ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2015 July 18; 6(6): 446-504

Published by Baishideng Publishing Group Inc

WJO World Journal of Orthopedics

A peer-reviewed, online, open-access journal of orthopedics

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World Journal of Orthopedics is now indexed in PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

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NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

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July 18, 2015

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DOI: 10.5312/wjo.v6.i6.446

World J Orthop 2015 July 18; 6(6): 446-448
ISSN 2218-5836 (online)

EDITORIAL

Current concepts in total knee arthroplasty: Patient specific instrumentation

Patrick Sadoghi

Patrick Sadoghi, Department of Orthopedic Surgery, Medical University of Graz, 8036 Graz, Austria

Author contributions: Sadoghi P contributed to this paper.

Conflict-of-interest statement: I hereby declare to have no potential conflict of interest including but not limited to commercial, personal, political, intellectual, or religious interests.

Correspondence to: Dr. Patrick Sadoghi, MD, PhD, Professor, Department of Orthopedic Surgery, Medical University of Graz, Auenbruggerplatz 5, 8036 Graz, Austria. patricksadoghi@gmx.at
Telephone: +43-316-38580971
Fax: +43-316-38514806

Received: April 5, 2015
Peer-review started: April 6, 2015
First decision: May 13, 2015
Revised: May 23, 2015
Accepted: June 15, 2015
Article in press: June 16, 2015
Published online: July 18, 2015

Abstract

Patient specific instrumentation (PSI) in total knee arthroplasty (TKA) promises faster operation time (by using less instruments and individual cutting jigs), less blood loss, faster rehabilitation, better implant sizing and accuracy, superior overall outcome, and at the end - less costs. However, as evident for every new development, its superiority remains to be proven over the conventional systems. Whilst dissatisfaction is reported to be eminent in up to 30% of patients having undergone conventional TKA, it is unclear, whether PSI can address to these patients as a suitable option in the future. The author believes that the current evidence does not support superiority of PSI in TKA over conventional systems. However, future long-term level I and II studies might aid to show its cost-effectiveness stating same results, accuracy, and overall outcome with less operation time.

Key words: Total knee arthroplasty; Patient specific instrumentation; Accuracy; Outcome analysis; Cost-effectiveness

Core tip: Patient specific instrumentation (PSI) in total knee arthroplasty (TKA) promises faster operation time, less blood loss, faster rehabilitation, superior implant accuracy, superior overall outcome, and less costs. However, as evident for every new development, its superiority remains to be proven over the conventional systems. Whilst dissatisfaction is reported to be eminent in up to 30% of patients having undergone conventional TKA, it is unclear, whether PSI can address to these patients as a suitable option in the future. The author believes that the current evidence does not support superiority of PSI in TKA over conventional systems.

Sadoghi P. Current concepts in total knee arthroplasty: Patient specific instrumentation. *World J Orthop* 2015; 6(6): 446-448 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/446.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.446

INTRODUCTION

Patient specific instrumentation (PSI) in total knee

arthroplasty (TKA) was developed to reach the goal of superior component positioning and adequate sizing in less operative time[1-3]. There exist various different devices to achieve these goals; most of them include preoperative planning using MRI or CT scans to investigate bony landmarks for the use of adequate positioning of tibial and femoral cutting blocks and jigs[1-3]. The promises of PSI are less surgical time, better alignment, fewer outliers, less surgical time, less costs, and overall superior outcome for our patients[1]. Whilst dissatisfaction is reported to be eminent in up to 30% of patients having undergone conventional TKA, it is unclear, whether PSI can address to these patients as a suitable option in the future[4]. However, as evident for every new development, its superiority remains to be proven over the conventional systems and some controversies have to be discussed when it comes to PSI in TKA. New developments in TKA are often industry driven and whilst adequate component sizing is always beneficial in TKA not all presented devices are reasonable for our patients such as discussed with respect to the gender knee in the past[5,6].

Whilst surgeons argue that PSI saves money and decreases operative time by less turnover time, less sterilization material, faster surgery, and therefore saves costs, it is essential, that the preoperative planning time might not be underestimated[7]. This factor might be outsourced but still has to be done prior to using adequate cutting blocks and jigs or similar devices[2]. It is therefore questionable, if the overall costs would really decrease over time or if the overall costs for the orthopedic setting would decrease whilst costs and work load for others included in the process of the development of these devices would increase. In addition, the aspect of intraoperative component sizing and positioning is a mandatory ability of the experienced knee surgeon. One might argue that the way to find adequate sizes and component positioning is in fact one of the major qualities of a skilled knee surgeon and therefore should not be given away to a computer and or other form of technical device[2]. However, using PSI, this is either given away by using preoperatively designed cutting blocks and jigs or it has to be re-evaluated intra-operatively using conventional methods giving away the benefit of faster surgery[8]. As evident for every new development the superiority of PSI in TKA remains to be proven over conventional systems and future long-term level I and II trials are needed in doing so.

IMPLANT POSITIONING AND ACCURACY

Carpenter *et al*[7] investigated PSI in unicompartmental knee arthroplasty (UKA). They prospectively evaluated 30 patients undergoing UKA and performed virtual surgery in a medial and a lateral cohort resulting in 180 virtual surgeries (30 for each of 5 different brands) in total. They evaluated overhang and undercoverage and cortical rim coverage in PSI *vs* conventional cases and found that PSI implants for unilateral indication provide significantly less overhang and undercoverage and superior coverage of the cortical rim compared to conventional systems.

Stronach *et al*[9] retrospectively evaluated 54 patients who had undergone conventional TKA *vs* PSI in TKA with respect to the accuracy of implant alignment regarding overall mechanical alignment and sagittal and coronal alignment of the femoral and tibial components. They additionally measured tourniquet time and blood loss. They found the alignment to be similar in both groups but PSI with fewer knees in the target range for posterior slope in addition to a trend for fewer knees in a target range for femoral flexion. These authors concluded that PSI showed no advantage in overall alignment but a worsening of the tibial slope.

Voleti *et al*[10] performed a meta-analysis to evaluate implant positioning in PSI *vs* conventional TKA and found PSI with improved accuracy in the femorotibial angle *vs* standard instrumentation that demonstrated improved accuracy in the hip-knee-ankle angle. They included 9 studies in total with 428 standard TKAs *vs* 529 PSI TKAs. They concluded that the current evidence does not support the routine use of PSI in TKA.

Conteduca *et al*[11,12] evaluated the accuracy of PSI in TKA in various studies and used an intraoperative knee navigation software during the surgical procedure in 15 patients. They found PSI not to be more accurate or adequate. These authors recommended to control every step before making the definite cuts.

OUTCOME, OPERATIVE TIME, AND COST EFFECTIVENESS

Lionberger *et al*[3] performed a prospective study evaluating the difference of operation time with respect of implant accuracy in 60 patients undergoing TKA randomized to a group with PSI *vs* computer assisted surgery (CAS). They showed that the mechanical alignment was not different between both groups and that operative time was significantly decreased in PSI allowing for 3 PSI cases *vs* only 2 CAS cases in one 8 h operating room (OR) day. The authors concluded that the accuracy of CAS is superior to PSI and that PSI provides a slight benefit in reducing OR time.

