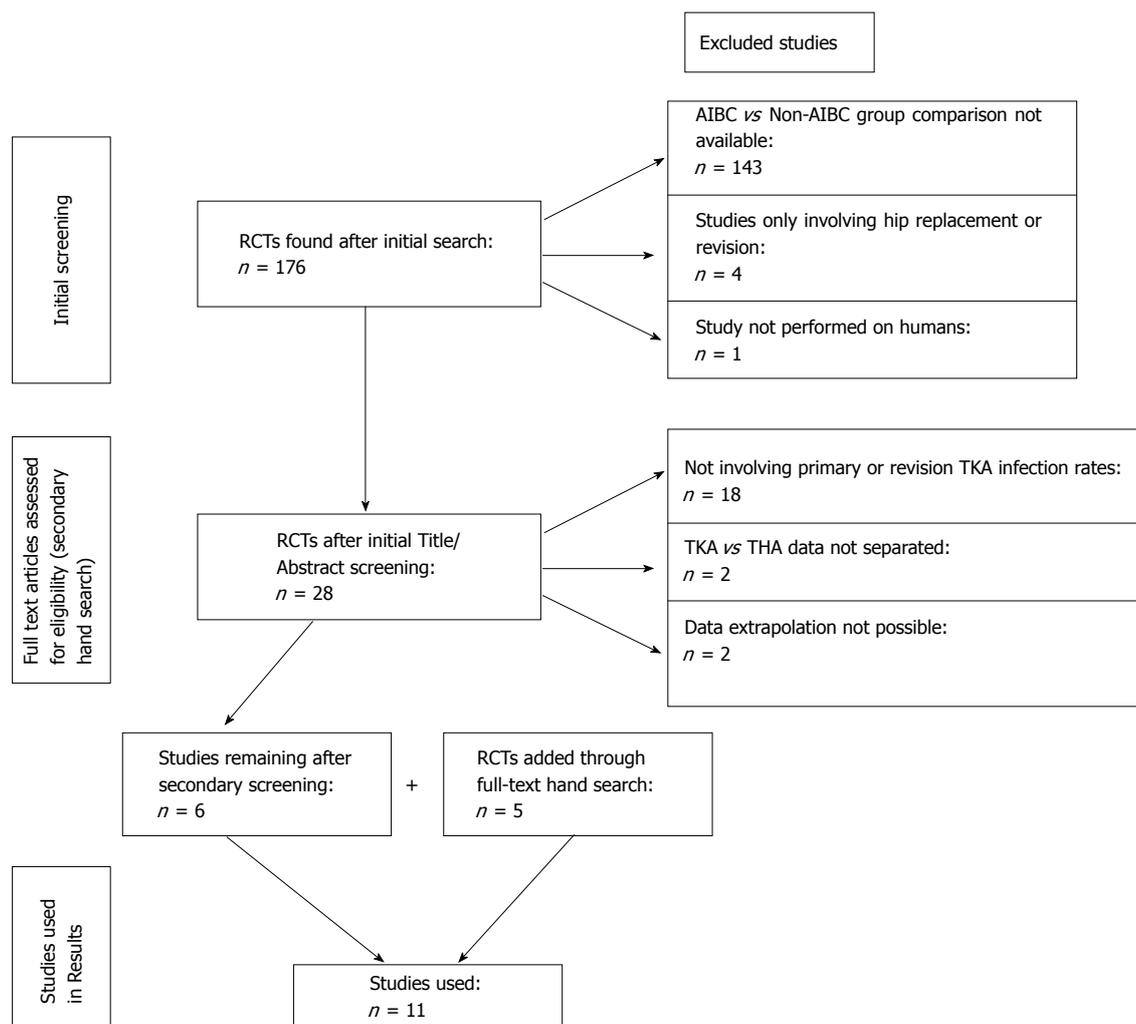


Figure 1 Flow diagram for studies included in result analysis. This flow chart describes the articles that were included and excluded in the analysis based on the initial screening and further full-text assessment. Articles that were assessed and screened are shown to the left. Articles that were excluded are shown to the right. Right pointing arrows lead to excluded articles in different parts of the screening and evaluation processes. Downward pointing arrows show points from one set of screenings to the next, displaying how many articles were left after exclusion criteria had been considered. Reasons for exclusion were also shown in the right column. AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty; THA: Total hip arthroplasty; RCTs: Randomized controlled trials /studies.

Table 2 Data from revision TKA RCTs

Paper	AIBC group number of TKAs infected	Infection rate of AIBC group	Non-AIBC number of TKAs infected	Infection rate of non-AIBC group	Reason for procedure	Follow-up (mo)
Nelson <i>et al</i> ^[27] , 1993	0/3	0	0/3	0	Previous infection	36
Chiu <i>et al</i> ^[17] , 2009	0/93	0	7/90	7.78%	Osteoarthritis	89
	Total: 0/96 (0.00%)		Total: 7/93 (7.53%)			Average: 62.5

RCTs: Randomized controlled trials/studies; AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty.

Also, eight of the 11 studies had an infection rate of 0.0% when AIBC was used, even with an average follow up of over 47 mo amongst those studies. However, only three of the 11 studies found a 0.0% infection rate when AIBC was not used. These differences were not large enough in the primary TKA group to indicate statistical significance, but did indicate AIBCs crucial role in preventing infection post-revision. Overall, AIBC groups were compared to PBC groups, systemic antibiotic groups, and hydroxyapatite coated prostheses groups. All studies used in the results/analysis were published

between 1987-2016 with an average publication year of 2003.

Infection rates

A two-tailed Fisher’s exact test was done to check if infection rates differed significantly between the groups. Deep infection rates were analyzed in this review because superficial infection rates were not reported to be statistically significant in any of the articles. In the primary TKA group, a statistically significant difference between AIBC and non-AIBC groups’ infection rates

Table 3 Comparisons made between groups in primary TKA RCTs

Paper	Comparison
Chiu <i>et al</i> ^[18] , 2001	Cefuroxime-impregnated cement <i>vs</i> PBC
Vrabec <i>et al</i> ^[23] , 2016	Intravenous tobramycin <i>vs</i> AIBC with tobramycin
Chiu <i>et al</i> ^[19] , 2002	Cefuroxime-impregnated cement <i>vs</i> PBC
Lizaur-Utrilla <i>et al</i> ^[24] , 2014	Tibial fixation with either a cemented (Palacos with Gentamicin) <i>vs</i> cementless with screw augmentation (systemic antibiotics only)
Nilsson <i>et al</i> ^[25] , 1999	Vacuum mixed bone cement (Palacos-Gentamicin) <i>vs</i> hydroxyapatite-coated prostheses
Bercovy <i>et al</i> ^[26] , 2012	Hydroxyapatite-coated prostheses <i>vs</i> cemented (Refobacin) tibial components
Hinarejos <i>et al</i> ^[20] , 2013	Simplex P cement loaded with 0.5 g of erythromycin and three million units of colistin in 40 g of cement (Stryker) <i>vs</i> simplex cement without antibiotic
McQueen <i>et al</i> ^[22] , 1987	Cefuroxime in bone cement (1.5 g of cefuroxime powder was added to 40 g of CMW cement powder) <i>vs</i> systemic (1.5 g) cefuroxime
McQueen <i>et al</i> ^[21] , 1990	Cefuroxime in bone cement (1.5 g of cefuroxime powder was added to 40 g of CMW cement powder) <i>vs</i> systemic (1.5 g) cefuroxime