Voleti *et al*[10] performed a meta-analysis to evaluate OR time, blood loss, and costs in PSI *vs* conventional TKA and found PSI with improved accuracy in the femorotibial angle *vs* standard instrumentation that demonstrated improved accuracy in the hip-knee-ankle angle. Differences in OR time, blood loss, and costs were not statistically significant between both groups.

Sassoon *et al*[13] performed a systematic review and found 16 studies to evaluate accuracy of the implant and 13 studies to evaluate potential cost effectiveness of PSI over conventional TKA. They found no improvement of PSI in postoperative limb or component alignment when compared to standard procedures with a positive

evidence of fewer surgical trays in PSI. In addition, they found no improved overall surgical efficiency or cost-effectiveness of PSI over TKA.

CONCLUSION

PSI seems to allow for the same accuracy as conventional TKA or computer assisted surgery in TKA. However, accurate control of the alignment before and after the tibial and femoral cuts is recommended questioning the benefit of less operative time and therefore overall cost effectiveness[14]. The author believes that the current evidence does not support superiority of PSI in TKA over conventional systems and therefore would not recommend it as a standard in clinical practice. However, future long-term level I and II studies might aid to show its cost effectiveness stating same results, accuracy, and overall outcome with less operation time.

REFERENCES

1 **Mont MA**, Callaghan JJ, Hozack WJ, Krebs V, Mason JB, Parvizi J. Patient specific instrumentation. *J Arthroplasty* 2014; **29**: 1693 [PMID: 25218189 DOI: 10.1016/j.arth.2014.08.008]

2 **Kastner N**, Gruber G, Sadoghi P. Can we always trust in the computer? Adequate tibial alignment and flexion-gap balancing using personalised knee arthroplasty cutting blocks. *Int Orthop* 2012; **36**: 2395 [PMID: 22915238 DOI: 10.1007/s00264-012-1647-x]

3 **Lionberger DR**, Crocker CL, Chen V. Patient specific instrumentation. *J Arthroplasty* 2014; **29**: 1699-1704 [PMID: 24810539 DOI: 10.1016/j.arth.2014.03.019]

4 **Carr AJ**, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ. Knee replacement. *Lancet* 2012; **379**: 1331-1340 [PMID: 22398175 DOI: 10.1016/S0140-6736(11)60752-6]

5 **Kastner N**, Aigner BA, Meikl T, Friesenbichler J, Wolf M, Glehr M, Gruber G, Leithner A, Sadoghi P. Gender-specific outcome after implantation of low-contact-stress mobile-bearing total knee arthroplasty with a minimum follow-up of ten years. *Int Orthop* 2014; **38**: 2489-2493 [PMID: 25027979 DOI: 10.1007/s00264-014-2453-4]

6 **Sadoghi P**, Kastner N. Size measurement and flexion gap balancing in total knee arthroplasty--new benefits of the Attune™ system? *Int Orthop* 2013; **37**: 2105 [PMID: 23801236 DOI: 10.1007/s00264-013-1953-y]

7 **Carpenter DP**, Holmberg RR, Quartulli MJ, Barnes CL. Tibial plateau coverage in UKA: a comparison of patient specific and off-the-shelf implants. *J Arthroplasty* 2014; **29**: 1694-1698 [PMID: 24768541 DOI: 10.1016/j.arth.2014.03.026]

8 **Conteduca F**, Iorio R, Mazza D, Caperna L, Bolle G, Argento G, Ferretti A. Are MRI-based, patient matched cutting jigs as accurate as the tibial guides? *Int Orthop* 2012; **36**: 1589-1593 [PMID: 22426932 DOI: 10.1007/s00264-012-1522-9]

9 **Stronach BM**, Pelt CE, Erickson JA, Peters CL. Patient-specific instrumentation in total knee arthroplasty provides no improvement in component alignment. *J Arthroplasty* 2014; **29**: 1705-1708 [PMID: 24890995 DOI: 10.1016/j.arth.2014.04.025]

10 **Voleti PB**, Hamula MJ, Baldwin KD, Lee GC. Current data do not support routine use of patient-specific instrumentation in total knee arthroplasty. *J Arthroplasty* 2014; **29**: 1709-1712 [PMID: 24961893 DOI: 10.1016/j.arth.2014.01.039]

11 **Conteduca F**, Iorio R, Mazza D, Ferretti A. Patient-specific instruments in total knee arthroplasty. *Int Orthop* 2014; **38**: 259-265 [PMID: 24390008 DOI: 10.1007/s00264-013-2230-9]

12 **Conteduca F**, Iorio R, Mazza D, Caperna L, Bolle G, Argento G, Ferretti A. Evaluation of the accuracy of a patient-specific instrumentation by navigation. *Knee Surg Sports Traumatol Arthrosc* 2013; **21**: 2194-2199 [PMID: 22735977 DOI: 10.1007/s00167-012-2098-z]

13 **Sassoon A**, Nam D, Nunley R, Barrack R. Systematic review of patient-specific instrumentation in total knee arthroplasty: new but not improved. *Clin Orthop Relat Res* 2015; **473**: 151-158 [PMID: 25059850 DOI: 10.1007/s11999-014-3804-6]

14 **Ollivier M**, Tribot-Laspiere Q, Amzallag J, Boisrenoult P, Pujol N, Beaufils P. Abnormal rate of intraoperative and postoperative implant positioning outliers using "MRI-based patient-specific" compared to "computer assisted" instrumentation in total knee replacement. *Knee Surg Sports Traumatol Arthrosc* 2015; Epub ahead of print [PMID: 25994474]

P- Reviewer: Macheras GA, Musumeci G, Zayni R **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i6.449

World J Orthop 2015 July 18; 6(6): 449-456
ISSN 2218-5836 (online)

MINIREVIEWS

Bone graft substitutes for spine fusion: A brief review

Ashim Gupta, Nitin Kukkar, Kevin Sharif, Benjamin J Main, Christine E Albers, Saadiq F El-Amin III

Ashim Gupta, Benjamin J Main, Saadiq F El-Amin III, Department of Medical Microbiology, Immunology and Cell Biology, Southern Illinois University School of Medicine, Springfield, IL 62794, United States

Ashim Gupta, Institute for Plastic Surgery, Department of Surgery, Southern Illinois University School of Medicine, Springfield, IL 62794, United States

Nitin Kukkar, Kevin Sharif, Benjamin J Main, Christine E Albers, Saadiq F El-Amin III, Division of Orthopaedics and Rehabilitation, Department of Surgery, Southern Illinois University School of Medicine, Springfield, IL 62794, United States

Benjamin J Main, Department of Surgery, Kansas City University of Medicine and Biosciences, Kansas City, MO 64106, United States

Author contributions: Gupta A, Kukkar N, Sharif K, Main BJ, Albers CE, and El-Amin III SF contributed to the writing, editing, and updating of this review article.

Conflict-of-interest statement: Authors have no conflicts of interest to disclose.

Correspondence to: Saadiq F El-Amin III, MD, PhD, Division of Orthopaedics and Rehabilitation, Department of Surgery, Southern Illinois University School of Medicine, 701 North First Street, Springfield, IL 62794,
United States. sel-amin@siumed.edu
Telephone: +1-212-5457700
Fax: +1-212-5457901

Received: March 9, 2015
Peer-review started: March 12, 2015
First decision: March 20, 2015
Revised: April 17, 2015
Accepted: May 16, 2015
Article in press: May 18, 2015
Published online: July 18, 2015

Abstract

Bone graft substitutes are widely used in the field of orthopedics and are extensively used to promote vertebral fusion. Fusion is the most common technique in spine surgery and is used to treat morbidities and relieve discomfort. Allograft and autograft bone substitutes are currently the most commonly used bone grafts to promote fusion. These approaches pose limitations and present complications to the patient. Numerous alternative bone graft substitutes are on the market or have been developed and proposed for application. These options have attempted to promote spine fusion by enhancing osteogenic properties. In this review, we reviewed biology of spine fusion and the current advances in biomedical materials and biological strategies for application in surgical spine fusion. Our findings illustrate that, while many bone graft substitutes perform well as bone graft extenders, only osteoinductive proteins (recombinant bone morphogenetic proteins-2 and osteogenic protein-1) provide evidence for use as both bone enhancers and bone substitutes for specific types of spinal fusion. Tissue engineered hydrogels, synthetic polymer composites and viral based gene therapy also holds the potential to be used for spine fusion in future, though warrants further investigation to be used in clinical practice.

Key words: Bone enhancers; Bone graft substitutes; Spine fusion; Autograft; Allograft

Core tip: In this review, we discussed the biology of spine fusion and the current advances in biomedical materials and biological strategies for application in surgical spine fusion. Our findings illustrate that, while

many bone graft substitutes perform well as bone graft extenders, only osteoinductive proteins (recombinant bone morphogenetic proteins-2 and osteogenic protein-1) provide evidence for use as both bone enhancers and bone substitutes for specific types of spinal fusion. Tissue engineered hydrogels, synthetic polymer composites and viral based gene therapy also holds the potential to be used for spine fusion in the future, though further investigation is needed before being used in clinical practice.

Gupta A, Kukkar N, Sharif K, Main BJ, Albers CE, El-Amin III SF. Bone graft substitutes for spine fusion: A brief review. *World J Orthop* 2015; 6(6): 449-456 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/449.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.449

INTRODUCTION

Bone graft substitutes are widely used in the field of orthopaedics. They account for more than 2 million surgeries/year worldwide[1]. Spine fusion is the most common process in spine surgery[2] treating numerous morbidities such as trauma, deformity and degeneration[1]. Currently, autografts and allografts are the foremost treatment options for patients undergoing spine fusion.

Autogenous bone grafts (ABGs) are the frequently used grafts for spine fusion. They impart osteogenic, osteoinductive, and osteoconductive properties and warrant no risk of disease transmission. However, limitations posed by ABGs include increased surgical time, increased cost, persistent post-operative pain, and pseudarthrosis[3-7], which assert an immediate necessity for bone grafts substitutes.

Allografts derived from cadavers have traditionally been used when ABGs are absent. Allografts are easily harvested and alleviate removal of healthy bone; however, limitations such as risk of disease transfer, decreased mechanical strength, and poor osteogenic properties restrict their applicability. When compared to ABGs, integration of allografts with native bone is slow, they lack complete vascularization, and show diminished osteoinduction and osteoconduction[8,9].

To circumvent the morbidity related with ABG and cadaveric allograft bone graft substitutes are developed. All existing bone graft substitutes lack appropriate osteoinduction, osteoconduction and osteogenicity. However, some of them have exhibited potential in basic science and clinical studies. Present-day research in the fields of molecular biology, tissue engineering and regenerative medicine has focused on new stratagems. Progress in the field of osteoinductive proteins, osteoconductive carrier matrices, gene therapy and tissue engineered scaffolds are advancing the practice of spine fusion. In this review, we will address the biology of spine fusion and current advances in biomedical materials and biological strategies for applications in surgical spine fusion.

SPINE FUSION BIOLOGY

Current progress in the practice of spinal fusion has hinged on advancements in minimally invasive surgery and a complete understanding of the *in vivo* biological process of bone substitutes. Spine fusion healing is a complex process that is extremely difficult to properly assess in a clinical setting due to a lack of available techniques[10]. Therefore, an animal model provides a valuable alternative, enabling each individual factor in this complex process to be accurately assessed[11].

Boden[2] delineated the complex biology of spinal fusion in New Zealand white rabbits. The authors divided the process of autogenous graft incorporation into five stages: (1) inflammation: Inflammation lasts for approximately 7-14 d. Initial insult to local blood supply and decortications results in hematoma formation around the bone graft; which is invaded by inflammatory cells. The fibroblast-like cells in the inflammatory tissue gets transformed into fibrovascular stroma. The decrease in fusion rates seen with the use of anti-inflammatory medications in the perioperative period shows the importance of this inflammatory phase[12]; (2) vascularization: Vascular buds appear in the fibrovascular stroma, resembling the formation of scar tissue. Primary membranous bone forms near the decorticated bone followed by minimal cartilage and endochondral ossification; (3) osteoinduction: Week 4-5 is a phase of reparation consisting of increased vascularization, necrotic tissue resorption, and osteoblasts and chondroblasts differentiation. The hallmark of osteoinduction is the differentiation of stem cells into osteoblasts. Extension of new bone towards the central zone of fusion mass and continued resorption of the cortical portion of the graft is also a feature of this stage; (4) osteoconduction: Osteoconduction is characterized by ingrowth into host bone and creeping substitution. The simultaneous creation of new bone by osteoblasts and graft bone resorption by osteoclasts occur. A central zone of endochondral interface is observed at the center of fusion mass, uniting lower and upper half of fusion. Pluripotent cells in this central zone differentiate into a less vascular cartilaginous tissue; and (5) remodeling: For 6-10 wk, a peripheral cortical rim forms around fusion, and there is increased bone marrow activity with formation of secondary spongiosa. The cortical rim thickens and the trabecular process extends to the center of fusion. Remodeling is typically complete by 1 year[8].

BONE GRAFT SUBSTITUTES FOR SPINE FUSION

Demineralized bone matrix

In 1965, Urist[13] isolated bone morphogenetic pro-

teins (BMP) from extracts of demineralized bone. demineralized bone matrix (DBM) is an allograft material devoid of mineral phase, leaving behind the organic phase comprising of an osteoconductive composite matrix of collagen and non-collagenous proteins. DBM is produced by acid extraction processing of allograft bone. This results in loss of the majority of the mineralized element. The remaining product contains collagen-I, non-collagenous proteins, and growth factors. DBM possess osteoconductivity and osteoinductivity, but lacks structural integrity. BMPs constitute the osteoinductive capacity of DBM. In rat spinal fusion models[14-16], various commercially available DBM have demonstrated variable potential to stimulate bone regeneration. DBM is available in multiple forms, including putty, gel, flexible sheets, or mixed with cortical chips. DBM with varying BMP content are available from the following manufacturers: Grafton (Osteotech, New Jersey), musculoskeletal transplant foundation (MTF) (Synthes, Pennsylvania), and AlloMatrix (Wright Medical, Tennessee). Peterson *et al*[15] found differing fusion rates among each product in an animal model. Using ELISA, Bae *et al*[17] showed the high variability in BMP-2, -7, and -4 content among different manufacturers of DBM, and different batches from the same manufacturer.