CMW: A kind of bone cement made by CMW laboratories of DePuy Synthes Companies; RCTs: Randomized controlled trials/studies; PBC: Plain bone cement; AIBC: Antibiotic impregnated bone cement.

Table 4 Comparisons made between groups in revision TKA RCTs

Paper	Comparison
Nelson <i>et al</i> ^[27] , 1993	Gentamicin-PMMA beads <i>vs</i> conventional systemic antibiotics
Chiu <i>et al</i> ^[17] , 2009	AIBC (vancomycin-impregnated) <i>vs</i> PBC in TKA Revision

RCTs: Randomized controlled trials/studies; PMMA: Polymethyl methacrylate; AIBC: Antibiotic impregnated bone cement; TKA: Total knee arthroplasty; PBC: Plain bone cement.

was not found (AIBC infection rate = 23/1979, non-AIBC infection rate = 35/1924, $P = 0.1132$). In the revision TKA group, a statistically significant difference between the groups' infection rates was found (AIBC infection rate = 0/96, non-AIBC infection rate = 7/93, $P = 0.0062$). AIBC used directly in the revision prosthesis benefitted patients and helped prevent infection. Further information for individual articles having to do with the items mentioned in this paragraph was noted in Tables 1 and 2.

Other quantifiable variables reported

Other variables reported in more than one study were loosening rates^[17,18,24,26,29], postoperative KSS scores^[24-26], and postoperative HSS scores^[17-19]. Loosening rates did not significantly differ between groups ($P = 1.00$). Postoperative HSS and KSS scores also did not differ significantly between groups ($P = 0.1208$ and $P = 0.38496$ respectively). Tables 1 and 2 reported numbers of TKA procedures and rates of infection for each paper. Table 5 supplied additional information on loosening rates and KSS/HSS scores.

In all studies that reported superficial infection rates, there were no statistically significant differences between AIBC and non-AIBC groups. Superficial infection rates were almost always higher than deep infection rates in both groups. Three papers reported having statistical significance when comparing deep

infection rates amongst groups^[17-19]. More than half of the studies reported deep infections to occur in an early to moderate time period after the operation, while none of the studies reported chronic deep infection to be the most common type of infection after procedures.

Significant results from individual papers

Vrabec *et al*^[23] described that local concentrations of antibiotics from AIBC not only had suprathreshold concentrations in the joint fluid, but also achieved therapeutic concentrations locally within the first 48 h postoperatively. Systemic antibiotics, on the other hand, only achieved subtherapeutic levels locally, not in the joint fluid.

In Lizaur-Utrilla *et al*^[24], statistically significant differences were found in clinical outcomes such as knee score ($P = 0.022$), range of motion ($P = 0.042$), and WOMAC ($P = 0.036$) between groups, all favoring cementless components. Lizaur-Utrilla *et al*^[24] also reported that cementless TKA was the better option for younger patients with osteoarthritis even though revision rates and survival rates were similar between cemented and cementless groups.

Results from three different studies found *Staphylococcus aureus*, *Staphylococcus epidermidis*, coagulase-negative *Staphylococcus*, and group-B *Streptococcus* to be the most common organisms found in TKA deep infection cultures^[17,18,21]. Also, Chiu *et al*^[17] reported that those organisms identified through culture in revision infections are more virulent and less sensitive to certain cephalosporin antibiotics than those found in primary TKA infections.

All studies done by Chiu *et al*^[17-19] were conducted in a country outside of the United States, where operating room standards are unequivocal to more medically advanced nations. Their results were therefore most relevant for TKAs performed in an operative setting lacking "clean-air measures" such as ultraviolet light, laminar flow, and body exhaust systems. Chiu *et al*^[18] 2001 and Chiu *et al*^[17] 2009 reported that adding certain antibiotics such as cefuroxime or vancomycin only cost

Table 5 HSS, KSS knee scores, and loosening rates

Paper	Statistically significant differences in deep infection rate	HSS knee score AIBC	HSS knee score non-AIBC	KSS score AIBC	KSS score non-AIBC	Loosening AIBC	Loosening non-AIBC
Chiu <i>et al</i> ^[18] , 2001	Yes ($P = 0.021$)	91	86	-	-	0/41	2/37
Vrabec <i>et al</i> ^[23] , 2016	No (P value not reported)	-	-	-	-	-	-
Chiu <i>et al</i> ^[19] , 2002	Yes ($P = 0.0238$)	90	88	-	-	1/178	0/162
Lizaur-Utrilla <i>et al</i> ^[24] , 2014	No (P value not reported)	-	-	89	94	4/48	1/45
Nilsson <i>et al</i> ^[25] , 1999	No (P value not reported)	-	-	93	93	0/28	1/29
Bercovy <i>et al</i> ^[26] , 2012	No (P value not reported)	-	-	94.3	94.6	1/164	1/157
Hinarejos <i>et al</i> ^[20] , 2013	No ($P = 0.96$)	-	-	-	-	-	-
McQueen <i>et al</i> ^[22] , 1987	No (P value not reported)	-	-	-	-	-	-
McQueen <i>et al</i> ^[21] , 1990	No (P value not reported)	-	-	-	-	-	-
Nelson <i>et al</i> ^[27] , 1993	No (P value not reported)	-	-	-	-	-	-
Chiu <i>et al</i> ^[17] , 2009	Yes ($P = 0.0130$)	87	85	-	-	0/93	0/90

AIBC: Antibiotic impregnated bone cement; HSS: Hospital for special surgery scores; KSS: Knee society scores.

\$ 10-15 in Taiwan, where their studies were conducted. The price for adding antibiotics to bone cement was reported to cost much less than having to do a possible re-revision due to infection if antibiotics were not added to the cement. Chiu *et al*^[18] 2001, Chiu *et al*^[17] 2009, and Hinarejos *et al*^[20] 2013 considered other factors that could correlate with the development of infection such as age, sex, side of the lesion, reason for the revision, time between the primary and revision procedures, body mass index, ASA grade, tourniquet time, operative time, hospital stay, HSS score, and period of follow-up. None of these factors were significant in the development of infections in any of these studies.