DBM has been widely studied in rabbits and primates[18,19], and clinical studies have supported DBM use in posterolateral spinal fusion[20,21]. Girardi *et al*[20] compared the efficacy of Grafton DBM gel composites and iliac crest autografts in posterolateral spinal fusion. Results of the study demonstrated that Grafton DBM gel composite extends a smaller autograft than that used in spinal fusion, but results using a larger autograft were uneventful. A comparable study by Vaccaro *et al*[22] demonstrated that a DBM putty as well as aspirated bone marrow composite achieved similar posterolateral spinal fusion as that of an iliac crest autograft.

Bone graft extenders may provide promise in spine fusion for scoliosis due to the need for many bone grafts in the surgical repair process. Price *et al*[23] determined that a DBM and bone marrow composite performed similar to iliac crest autograft when assessing posterolateral spine fusion for scoliosis cases.

DBM for use in anterior spinal fusion has only limitedly been explored and is currently not recommended in clinical practice. Although research has demonstrated the efficacy of DBM when supplemented with titanium mesh[24], results of DBM composites for anterior spinal fusion have also shown a higher rate of graft collapse and pseudarthrosis when compared to autograft[25].

Ceramic-based substitutes

During the 1990s, it was discovered that marine invertebrate corals shared a strikingly similar microscopic porous structure with bone. Chiroff *et al*[26] proposed the use of these corals as bone graft substitute. Ceramics were named after these corals and were composed of calcium sulfate [hydroxyapatite (HA) and tricalcium phosphate], bovine collagen, natural coral, calcium carbonate, or a combination of these. Ceramic scaffolds are osteoconductive, biodegradable and pose virtually no risk of infection or donor site morbidity. Additionally, ceramics are nontoxic and nonimmunogenic, they are easily sterilized, and they can be fashioned to many different sizes and shapes. The disadvantages of ceramics are that they possess limited shear and compressive strength.

Ceramics are neither osteogenic nor osteoinductive. Their pore size (100-500 mm) is critical for cell migration and nutrient/waste exchange. This allows for the fibrovascular ingrowth of osteoid matrix. Biologically, mineralization of osteoid proceeds over the scaffold in intramembranous ossification and is remodeled by means of multinucleated giant cell-like cells[27].

Hydroxyapatite, or tricalcium phosphate, or some combination of these materials is the most ordinarily used ceramic scaffolds. However, in the last decade, research into synthetic material composites as bone graft substitutes has increased due to the ability to manipulate composite properties[28,29]. There have been several animal studies to confirm osteoconductivity of ceramics but there is paucity of studies in clinical setting[30].

Ceramic scaffolds are currently used clinically as bone graft extender for posterolateral fusion of spine. Several studies confirmed the effectiveness of ceramics as bone graft extenders[31,32]. However, in a prospective randomized study by Korovessis *et al*[33], iliac crest autograft outperformed coralline HA supplemented with bone and bone marrow in posterolateral spinal fusion.

Ceramic scaffolds have also shown to be effective in surgical repair of scoliosis. Ransford *et al*[34] conducted a study in which a porous ceramic scaffold was used for posterolateral spinal fusion in the treatment of scoliosis. Muschik *et al*[35] used a tricalcium phosphate ceramic scaffold for posterior spinal fusion in the treatment of scoliosis. Both composites demonstrated efficacy for use as bone graft extenders in posterolateral spinal fusion[34,35]. Thalgott *et al*[36] proposed the use of a coralline hydroxyapatite ceramic scaffold for anterior interbody fusion, however the ceramic was unable to withstand natural forces without additional reinforcement.

Other synthetic forms of ceramic are injectable (used in vertebroplasty) and noninjectable Tri Calcium Phosphate. Noninjectable tri calcium phosphate was shown to have good radiographic fusion in both single and double level lumbar fusion when mixed with local laminar autografts[37].

DBM and ceramic scaffolds show promise for application in posterolateral spinal fusion. However, the use of other osteoinductive, osteoconductive, and osteogenic agents may provide additional promise.

BMP

BMP are members of the transforming growth factor

beta (TGF-β) family[38-41]. Binding of BMP to its receptors located on osteogenic progenitor cell surface leads to an intracellular cascade triggering endochondral ossification. BMP consists of 0.1% (w/w) of all bone proteins. These proteins are available only after the bone matrix has undergone demineralization. A massive amount of bone is required to extract even a small amount of BMP, thereby making it expensive[42,43]. Advances in technologies such as molecular sequencing and cloning, have made it possible to produce large quantities of recombinant proteins such as BMP.

Recombinant BMP-2 (rhBMP-2) along with recombinant BMP-7 (osteogenic protein-1, OP-1) are clinically used and studied. rhBMP are soluble, quickly diffuse from the fusion site, and are inactivated when used unaided. Because of these properties, rhBMP must be incorporated with a carrier matrix that releases rhBMP intermittently.

Several animal studies have showed the ability of rhBMP-2 and OP-1 in anterior and posterolateral spinal fusion. Results of these studies demonstrate prompt, controlled healing[44-46].

A study by Boden *et al*[47] assessed fusion rates for rhBMP-2 ceramic composites with and without instrumentation, and autografts with instrumentation. The results demonstrated fusion rates of 100% for rhBMP-2 ceramic composites without instrumentation, greater than that observed for autografts with instrumentation (40%)[47]. Another study by Dimar *et al*[48] compared a similar rhBMP-2 bovine collagen and tricalcium/hydroxyapatite composite to iliac crest autografts for single-level posterolateral spinal fusions. The rhBMP-2 bovine collagen and tricalcium/hydroxyapatite composite demonstrated greater fusion rate than that of the iliac crest autograft. Boden *et al*[49] also described the use of rhBMP-2 collagen composites inside lumbar interbody fusion cages. They stated that rhBMP-2 collagen composites achieved greater fusion than an autograft control. Additionally, multiple prospective studies showed promising results for rhBMP-2 supplemented composites for anterior lumbar interbody fusion[50-53].

Another retrospective study by McClellan *et al*[54] reported greater rate of bone resorption for the rhBMP-2 group and hypothesized that poor fusion rates are due to resorption preceding vertebral interbody fusion. Likewise, a study by Pradhan *et al*[55] reported similar results, identifying that patients receiving femoral ring allografts with rhBMP-2 experienced non-union greater than patients receiving femoral ring allografts with iliac bone autografts.

For anterior cervical spinal fusion, a study by Baskin *et al*[56] demonstrated a 100% fusion rate for rhBMP-2 collagen composites with a fibular allograft, and neck disability and arm pain scores were superior to that of autograft control. In distinction, side-effects and impediments of using high doses of rhBMP-2 are plentiful such as high rates of hematomas and edema[57,58].

High spine fusion rates were revealed in another studies performed using other recombinant BMP for non-instrumented posterolateral spinal fusions[59,60]. A study by Vaccaro *et al*[61-63] showed successful spinal fusion with OP-1 putty, when no iliac crest autograft was present. Additionally, fusion rates were equivalent to iliac crest autograft at a 4-year follow-up thus supporting usage of OP-1. In instrumented posterolateral lumbar fusion, a prospective study by Kanayama *et al*[64] demonstrated that OP-1 induced viable bone formation, but the fusion was inferior to the autograft HA-tricalcium phosphate control.

Autologous platelet concentrate

Degranulation of platelets and release of growth factors initiates fracture healing. Growth factors, such as platelet derived growth factor and TGF-β enhance bone healing by promoting mesenchymal stem cell and osteoblast proliferation[65,66]. Autologous growth factor concentrate (AGF) is prepared from the ultra-concentration of platelets. It has been reported that AGF may enhance new bone formation in lumbar spine fusion[67].

Weiner *et al*[68] performed a retrospective study that compared autograft with autograft plus AGF in a posterolateral spinal fusion. The authors reported that autograft plus AGF did not improve fusion rate. Additionally, a prospective study by Hee *et al*[69] demonstrated that AGF in TLIF procedures did not improve fusion rates. Furthermore, Carreon *et al*[70] demonstrated that platelet gel, when added to autograft, failed to enhance fusion rate in posterolateral fusion superior to that of autograft control.

The self-renewal potential and multipotency of MSC have led to a great deal of interest in clinical arena. Bone marrow-derived mesenchymal stem cells (BMSC) have presented efficacy for fusion of spine. A study by Caplan *et al*[71], who evaluated BMSC for posterolateral lumbar transverse process fusion in a rabbit model, found that BMSC exhibited results comparable to that of autograft. Another study by Wang *et al*[72] involving seeding of autologous BMSC on calcium phosphate ceramic composite in a rhesus monkey model showed that BMSC seeded ceramic scaffolds enhanced anterior interbody spinal fusion.

Tissue engineered scaffolds for spine fusion

Tissue engineering is currently an exciting field showing great promise and applicability. Tissue engineered scaffolds incorporate a biomaterial scaffold and an appropriate cell type. A biomaterial must be biocompatible for a specific cell type, and possess physical and chemical properties comparable to native tissue. Studies have yet to identify a tissue engineered scaffold for spine fusion, but preliminary results are promising.

Synthetic polymers are highly applicable biomaterials due to highly porosity, a biocompatible profile, and a high cell seeding capacity. Many synthetic polymers have already been applied to other areas of tissue

engineering, and those materials that exhibit attractive osteogenic properties must be studied for spine fusion. In a study by Yong *et al*[73], a polycaprolactone scaffold with recombinant hBMP-2 exhibited higher fusion grades than an autograft control in a sheep model. These findings are promising, but more synthetic polymers must be studied in order to optimize fusion.

Hydrogels also present tremendous promise in the arena of tissue engineering. Hydrogels consist of highly hydrated polymers with varying mechanical and degradation properties. Hydrogels may operate by releasing nutrients into the environment or by bridging the gap between a nonunion to stimulate fusion. A study by Okamoto *et al*[74] revealed that there were no significant osteogenic changes in a rat model of posterolateral fusion between an autograft and a gelatin hydrogel supplemented with tricalcium phosphate and growth factors. Although this field is just starting to grow, the ability for controlled release of growth factors during spine fusion makes hydrogels an attractive scaffold for spine fusion.

Gene therapy

Gene therapy was formerly used in the treatment of hereditary disorders. Recent research has focused more on gene delivery and sustained release to biologically active target gene proteins. In spine fusion, genes encoding for osteoinductive and osteogenic factors can be targeted. Cells then release target protein into the extracellular environment to maximize the osteoinductive and osteogenic properties of these growth factors.

Gene therapy has many potential clinical benefits: it is relatively cost effective, it does not require culturing of autogenous cells, and the transduction technique is relatively simple. The major disadvantage associated with gene therapy is that it is difficult to assess transduction *in vivo*.

Gene therapy has proven successful *in vivo* in an animal model for spine fusion. Alden *et al*[75] injected *BMP-2* gene into the paraspinal region of nude rats and observed endochondral bone formation at 12-wk post-injection. In a similar study, Helm *et al*[76] injected *BMP-9* gene into the paraspinal muscles of nude rats. Bone formation was observed at the injection site 16 wk post-injection. These studies demonstrate that gene therapy shows promise in the practice of spinal fusion.

Gene therapy can also be approached using an *ex vivo* technique. The *ex vivo* technique requires autogenous target cells to be harvested from a donor site. The harvested cells are then expanded in culture, transduced, and then implanted back into the patient. The advantages of *ex vivo* technique are that cell type can easily be selected and that cultured cells can be expanded to adequate number. The major disadvantages of this technique are that an extra harvesting step is required and that time and cost is increased. In spinal fusion, MSC can be used as a vehicle for *ex vivo* gene therapy because of the osteogenic and osteoinduction properties they express.

For posterior spinal fusion, Boden *et al*[77] supplemented MSC with LIM mineralization protein (LMP-1) using *ex vivo* technique and reported successful spinal fusion. A similar study by Viggeswarapu *et al*[78] reported successful posterolateral spinal fusion in a rabbit model using BMSC with LMP-1 (Ad-LMP-1). Wang *et al*[79] also reported successful *ex vivo* gene therapy for posterolateral spinal fusion in a Lewis rat model using BMSC with Ad-BMP-2. Another study by Dumont *et al*[80] injected human MSC with Ad-BMP-9 into the paraspinal muscles of nude rats and demonstrated bone formation at the injection site 8 wk post-injection. These studies demonstrate the promise of *ex vivo* technique for spinal fusion.

Multiple additional studies have sought to improve gene therapy efficacy. Zhu *et al*[81] assessed the *in-vitro* capacity of combined Ad-BMP-2 and Ad-BMP-7 in posterolateral spinal fusion. The authors concluded that osteogenic activity was greater for combined Ad-BMP-2 and Ad-BMP-7 than for each BMP alone.

Adenoviruses are the most common viral delivery vehicles for bone healing due to its high transfection capacity and its ability to produce large quantities of cytokines. However, there are limitations associated with using adenoviral vectors. Protein production is largely limited due to the vectors inability to integrate into the host's genome[82]. This is most likely due to the episomal nature of the adenoviral DNA, which makes the DNA more susceptible to nuclease degeneration. Adenoviral vectors also may stimulate the host immune response by directly producing proteins[83]. The immune system of the host may then destroy the transduced cell, rendering the cell clinically useless. Various viral vectors, including adeno-associated viral vector and lenti-viral vector, have been recently studied in order to compensate the issues associated with adenoviral vectors[84,85].

Though viral based gene therapy shows promise, major concerns remain regarding the safety of viral vectors for use in the clinical setting. It is important that viral vectors are further studied and long-term effects are elucidated before viral vectors are used in clinical practice.