Hinarejos *et al*^[20] did not report erythromycin and colistin-loaded cements to significantly impact infection rates in primary TKAs. In Hinarejos *et al*^[20] study, there was an average operation time 4.4 min longer in the group with an infection and the group with deep infections had significantly higher percentages of procedures over 125 min. With this data, Hinarejos *et al*^[20] found that male sex and an operating time of > 125 min were factors related to a higher rate of deep infection.

McQueen *et al*^[22] 1987 detailed that the knee arthroplasty that had been diagnosed with a deep infection in the group not using AIBC had previously undergone a medial meniscectomy and a proximal tibial osteotomy, which accounted for higher chances of infection following that operation.

When looking at hydroxyapatite (HA) coating vs cemented TKA components, Nilsson *et al*^[25] and Bercovy *et al*^[26] both found that HA-coated implants were more stable than cemented implants. Bercovy *et al*^[26] noted that HA-coated components performed similarly to cemented components and both Bercovy *et al*^[26] and Nilsson *et al*^[25] reported HA-coated implants to be a reliable option in primary TKA procedures. Other various elements were described in all of the studies, however, only the most frequent were reported in this analysis. More information on comparison details from individual articles was noted in Tables 3 and 4.

Bone cements and antibiotics

Different types of antibiotics added to bone cements

involved in this analysis included cefuroxime, vancomycin, tobramycin, gentamicin, refobacin, colistin, and erythromycin. Cefuroxime and vancomycin were the antibiotics used in studies with significant differences in infection rates. More information about types and amounts of bone cements/antibiotics used in these papers was presented in Tables 3 and 4.

DISCUSSION

Overall analysis displayed AIBC's potential as an infection prevention tool. It was found that the use of AIBC did not reduce the infection rates in primary TKAs. A possible explanation for this insignificant difference could be that primary TKA procedures are 2-3 times less susceptible to infection^[10] than TKA revisions, making AIBC less relevant in the prevention of infection outcomes in primary vs revision TKA procedures. In primary TKA procedures, both AIBC and other forms of systemic antibiotics have been proven to be equally effective in infection prevention^[7]. However, the opposite is true for revision TKA. With revision TKAs, the only outcome found to vary significantly between AIBC and non-AIBC groups was infection rates. Since revision TKAs have higher chances of infection and are oftentimes undergone because of previous infection, the added benefits of AIBC during the revision procedure could significantly decrease infection post-revision. With this data, the hypothesis that AIBC would lower infection rates in TKA revisions was supported. The hypothesis that AIBC would lower infection rates in primary TKAs was not supported.

Some individual papers noted significant differences between groups in multiple ways, but with the strict inclusion criteria used in this paper, perhaps not enough papers were included to obtain significant results for variables besides infection rates. There were no differences in clinical knee scores found in this study or in the systematic review done by Wang *et al*^[7]. None of the studies noted differences in superficial infection rates. Josefsson *et al*^[28] proposed that the antibiotics from loaded cement do not reach the superficial parts of the wound in a sufficient concentration to prevent infection. This gave one explanation for the lack of

statistical significance in superficial infection rates found throughout literature reviews as well^[7,13-15].

This systematic review differed from other systematic reviews in multiple ways. The systematic review and meta-analysis done previously on primary TKA and THA AIBC vs non-AIBC groups was published in 2013^[7]. That systematic review had articles published up until 2013 and used four RCTs^[19-22] that were used in this analysis paper. With the goal of including the most recent published results in the field, this study included two papers^[23,24] published after 2013. This study also included seven other RCTs that the previous meta-analysis^[7] did not (five extra primary TKA RCTs and two revision TKA RCTs). In that systematic review^[7], there were also no significant differences in infection rates in the TKA group found. Other reviews^[14,15] published with similar search criteria as Wang *et al.*^[7] found insignificant results as well. However, these reviews did not include similar search criteria and were not limited to RCTs only. None of these reviews considered TKA revisions.

Even though this study sought to include a large number of revision TKA procedures, there were a limited number of patients found that were evaluated in revision TKAs. As noted in the limitations section, this was a drawback to this study. If a larger sample size in the revision TKA group were possible, this data would be even more clinically significant. Without such additional data, conclusions would be hard to make, but considering data from this study it is speculated that revision TKA procedures would continue to show significant differences in AIBC vs non-AIBC infection rates.

Most studies suggest that both systemic antibiotics and AIBC be used when treating septic patients. In the results of this analysis, it was found that the use of systemic antibiotics in conjunction with AIBC was the standard in all 11 articles. One comprehensive literature review^[29] recommended that for best results prophylactic antibiotics be used before revision TKA, AIBC used during the procedure, and the surgery should also be followed with systemic antibiotics.

The primary advantage of preventing deep peri-prosthetic joint infection often outweighs the minor shortcoming of AIBC. According to Chiu *et al.*^[17], there is a significant cost benefit to adding antibiotics to bone cement. Chiu *et al.*^[17] stated that adding antibiotics to bone cement in revision procedures would cost much less than having a re-revision performed. The reality is that most surgical revisions use AIBC with antibiotics and bone cements in various combinations. It is evident that standards for safe use of AIBC must be followed for successful clinical results.

Even though the data suggests that AIBC significantly reduces the risk of infection in revision, there is clearly a shortage of high quality randomized controlled studies comparing AIBC to non-AIBC use in knee revision procedures. Furthermore, only two of the RCTs^[17,27] meeting criteria in the study had data comparing an AIBC group with a group not using AIBC during revision. This

could be explained by the strict inclusion and exclusion criteria set for this literature search. In the future, a literature search encompassing a more broad scope of papers that fit a different set of criteria could be done to get a larger sample size and more significant results from analysis. In order to have more significant results for AIBC in TKA procedures, more RCTs also need to be conducted with the specific aim of comparing AIBC use in TKA procedures vs procedures not using AIBC or some other form of antibiotic therapy. Although this study was limited to primary and revision TKAs, even more possibilities exist with AIBC in other joint reconstructive surgeries. With an increasing population, numbers of primary TKA and TKA revisions are bound to increase in the near future^[12]. The availability of potential patients needing TKA procedures that can be used in studies will therefore soon also be increasing. With this increase, hopefully more high quality studies and data can be accumulated on this topic.

Limitations

In spite of the fact that strong efforts were made to create a well-designed study, there were some intrinsic limitations in this review. One of the first limiting factors of note came about in the literature search. After some time searching for RCTs based through PubMed on this topic, it was clear that not many were available for use that met inclusion criteria. It was especially difficult to find RCTs that compared AIBC to a non-AIBC control in total knee revisions (only two studies found on this). Upon search, more articles were found pertaining to primary TKA/THA with AIBC. Revision procedures were seen to a much smaller extent. For these reasons, the sample size was relatively small and could potentially be expanded if studies outside of RCTs found using only the PubMed "filters" setting were included. Another limitation was that not all studies were held to the same standard of evaluation during patient follow up. Due to the fact that some studies were only focused on infection rates while others were focused on clinical knee scores and patient satisfaction, there was not a standard of comparison across each and every study evaluated. Along those same lines, knee scores were reported in two different ways (Knee Society Score and Hospital for Special Surgery Score), making them difficult to compare amongst papers. As expected, not all studies had the same follow up times, which made comparison between short, intermediate, and long term results more difficult. Also, not all revisions were done for the same purposes. Also, eligible studies came from hospitals located across many different countries, which have different populations of patients and populations of bacteria. Since we did not restrict our study to a certain type of bone cement or prostheses, many types of bone cements and implants were used across articles. All of these limitations may affect outcomes of this review and meta-analysis in some way.

AIBC did not have a significant effect on primary TKA infection rates. AIBC did have a significant effect on

revision TKA infection rates.

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Systematic review of bone marrow stimulation for osteochondral lesion of talus - evaluation for level and quality of clinical studies

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author "insert email", who will provide a permanent, citable and open-access home for the dataset.

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Abstract

AIM

To clarify the quality of the studies indicating lesion size and/or containment as prognostic indicators of bone marrow stimulation (BMS) for osteochondral lesions of the talus (OLT).

METHODS

Two reviewers searched the PubMed/MEDLINE and EMBASE databases using specific terms on March 2015 in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. Predetermined variables were extracted for all the included studies. Level of evidence (LOE) was determined using previously published criteria by the Journal of Bone and Joint Surgery and methodological quality of evidence (MQOE) was evaluated

using the Modified Coleman Methodology Score.

RESULTS

This review included 22 studies. Overall, 21 of the 22 (95.5%) included studies were level IV or level III evidences. The remaining study was a level II evidence. MQOE analysis revealed 14 of the 22 (63.6%) included studies having fair quality, 7 (31.8%) studies having poor quality and only 1 study having excellent quality.

CONCLUSION

The evidence supporting the use of lesion size and containment as prognostic indicators of BMS for OLTs has been shown to be of low quality.

Key words: Osteochondral lesion of talus; Arthroscopy; Bone marrow stimulation; Systematic review

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Core tip: Bone marrow stimulation (BMS) is a reparative procedure for osteochondral lesions of the talus, promising approximately 85% success rates in the short- and mid-term. To date, the prognostic factors for BMS are lesion size and containment of the lesion. No other factors have been shown to be universal predictors. However, the level of evidence and methodological quality of evidence for clinical studies accompanying both the lesion sizes and containment are low. Overall, 95.5% of the studies included in the analysis are level IV or level III. No level I study was identified. The methodological qualities of the included studies were not strong. In particular, the scores of "primarily evaluates outcome criteria and recruitment rates" were low.

Yasui Y, Ramponi L, Seow D, Hurley ET, Miyamoto W, Shimozono Y, Kennedy JG. Systematic review of bone marrow stimulation for osteochondral lesion of talus - evaluation for level and quality of clinical studies. *World J Orthop* 2017; 8(12): 956-963 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v8/i12/956.htm> DOI: <http://dx.doi.org/10.5312/wjo.v8.i12.956>

INTRODUCTION

Bone marrow stimulation (BMS) is a reparative procedure for osteochondral lesions of the talus (OLT)^[1]. The aim of this arthroscopic procedure is to stimulate mesenchymal stem cells (MSCs) to promote fibrous cartilage tissue by breaching the subchondral bone plate (SBP) using an awl or wire^[1]. Several investigators have demonstrated good to excellent clinical outcomes in around 85% of patients, treated with BMS for OLT, for the short to medium term^[2].

The main prognostic factor in the treatment of OLT has been regarded as the lesion size^[1,3,4]. The maximum size for BMS treatment is generally accepted as less than 15 mm in diameter or 150 mm² in area. Chuckpaiwong

et al^[4] found that smaller than 15 mm in diameter was the critical cut-off value to obtain a successful outcome following BMS. Choi *et al*^[5] concluded that 150 mm² is the critical defect area beyond clinical outcomes following BMS for OLT decreased significantly. However, a recent systematic review by Ramponi *et al*^[6] showed the critical lesion size to be 107.4 mm² in area and/or 10.2 mm in diameter, for BMS. Containment of the lesion has also been demonstrated as a universally accepted prognostic factor for good clinical outcomes following BMS for OLT^[3,7].

Recently, level of evidence (LOE) and methodological quality of evidence (MQOE) have been used to assess relative value of outcomes reported in the clinical studies^[8-11]. Despite the widespread clinical use of lesion size as a cut-off value for BMS in OLT, there has been no comprehensive assessment of LOE and QOE for clinical studies accompanying both the lesion size and clinical outcomes. The same can be said for the presence or absence of containment of OLT.

The purpose of this systematic review was to clarify the LOE and MQOE of for the published literature investigating clinical outcome following BMS for OLT, with special emphasis on studies investigating lesion size and containment as predictors.

MATERIALS AND METHODS

Search strategy

A systematic literature search of the PubMed/MEDLINE and EMBASE databases was performed in March 2015 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[12]. Each database was searched using the following key words, (microfracture OR microdrilling OR drilling OR drill OR bone marrow stimulation OR marrow stimulation OR BMS OR abrasion chondroplasty OR arthroscopy OR arthroscopic) AND (talus OR talar OR ankle) AND (cartilage OR osteochondritis dissecans OR chondral OR osteochondral OR transchondral OR osteochondral lesion OR OCL OR OCD).

Titles and abstracts were screened using specific inclusion and exclusion criteria. Full texts of potentially relevant studies were then reviewed. Citations and references of all articles and relevant studies were manually assessed. Studies were searched and independently assessed by two independent reviewers. Differences between reviewers were discussed together and resolved by consensus or if a persistent disagreement occurred, a senior author was consulted.