CONCLUSION

Several highly advanced bone-graft substitutes have been researched for application in spinal fusion and researchers are still probing for better alternatives. There seems to be strong evidence that osteoinductive proteins, such as rhBMP-2 and OP-1, can be used as bone enhancers for posterior spine fusion. Research also supports the use of all other presented alternatives as bone graft extenders. New innovational technologies, such as MSC, gene therapy, and tissue engineering, show tremendous promise in animal models. Future studies must further evaluate the clinical relevance and efficacy of these emerging fields.

REFERENCES

1 **Giannoudis PV**, Dinopoulos H, Tsiridis E. Bone substitutes: an update. *Injury* 2005; **36** Suppl 3: S20-S27 [PMID: 16188545 DOI: 10.1016/j.injury.2005.07.029]

2 **Boden SD**. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. *Spine* (Phila Pa 1976) 2002; **27**: S26-S31 [PMID: 12205416]

3 **Fernyhough JC**, Schimandle JJ, Weigel MC, Edwards CC, Levine AM. Chronic donor site pain complicating bone graft harvesting from the posterior iliac crest for spinal fusion. *Spine* (Phila Pa 1976) 1992; **17**: 1474-1480 [PMID: 1471005 DOI: 10.1097/00007632-199212000-00006]

4 **Russell JL**, Block JE. Surgical harvesting of bone graft from the ilium: point of view. *Med Hypotheses* 2000; **55**: 474-479 [PMID: 11090293 DOI: 10.1054/mehy.2000.1095]

5 **Zdeblick TA**. A prospective, randomized study of lumbar fusion. Preliminary results. *Spine* (Phila Pa 1976) 1993; **18**: 983-991 [PMID: 8367786 DOI: 10.1097/00007632-199306150-00006]

6 **Summers BN**, Eisenstein SM. Donor site pain from the ilium. A complication of lumbar spine fusion. *J Bone Joint Surg Br* 1989; **71**: 677-680 [PMID: 2768321]

7 **Silber JS**, Anderson DG, Daffner SD, Brislin BT, Leland JM, Hilibrand AS, Vaccaro AR, Albert TJ. Donor site morbidity after anterior iliac crest bone harvest for single-level anterior cervical discectomy and fusion. *Spine* (Phila Pa 1976) 2003; **28**: 134-139 [PMID: 12544929 DOI: 10.1097/00007632-200301150-00008]

8 **Malloy KM**, Hilibrand AS. Autograft versus allograft in degenerative cervical disease. *Clin Orthop Relat Res* 2002; : 27-38 [PMID: 11795743 DOI: 10.1097/00003086-200201000-00004]

9 **Ehrler DM**, Vaccaro AR. The use of allograft bone in lumbar spine surgery. *Clin Orthop Relat Res* 2000; **(371)**: 38-45 [PMID: 10693548 DOI: 10.1097/00003086-200002000-00005]

10 **Brodsky AE**, Kovalsky ES, Khalil MA. Correlation of radiologic assessment of lumbar spine fusions with surgical exploration. *Spine* (Phila Pa 1976) 1991; **16**: S261-S265 [PMID: 1862422 DOI: 10.1097/00007632-199106001-00017]

11 **Schimandle JH**, Boden SD. Spine update. The use of animal models to study spinal fusion. *Spine* (Phila Pa 1976) 1994; **19**: 1998-2006 [PMID: 7997936 DOI: 10.1097/00007632-199409000-00023]

12 **Dahners LE**, Mullis BH. Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft-tissue healing. *J Am Acad Orthop Surg* 2004; **12**: 139-143 [PMID: 15161166]

13 **Urist MR**. Bone: formation by autoinduction. *Science* 1965; **150**: 893-899 [PMID: 5319761 DOI: 10.1126/science.150.3698.893]

14 **Lee YP**, Jo M, Luna M, Chien B, Lieberman JR, Wang JC. The efficacy of different commercially available demineralized bone matrix substances in an athymic rat model. *J Spinal Disord Tech* 2005; **18**: 439-444 [PMID: 16189457 DOI: 10.1097/01.bsd.0000175696.66049.f7]

15 **Peterson B**, Whang PG, Iglesias R, Wang JC, Lieberman JR. Osteoinductivity of commercially available demineralized bone matrix. Preparations in a spine fusion model. *J Bone Joint Surg Am* 2004; **86-A**: 2243-2250 [PMID: 15466734]

16 **Wang JC**, Alanay A, Mark D, Kanim LE, Campbell PA, Dawson EG, Lieberman JR. A comparison of commercially available demineralized bone matrix for spinal fusion. *Eur Spine J* 2007; **16**: 1233-1240 [PMID: 17205237 DOI: 10.1007/s00586-006-0282-x]

17 **Bae HW**, Zhao L, Kanim LE, Wong P, Delamarter RB, Dawson EG. Intervariability and intravariability of bone morphogenetic proteins in commercially available demineralized bone matrix products. *Spine* (Phila Pa 1976) 2006; **31**: 1299-1306; discussion 1307-1308 [PMID: 16721289 DOI: 10.1097/01.brs.0000218581.92992.b7]

18 **Choi Y**, Oldenburg FP, Sage L, Johnstone B, Yoo JU. A bridging demineralized bone implant facilitates posterolateral lumbar fusion in New Zealand white rabbits. *Spine* (Phila Pa 1976) 2007; **32**: 36-41 [PMID: 17202890 DOI: 10.1097/01.brs.0000250982.41666.55]

19 **Louis-Ugbo J**, Murakami H, Kim HS, Minamide A, Boden SD. Evidence of osteoinduction by Grafton demineralized bone matrix in nonhuman primate spinal fusion. *Spine* (Phila Pa 1976) 2004; **29**: 360-366; discussion Z1 [PMID: 15094531]

20 **Girardi FP**, Cammisa FP. The effect of bone graft extenders to enhance the performance of iliac crest bone grafts in instrumented lumbar spine fusion. *Orthopedics* 2003; **26**: s545-s548 [PMID: 12755222]

21 **Sassard WR**, Eidman DK, Gray PM, Block JE, Russo R, Russell JL, Taboada EM. Augmenting local bone with Grafton demineralized bone matrix for posterolateral lumbar spine fusion: avoiding second site autologous bone harvest. *Orthopedics* 2000; **23**: 1059-1064; discussion 1064-1065 [PMID: 11045552]

22 **Vaccaro AR**, Stubbs HA, Block JE. Demineralized bone matrix composite grafting for posterolateral spinal fusion. *Orthopedics* 2007; **30**: 567-570 [PMID: 17672157]

23 **Price CT**, Connolly JF, Carantzas AC, Ilyas I. Comparison of bone grafts for posterior spinal fusion in adolescent idiopathic scoliosis. *Spine* (Phila Pa 1976) 2003; **28**: 793-798 [PMID: 12698123 DOI: 10.1097/00007632-200304150-00012]

24 **Thalgott JS**, Giuffre JM, Klezl Z, Timlin M. Anterior lumbar interbody fusion with titanium mesh cages, coralline hydroxyapatite, and demineralized bone matrix as part of a circumferential fusion. *Spine J* 2002; **2**: 63-69 [PMID: 14588290 DOI: 10.1016/S1529-9430(01)00155-3]