Inclusion and exclusion criteria

Currently BMS is defined as microfracture, drilling, or abrasion. The inclusion criteria of the current systematic review was the following: (1) therapeutic clinical studies evaluating both lesion size of OLT and outcomes in patients who underwent BMS; (2) all patients included had more than a 24 mo follow up; (3) published in a

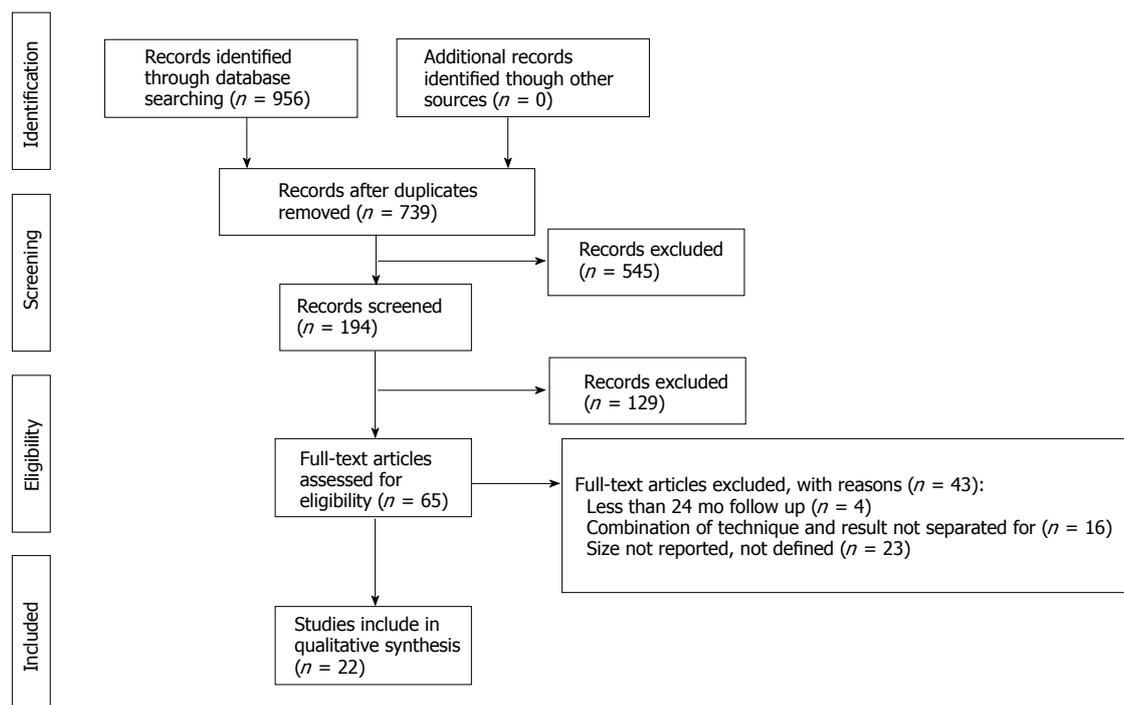


Figure 1 PRISMA study selection flow diagram.

peer-review journal; (4) published in English; and (5) full text of studies available. Exclusion criteria was the following: (1) cadaveric studies; (2) animal studies; (3) case reports; (4) review articles; (5) technique articles; (6) articles with unseparated results if more than one technique is described; (7) inadequately surgical technique description; (8) use of scaffolds; and (9) errors in reported data.

Data extraction and analysis

Two independent reviewers performed data extraction for each study. If any discrepancy existed, the senior author evaluated all available data and a consensus was reached. Studies that included more than one surgical procedure or a subgroup of patients with different follow-up times were included in the data for analysis^[13,14].

The primary outcome of current study was LOE and MQOE of included studies. LOE of each study was graded based on the previously published criteria^[15]. MQOE was assessed using the Modified Coleman Methodology Score (MCMS) (Table 1)^[6]. This score consists of 2 parts, Part A (primarily evaluates baseline study characteristics; 0-60) and Part B (primarily evaluates outcome criteria and recruitment rates; 0-40). According to Jakobsen’s CMS, the score of excellent studies are between 85 to 100 points; good studies 70 to 84 points, fair studies 55 to 69 points and poor studies scored under 55 points^[9].

Statistical analysis

The statistical analysis was performed using a commercially available contemporary statistical software package (SAS 9.3; SAS Institute, Cary, NC, United

States). In CMMS, all obtained scores were adjusted to percentage (each score/total score), the adjusted scores of CMMS were compared between Part A and Part B to determine statistical significance. As a Shapiro-Wilk’s *W* test showed non-normal distributed data, the Mann-Whitney *U* test was performed for this. Additionally, the adjusted score of each parameter were compared to investigate any difference using the Kruskal-Wallis test and Steel-Dwass test for data obtained without standard Gaussian distribution. A *P*-value < 0.05 was considered statistically significant.

RESULTS

The flow diagram is shown in Figure 1. After full texts articles were assessed based on the inclusion/exclusion criteria. There were 22 clinical studies included in the current systematic review^[3-5,7,13,16-32].

Demographics

Summary of the demographic data was shown in Table 2: 1.879 ankles were identified (931 males; 545 females)^[3-5,7,13,16-32]. The mean lesion area was 111.9 mm² and the mean diameter was 9.5 mm. The mean follow-up was 48.5 (range 24-146) mo.

LOE

Overall, 95.5% of the studies included were level IV^[4,7,17,18,20,22,25-29,31] or level III^[3,5,16,19,21,23,30,32]. No level I studies were included in the current review. Gobbi *et al.*^[13], was described as LOE I in the published journal, however, this study was re-assigned as LOE II (prospective cohort

Table 1 Modified Coleman Methodology Score^[6]

Section	No. or factor	Score
Part A: Only one score to be given for each section		
1 Study size - number of patients	> 60	10
	41-60	7
	20-40	4
	< 20, not stated	0
2 Mean follow up (mo)	> 24	5
	12-24	2
	< 12, not stated or unclear	0
3 Number of different surgical procedures included in each reported outcome. More than one surgical technique may be assessed but separate outcomes should be reported	One surgical procedure	10
	More than one surgical procedure, but > 90% of subjects undergoing the one procedure	7
	Not stated, unclear, or < 90% of subjects undergoing the one procedure	0
4 Type of study	Randomized controlled trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
5 Diagnostic certainty (MRI)	In all	5
	In > 80%	3
	In < 80%	0
6 Description of surgical procedure given	Adequate (technique stated and necessary details of that type of procedure given)	5
	Fair (technique only stated without elaboration)	3
	Inadequate, not stated, or unclear	0
7 Description of postoperative rehabilitation	Well described (ROM, WB and sport)	10
	Not adequately described (2 items between ROM and WB and sport)	5
	Protocol not reported	0
Part B: Scores may be given for each option in each of the three sections if applicable		
1 Outcome criteria	Outcome measures clearly defined	2
	Timing of outcome assessment clearly stated (<i>e.g.</i> , at best outcome after surgery or follow-up)	2
	Objective, subjective and imaging criteria	6
	2 items between objective, subjective and imaging criteria	4
	Objective or subjective or radiological criteria	2
2 Procedure for assessing outcomes	Subjects recruited (results not taken from surgeons files)	5
	Investigator independent of surgeon	4
	Written assessment	3
	Completion of assessment by subjects themselves with minimal investigator assistance	3
3 Description of subject selection process	Selection criteria reported and unbiased	5
	Recruitment rate reported	
	> 80% or	5
	< 80%	3
	Eligible subjects not included in the study satisfactorily accounted for, or 100% recruitment	5

MRI: Magnetic resonance imaging; ROM: Range of motion; WB: Weight bearing.

study). Table 2 shows information about LOE (Table 2).