25 **An HS**, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study. *Spine* (Phila Pa 1976) 1995; **20**: 2211-2216 [PMID: 8545714 DOI: 10.1097/00007632-199510001-00006]

26 **Chiroff RT**, White EW, Weber KN, Roy DM. Tissue ingrowth of Replamineform implants. *J Biomed Mater Res* 1975; **9**: 29-45 [PMID: 1176509 DOI: 10.1002/jbm.820090407]

27 **McAndrew MP**, Gorman PW, Lange TA. Tricalcium phosphate as a bone graft substitute in trauma: preliminary report. *J Orthop Trauma* 1988; **2**: 333-339 [PMID: 3074162 DOI: 10.1097/00005131-198802040-00011]

28 **Bertoldi C**, Zaffe D, Consolo U. Polylactide/polyglycolide copolymer in bone defect healing in humans. *Biomaterials* 2008; **29**: 1817-1823 [PMID: 18234328 DOI: 10.1016/j.biomaterials.2007.12.034]

29 **Adhikari R**, Gunatillake PA, Griffiths I, Tatai L, Wickramaratna M, Houshyar S, Moore T, Mayadunne RT, Field J, McGee M, Carbone T. Biodegradable injectable polyurethanes: synthesis and evaluation for orthopaedic applications. *Biomaterials* 2008; **29**: 3762-3770 [PMID: 18632149 DOI: 10.1016/j.biomaterials.2008.06.021]

30 **Baramki HG**, Steffen T, Lander P, Chang M, Marchesi D. The efficacy of interconnected porous hydroxyapatite in achieving posterolateral lumbar fusion in sheep. *Spine* (Phila Pa 1976) 2000; **25**: 1053-1060 [PMID: 10788847 DOI: 10.1097/00007632-200005010-00003]

31 **Chen WJ**, Tsai TT, Chen LH, Niu CC, Lai PL, Fu TS, McCarthy K. The fusion rate of calcium sulfate with local autograft bone compared with autologous iliac bone graft for instrumented short-segment spinal fusion. *Spine* (Phila Pa 1976) 2005; **30**: 2293-2297 [PMID: 16227892 DOI: 10.1097/01.brs.0000182087.35335.05]

32 **Xie Y**, Chopin D, Morin C, Hardouin P, Zhu Z, Tang J, Lu J. Evaluation of the osteogenesis and biodegradation of porous biphasic ceramic in the human spine. *Biomaterials* 2006; **27**: 2761-2767 [PMID: 16426679 DOI: 10.1016/j.biomaterials.2005.12.011]

33 **Korovessis P**, Repanti M, Koureas G. Does coralline hydroxyapatite conduct fusion in instrumented posterior spine fusion? *Stud Health Technol Inform* 2002; **91**: 109-113 [PMID: 15457705]

34 **Ransford AO**, Morley T, Edgar MA, Webb P, Passuti N, Chopin D, Morin C, Michel F, Garin C, Pries D. Synthetic porous ceramic compared with autograft in scoliosis surgery. A prospective, randomized study of 341 patients. *J Bone Joint Surg Br* 1998; **80**: 13-18 [PMID: 9460945 DOI: 10.1302/0301-620X.80B1.7276]

35 **Muschik M**, Ludwig R, Halbhübner S, Bursche K, Stoll T. Beta-tricalcium phosphate as a bone substitute for dorsal spinal fusion in adolescent idiopathic scoliosis: preliminary results of a prospective clinical study. *Eur Spine J* 2001; **10** Suppl 2: S178-S184 [PMID: 11716016 DOI: 10.1007/s005860100271]

36 **Thalgott JS**, Klezl Z, Timlin M, Giuffre JM. Anterior lumbar interbody fusion with processed sea coral (coralline hydroxyapatite) as part of a circumferential fusion. *Spine* (Phila Pa 1976) 2002; **27**: E518-E525; discussion E526-E527 [PMID: 12486360]

37 **Epstein NE**. A preliminary study of the efficacy of Beta Tricalcium Phosphate as a bone expander for instrumented posterolateral lumbar fusions. *J Spinal Disord Tech* 2006; **19**: 424-429 [PMID: 16891978 DOI: 10.1097/00024720-200608000-00009]

38 **Wozney JM**. Overview of bone morphogenetic proteins. *Spine* (Phila Pa 1976) 2002; **27**: S2-S8 [PMID: 12205411 DOI: 10.1097/00007632-200208151-00002]

39 **Mehler MF**, Mabie PC, Zhang D, Kessler JA. Bone morphogenetic proteins in the nervous system. *Trends Neurosci* 1997; **20**: 309-317 [PMID: 9223224 DOI: 10.1016/S0166-2236(96)01046-6]

40 **Heldin CH**, Miyazono K, ten Dijke P. TGF-beta signalling from cell membrane to nucleus through SMAD proteins. *Nature* 1997; **390**: 465-471 [PMID: 9393997 DOI: 10.1038/37284]

41 **Ebara S**, Nakayama K. Mechanism for the action of bone morphogenetic proteins and regulation of their activity. *Spine* (Phila Pa 1976) 2002; **27**: S10-S15 [PMID: 12205413 DOI: 10.1097/00007632-200208151-00004]

42 **Urist MR**, Silverman BF, Büring K, Dubuc FL, Rosenberg JM. The bone induction principle. *Clin Orthop Relat Res* 1967; **53**: 243-283 [PMID: 4870495 DOI: 10.1097/00003086-196707000-00026]

43 **Urist MR**, Strates BS. Bone formation in implants of partially and wholly demineralized bone matrix. Including observations on acetone-fixed intra and extracellular proteins. *Clin Orthop Relat Res* 1970; **71**: 271-278 [PMID: 5433388 DOI: 10.1097/00003086-197007000-00031]

44 **Blattert TR**, Delling G, Dalal PS, Toth CA, Balling H, Weckbach A. Successful transpedicular lumbar interbody fusion by means of a composite of osteogenic protein-1 (rhBMP-7) and hydroxyapatite carrier: a comparison with autograft and hydroxyapatite in the sheep spine. *Spine* (Phila Pa 1976) 2002; **27**: 2697-2705 [PMID: 12461396 DOI: 10.1097/00007632-200212010-00009]

45 **Boden SD**, Martin GJ, Horton WC, Truss TL, Sandhu HS. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. *J Spinal Disord* 1998; **11**: 95-101 [PMID: 9588464 DOI: 10.1097/00002517-199804000-00001]

46 **Boden SD**, Martin GJ, Morone MA, Ugbo JL, Moskovitz PA. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. *Spine* (Phila Pa 1976) 1999; **24**: 1179-1185 [PMID: 10382242 DOI: 10.1097/00007632-199906150-00002]

47 **Boden SD**, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. *Spine* (Phila Pa 1976) 2002; **27**: 2662-2673 [PMID: 12461392 DOI: 10.1097/00007632-200212010-00005]

48 **Dimar JR**, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine* (Phila Pa 1976) 2006; **31**: 2534-2559; discussion 2540 [PMID: 17047540 DOI: 10.1097/01.brs.0000240715.78657.81]