MQOE

The mean MCMS was 57.5 ± 10.2 out of 100 points (range 38-89) (Table 3). Part A was 38.1 ± 8.1 (range 22-60; percentage: 63.5%) and Part B was 19.2 ± 5.5 (range 11-29; percentage: 48.0%), respectively. The adjusted

MCMS of Part A were significantly higher than that of Part B ($P < 0.05$). In the part A, the adjusted MCMS of "Type of study" were significantly lower among all the parameters ($P < 0.05$). With regard to Part B, "Outcome criteria" had significantly higher scores compared with the others ($P < 0.05$). Of the 22 included studies, 14 studies (63.6%) were of fair quality^[3-5,13,19,20,23-25,27,28,30-32], 7 (31.7%) of poor

Table 2 Studies included and demographic datas

Ref.	Year	No. of ankles	No. of males	No. of females	Follow -up (mo)	Lesion area (mm ²)	Lesion diameter (mm)	Prognostic factors	LOE	MCMS (points)
[23]	2013	50	20	30	35.5	61.7	8.8	Lesion size	III	58
[29]	2015	15	7	8	94.8	87		Lesion size	IV	50
[5]	2009	120	80	37	35.6	111.7	11.4	Lesion size	III	56
[3]	2013	399			74	111.3		Lesion size, contained	III	61
[32]	2015	90	68	22	38.3	100		Lesion size	III	67
[24]	2013	298	184	114	52	98.5		Lesion size	III	57
[19]	2012	173	121	52	70.3	95.4		Lesion size	III	54
[4]	2008	105	73	32	31.6		8.84	Lesion size	IV	57
[16]	2000	17	13	4	84	85.2		Lesion size	III	33
[13]	2006	10	6	4	53	450		Lesion size	III	61
[18]	2011	22	16	6	32	76		Lesion size	IV	45
[30]	2014	50	28	22	27.1			Lesion size	III	69
[20]	2012	22	12	10	24			Lesion size	IV	56
[21]	2012	81	64	17	37.4	100		Lesion size	III	89
[17]	2010	35	27	8	33	90		Lesion size	IV	50
[31]	2014	58	37	21	35	124		Lesion size	IV	65
[25]	2013	50	30	20	141		8.8	Lesion size	IV	62
[26]	2013	38	23	15	52.8	100		Lesion size	IV	52
[27]	2013	50	22	28	36.3	62		Lesion size	IV	66
[28]	2015	41	17	24	42.5	67		Lesion size	IV	56
[22]	2012	25	19	5	32	110		Lesion size	IV	48
[7]	2011	130	64	66	37.2	84		Lesion size, contained	IV	50

LOE: Level of evidence; MCMS: Modified coleman methodology score.

quality^[7,16-18,22,26,28] and only 1 (4.5%) study^[21].

DISCUSSION

The aim of this systematic review is to clarify LOE and MQOE of published literature on BMS for OLT. Twenty-two studies with 1,879 patients were included, however, no level I study was identified in the study cohort. The result demonstrated that most of the studies reported the lesion sizes and the containment of the lesion were graded as low LOE. The quality of evidence in these studies demonstrated an average MCMS of 57.5 out of 100 points and only 4.5% of included studies were graded as excellent, which suggests that the methodological quality of the included studies was weak. In addition, scores of Part B (primarily evaluates outcome criteria and recruitment rates) was marked significantly lower than Part A (primarily evaluates baseline study characteristics). This systematic review has revealed that studies with low LOE and weak MQOE have supported this paradigm despite lesion size and the containment of the lesion being a common criteria value for the indication for BMS in treating OLT.

Lesion size and the containment of the lesion are accepted prognostic factors to use when making a decision in operative treatment for OLT^[3,7]. In general, lesion size with less than 15 mm in diameter or less than 150 mm² are applied for BMS. It is also well known that a non-contained OLT have a worse outcome than a contained OLT^[7]. However, this systematic review has revealed that most of these studies were of low LOE, and

recently, several investigators evaluated the trend of LOE of published clinical studies in sport-related journals^[33]. Unfortunately greater than 80% of studies in foot and ankle surgery remain to have low LOE despite increasing numbers of the LOE I and LOE II studies in the clinical sports medicine literature^[9,10,33]. High-level clinical evidence can fundamentally provide adequate treatment for patients based on the principles of evidence-based medicine^[34]. Additionally, Moher *et al*^[35] described that non-blinded clinical studies without allocation concealment tended to describe an overestimated treatment effect than blinded clinical studies and well-designed blinded case control studies are required to establish prognostic factors in BMS for OLT.

The current systematic study revealed that the MQOE of the included 22 studies have been weak (Table 3)^[9]. Of those clinical studies "Procedure for assessing outcomes" and "Description of subject selection process" in Part B (primarily evaluates outcome criteria and recruitment rates) were significantly low. These findings are consistent with the outcomes found by a recent systematic review that analyzed the outcome data following microfracture for OLT in 24 clinical studies^[36]. The authors found that approximately half of included studies did not have a patient history or patient-reported outcome data, despite the presence of well described general demographics and study design. Additionally, clinical variables (48%) and imaging data (39%) has been the least reported in these studies. Poor methodological quality of the clinical study decreases the reliability of study's outcomes^[37]. However, caution

Table 3 Outcome of modified Coleman methodology scores

Ref.	Part A							Part B			Total
	1 Study size - number of patients	2 Mean follow-up (mo)	3 No. of different surgical procedures included in each reported outcome	4 Type of study	5 Diagnostic certainty (MRI)	6 Description of surgical procedure given	7 Description of postoperative rehabilitation	1 Outcome criteria	2 Procedure for assessing outcomes	3 Description of subject selection process	
[23]	7	5	10	0	5	3	10	8	5	5	58
[29]	0	5	10	0	0	5	10	10	5	5	50
[5]	10	5	10	0	5	5	10	8	5	0	58
[3]	10	5	10	0	5	5	10	8	8	0	61
[32]	10	5	10	0	5	5	5	6	3	8	57
[24]	10	5	10	0	5	5	10	10	9	3	67
[18]	10	5	10	0	5	5	10	8	3	0	56
[4]	10	5	10	0	5	3	10	6	8	0	57
[16]	4	5	10	0	0	3	0	8	5	3	38
[13]	4	5	0	10	5	5	10	10	9	3	61
[18]	4	5	10	0	5	5	5	6	5	0	45
[30]	7	5	10	0	5	5	10	10	9	8	69
[20]	4	2	10	0	5	3	5	10	9	8	56
[21]	10	5	10	15	5	5	10	10	9	10	89
[17]	4	5	10	0	5	5	5	8	5	3	50
[31]	7	5	10	0	5	5	10	10	5	8	65
[25]	7	5	10	0	0	3	5	10	12	5	57
[26]	4	5	10	0	5	3	10	10	5	0	52
[27]	7	5	10	0	5	3	10	8	8	10	66
[28]	7	5	10	0	5	3	10	8	5	3	56
[22]	4	2	10	0	5	5	5	8	9	0	48
[7]	10	5	0	0	5	0	10	10	5	5	50
mean	6.8	4.7	9.1	1.1	4.3	4	8.2	8.6	6.6	4	57.5
SD	3	0.9	2.9	3.8	1.8	1.3	2.9	1.4	2.4	3.5	10.2

MRI: Magnetic resonance imaging.

should be taken when interrupting the outcomes of methodological quality. The methodological deficiencies have been reported using Coleman Methodological Score for tendinopathy^[8,38], knee cartilage lesion^[9], fracture^[39], ligament injury^[40-42] and OLT^[43]. However, to our knowledge, the validity and reliability of this score for OLT is unknown. Nevertheless, we believe the outcome of the current study is important because the modification for MCMS in the current study could improve the validity and reliability of this score for OLT.

Several limitations of the current study exist mainly due to the inclusion criteria. Studies published in database other than MEDLINE and EMBASE were not included. Clinical studies not written in English were not evaluated. Nevertheless, this study does demonstrate important findings of that the LOE and QOE of published literature, on using BMS for OLT, are insufficient to produce any solid conclusion. A further limitation was that the current study focused only on the available clinical studies. As a result, the outcomes have addressed very little of the underlying mechanisms and intrinsic limitations of BMS for OLT. Currently, underlying biological aspects of cartilage regeneration has been well discussed due to low intrinsic activity of reparative cartilaginous tissue following BMS and potential ability of biological factors, although a recent systematic review has suggested a comprehensive assessment of the evidence behind the translation of basic science to the clinical practice^[44,45]. Thus, the usefulness of the

outcomes from the current study depends essentially on critical appraisal of the literature on the clinical application.

In conclusion, lesion size and the containment of OLT is a commonly used prognostic parameter in the treatment of osteochondral lesion of the talus. However, this systematic review has revealed that low levels of evidence and weak quality of evidence in clinical studies need to be improved before this paradigm can be fully supported.

COMMENTS

Background

Lesion sizes and containment are commonly used in the orthopaedic community to predict the clinical outcomes of bone marrow stimulation for osteochondral lesion of talus.

Research frontiers

The widespread use of lesion size and containment as prognostic indicators prompts a much-needed comprehensive assessment of the studies supporting this data.

Innovations and breakthroughs

The evidence supporting the use of lesion size and containment as prognostic indicators of bone marrow stimulation (BMS) for osteochondral lesion of the talus (OLTs) have been revealed in this study to be of low level of evidence (LOE) and of weak methodological quality of evidence. Future studies with more robust study designs are warranted should the current paradigm ever need to be fully supported.

Applications

This systematic review has revealed that low levels of evidence and weak quality of evidence in clinical studies need to be improved before this paradigm can be fully supported.

Terminology

BMS: Bone marrow stimulation; LOE: Level of evidence; MCMS: Modified Coleman Methodology Score; MQOE: Methodological quality of evidence; OLT: Osteochondral lesion of the talus.

Peer-review

This is a timely, objective, well-written, well-conducted systematic review of a topic relevant to the field of orthopaedics.

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Acute compartment syndrome of the thigh following hip replacement by anterior approach in a patient using oral anticoagulants

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Abstract

Acute compartment syndrome (ACS) of the thigh following primary total hip arthroplasty (THA) is a highly uncommon complication and has not yet been reported before with regards to the anterior approach through the anterior supine interval. We present a case of a 69-year-old male patient with a history of stroke, who developed ACS of the thigh after elective THA while using therapeutic low molecular weight heparin as bridging for regular oral anticoagulation. ACS pathogenesis, diagnostic tools, treatment and relevant literature are discussed. The patient's ACS was recognized in time and treated by operative decompression with fasciotomy of the anterior compartment. Follow-up did not show any neurological deficit or soft-tissue damage.

Key words: Orthopedics; Total hip arthroplasty; Anterior supine intermuscular approach; Acute compartment syndrome; Anticoagulation therapy

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Core tip: Acute compartment syndrome of the thigh is an uncommon complication following total hip arthroplasty, which has not yet been reported after hip replacement by anterior approach through the anterior supine interval. Global increase in venous thromboembolism chemoprophylaxis may lead to an increase in incidence of postoperative bleeding and with this an increase in acute compartment syndrome of the thigh following primary total hip arthroplasty. Onset of severe pain of the upper leg postoperatively should warrant a high index of suspicion of this condition. Diagnostic tools such as ultrasound, computed tomography or intra-compartmental pressure measurements can be useful but should not lead to any delay of treatment.

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INTRODUCTION

Acute compartment syndrome (ACS) is a known complication often following trauma such as fractures or crush injuries. However, ACS of the thigh is an uncommon complication, which has not been reported before after hip replacement by anterior approach through the anterior supine interval. Known causes for ACS of the thigh include femoral fractures, acetabular or proximal femur surgery, tourniquet application and extensive deep vein thrombosis^[1-4]. With the current trend of more oral anticoagulants being used and perioperative bridging therapy using LMWH it is noted that postoperative bleeding and the hereby possibly inferred ACS may be on the rise.

CASE REPORT

A 69-year-old male, using oral anticoagulation medication (Fenprocoumon 3 mg) due to a history of stroke, underwent total hip replacement of the right hip using the anterior approach through the anterior supine interval, as treatment for his end stage osteoarthritis. Only uncemented materials were used. Following hospital protocol, the administration of oral anticoagulation (OAC) medication was discontinued 5 d before surgery and the patient was bridged using LMWH (Tinzaparin 18.000 IE, subcutaneously) as venous thromboembolism (VTE) chemoprophylaxis. Preoperatively the patients' international normalized ratio was 1.3. Additionally, tranexamic acid, as part of hospital protocol regarding postoperative hemorrhage prophylaxis, was administered intraoperatively. THA was performed without any complications. However, total intraoperative blood loss was 600 cc, slightly higher than average. This was attributed to the patients' regular use of anticoagulation medication and current bridging therapy. The night following the operation the patient complained of pain in the ipsilateral leg which was interpreted as postoperative pain for which additional opioids were prescribed. One day following surgery hemoglobin levels were 7.0 g/dL (Preoperative Hemoglobin levels were 9.4 g/dL). During the course of the day the patient needed additional opioids to perform routine exercises. However, during the evening the pain aggravated and additional opioids could not suppress the pain with progressing symptoms of swelling, hematoma and paresthesia of the right leg.

Ultrasound of the thigh was performed which showed an intramuscular hematoma of the anterior



Figure 1 Ultrasound of the thigh showing an intramuscular hematoma of the anterior compartment.

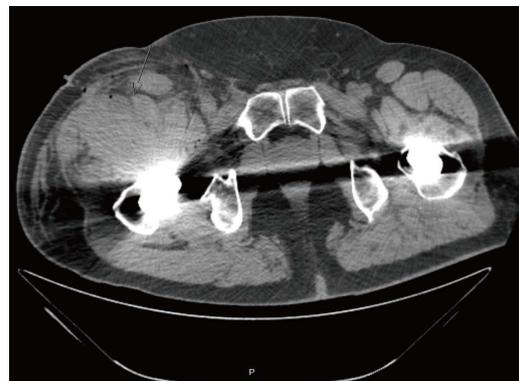


Figure 2 Transverse plane computed tomography scan showing a hematoma ventrally in the anterior compartment.

compartment of 8.3 cm by 3.5 cm (Figure 1). Additional computed tomography (CT-scan) was performed which confirmed the diagnosis and showed 2 hematomas of the anterior compartment (Figures 2-4). No intra-compartmental pressure measurements were performed as the diagnosis had already been confirmed and would only have delayed treatment. Delay of diagnosis in this case can be attributed to the fact that the patients' need for additional opioids to perform routine exercises one day postoperatively is not an uncommon occurrence. Furthermore, the first postoperative Hemoglobin levels were slightly decreased (7.0 g/dL), however within acceptable postoperative range and thus warranted no further investigation at the time.

To prevent further expansion of the hematoma VTE prophylaxis was discontinued and an emergency fasciotomy through the anterior compartment of the thigh was performed. A large hematoma was evacuated, the surgical site was extensively irrigated with normal saline solution and tranexamic acid was administered topically in the wound. Cultures of the surgical site showed no infection. The following day postoperative hemoglobin levels were at 3.9 g/dL for which the patient received multiple 4 blood transfusions over the course of several days after which hemoglobin levels were normalized to 7.3 g/dL.



Figure 3 Transverse plane computed tomography scan showing a hematoma dorsally in the anterior compartment.



Figure 4 Coronal plane computed tomography scan showing a hematoma of the anterior compartment.

Directly after emergency fasciotomy the neurological deficit and the severe pain the patient had previously been experiencing, disappeared. Over the next few days mobilization was increased and at 6 d after emergency fasciotomy patient was discharged with low dose LMWH (Nadroparin 2850 IE, subcutaneously) as VTE prophylaxis. 11 d after emergency fasciotomy OAC therapy was resumed without any further complications.

At 8 and 12 wk follow-up, the patient did not have signs of any residual neurological deficit.

DISCUSSION

ACS is defined by increased pressure in a closed fascial space compromising the circulation to the nerves and muscles within the involved compartment^[5]. ACS in the thigh is a rare complication following primary THA. This can be due to several reasons.

From an anatomical perspective, it could be explained by the large volume of soft tissue of the thigh, therefore requiring extravasation of a large volume of fluid to cause compression of local structures^[3]. Aside from the large volume of the three compartments in the thigh, the fascia of the thigh seems to be more dilative compared to the fascia of the lower leg^[6]. Furthermore, the compartments of the upper leg are partly open to the pelvis explaining the higher compensation space for

increasing an intra-compartmental hematoma^[7].

Literature shows cases with ACS both shortly after operation as well as several days following THA, the common denominator often being VTE prophylaxis^[3,4,8]. It is our belief that in our patient, the increased intra-compartmental pressure was most likely caused by iatrogenic laceration to the branches of the circumflex femoral arteries aggravated by his regular use of anticoagulation medication and current bridging therapy. We noticed that the ACS progressively developed during the postoperative mobilization, which possibly severed the vessels during exercise. The classical sign of ACS, *i.e.* disproportionate pain, is difficult to judge in a patient after THA in which opiates are regularly required. However due to the alertness of the nurse staff and ward physician the diagnosis was confirmed shortly after the paresthesia developed, which prevented permanent neurological and vascular damage.

ARTICLE HIGHLIGHTS

Case characteristics

A 69-year-old male presented with severe pain, swelling, hematoma and paresthesia of the right leg following elective total hip replacement by anterior approach.

Clinical diagnosis

Severe pain, swelling and hematoma of the upper leg, as well as paresthesia of the lower leg.

Differential diagnosis

Postoperative pain, postoperative dislocation of the hip, periprosthetic fracture, iatrogenic neurological damage.

Laboratory diagnosis

Preoperative international normalized ratio was 1.3 and Hemoglobin level 9.4 g/dL, postoperative Hemoglobin levels were 7.0 g/dL and 3.9 g/dL.

Imaging diagnosis

Ultrasound of the thigh showed an intramuscular hematoma of the anterior compartment of 8.3 cm by 3.5 cm and computed tomography revealed two hematomas of the anterior compartment.

Pathological diagnosis

Cultures of the surgical site showed no infection.

Treatment

Venous thromboembolism (VTE) prophylaxis was discontinued and an emergency fasciotomy through the anterior compartment of the thigh was performed during which a large hematoma was evacuated, the surgical site was extensively irrigated with normal saline solution and tranexamic acid was administered topically in the wound.

Related reports

Acute compartment syndrome is a known complication often following trauma such as fractures or crush injuries. However, a highly uncommon presentation and localization of acute compartment syndrome is that of the thigh following total hip replacement by the anterior approach. The first symptoms of acute compartment syndrome of the thigh can easily be confused with other causes for postoperative pain, swelling, hematoma and paresthesia.

Term explanation

Acute compartment syndrome is defined by increased pressure in a closed

fascial space compromising the circulation to the nerves and muscles within the involved compartment. VTE prophylaxis is a mechanical or pharmacologic method for prevention of venous thromboembolism.

Experiences and lessons

Acute compartment syndrome of the thigh is a highly uncommon complication following total hip replacement by anterior approach and as such should and must be considered in case of postoperative onset of severe pain of the upper leg.

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