49 **Boden SD**, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine* (Phila Pa 1976) 2000; **25**: 376-381 [PMID: 10703113 DOI: 10.1097/00007632-200002010-00020]

50 **Burkus JK**, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* (Phila Pa 1976) 2003; **28**: 372-377 [PMID: 12590213 DOI: 10.1097/00007632-200302150-00012]

51 **Burkus JK**, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002; **15**: 337-349 [PMID: 12394656 DOI: 10.1097/00024720-200210000-00001]

52 **Burkus JK**, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine* (Phila Pa 1976) 2002; **27**: 2396-2408 [PMID: 12438990 DOI: 10.1097/00007632-200211010-00015]

53 **Slosar PJ**, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. *Spine J* 2007; **7**: 301-307 [PMID: 17482113 DOI: 10.1016/j.spinee.2006.10.015]

54 **McClellan JW**, Mulconrey DS, Forbes RJ, Fullmer N. Vertebral bone resorption after transforaminal lumbar interbody fusion with bone morphogenetic protein (rhBMP-2). *J Spinal Disord Tech* 2006; **19**: 483-486 [PMID: 17021411 DOI: 10.1097/01.bsd.0000211231.83716.4b]

55 **Pradhan BB**, Bae HW, Dawson EG, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. *Spine* (Phila Pa 1976) 2006; **31**: E277-E284 [PMID: 16648733 DOI: 10.1097/01.brs.0000216442.12092.01]

56 **Baskin DS**, Ryan P, Sonntag V, Westmark R, Widmayer MA. A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. *Spine* (Phila Pa 1976) 2003; **28**: 1219-1224; discussion 1225 [PMID: 12811263 DOI: 10.1097/01.BRS.0000065486.22141.CA]

57 **Shields LB**, Raque GH, Glassman SD, Campbell M, Vitaz T, Harpring J, Shields CB. Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion. *Spine* (Phila Pa 1976) 2006; **31**: 542-547 [PMID: 16508549 DOI: 10.1097/01.brs.0000201424.27509.72]

58 **Vaidya R**, Carp J, Sethi A, Bartol S, Craig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. *Eur Spine J* 2007; **16**: 1257-1265 [PMID: 17387522 DOI: 10.1007/s00586-007-0351-9]

59 **Bomback DA**, Grauer JN, Lugo R, Troiano N, Patel TCh, Friedlaender GE. Comparison of posterolateral lumbar fusion rates of Grafton Putty and OP-1 Putty in an athymic rat model. *Spine* (Phila Pa 1976) 2004; **29**: 1612-1617 [PMID: 15284503 DOI: 10.1097/01.BRS.0000132512.53305.A1]

60 **Grauer JN**, Patel TC, Erulkar JS, Troiano NW, Panjabi MM, Friedlaender GE. 2000 Young Investigator Research Award winner. Evaluation of OP-1 as a graft substitute for intertransverse process lumbar fusion. *Spine* (Phila Pa 1976) 2001; **26**: 127-133 [PMID: 11154530 DOI: 10.1097/00007632-200101150-00004]

61 **Vaccaro AR**, Whang PG, Patel T, Phillips FM, Anderson DG, Albert TJ, Hilibrand AS, Brower RS, Kurd MF, Appannagari A, Patel M, Fischgrund JS. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. *Spine J* 2008; **8**: 457-465 [PMID: 17588821 DOI: 10.1016/j.spinee.2007.03.012]

62 **Vaccaro AR**, Anderson DG, Patel T, Fischgrund J, Truumees E, Herkowitz HN, Phillips F, Hilibrand A, Albert TJ, Wetzel T, McCulloch JA. Comparison of OP-1 Putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimum 2-year follow-up pilot study. *Spine* (Phila Pa 1976) 2005; **30**: 2709-2716 [PMID: 16371892 DOI: 10.1097/01.brs.0000190812.08447.ba]

63 **Vaccaro AR**, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz HN, Phillips F, Hilibrand A, Albert TJ, Wetzel T, McCulloch JA. A pilot study evaluating the safety and efficacy of OP-1 Putty (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis for degenerative spondylolisthesis. *Spine* (Phila Pa 1976) 2004; **29**: 1885-1892 [PMID: 15534410 DOI: 10.1097/01.brs.0000137062.79201.98]

64 **Kanayama M**, Hashimoto T, Shigenobu K, Yamane S, Bauer TW, Togawa D. A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and

histologic assessment. *Spine* (Phila Pa 1976) 2006; **31**: 1067-1074 [PMID: 16648739 DOI: 10.1097/01.brs.0000216444.01888.21]
65 **Ferrara N**, Houck K, Jakeman L, Leung DW. Molecular and biological properties of the vascular endothelial growth factor family of proteins. *Endocr Rev* 1992; **13**: 18-32 [PMID: 1372863 DOI: 10.1210/edrv-13-1-18]
66 **Lind M**, Deleuran B, Thestrup-Pedersen K, Søballe K, Eriksen EF, Bünger C. Chemotaxis of human osteoblasts. Effects of osteotropic growth factors. *APMIS* 1995; **103**: 140-146 [PMID: 7748538 DOI: 10.1111/j.1699-0463.1995.tb01089.x]
67 **Lowery GL**, Kulkarni S, Pennisi AE. Use of autologous growth factors in lumbar spinal fusion. *Bone* 1999; **25**: 47S-50S [PMID: 10458274 DOI: 10.1016/S8756-3282(99)00132-5]
68 **Weiner BK**, Walker M. Efficacy of autologous growth factors in lumbar intertransverse fusions. *Spine* (Phila Pa 1976) 2003; **28**: 1968-1970; discussion 1971 [PMID: 12973143]
69 **Hee HT**, Majd ME, Holt RT, Myers L. Do autologous growth factors enhance transforaminal lumbar interbody fusion? *Eur Spine J* 2003; **12**: 400-407 [PMID: 12761669 DOI: 10.1007/s00586-003-0548-5]
70 **Carreon LY**, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. *Spine* (Phila Pa 1976) 2005; **30**: E243-E246; discussion E247 [PMID: 15864142]
71 **Caplan AI**, Bruder SP. Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. *Trends Mol Med* 2001; **7**: 259-264 [PMID: 11378515 DOI: 10.1016/S1471-4914(01)02016-0]
72 **Wang T**, Dang G, Guo Z, Yang M. Evaluation of autologous bone marrow mesenchymal stem cell-calcium phosphate ceramic composite for lumbar fusion in rhesus monkey interbody fusion model. *Tissue Eng* 2005; **11**: 1159-1167 [PMID: 16144452 DOI: 10.1089/ten.2005.11.1159]
73 **Yong MR**, Saifzadeh S, Askin GN, Labrom RD, Hutmacher DW, Adam CJ. Establishment and characterization of an open mini-thoracotomy surgical approach to an ovine thoracic spine fusion model. *Tissue Eng Part C Methods* 2014; **20**: 19-27 [PMID: 23600860 DOI: 10.1089/ten.TEC.2012.0746]
74 **Okamoto S**, Ikeda T, Sawamura K, Nagae M, Hase H, Mikami Y, Tabata Y, Matsuda K, Kawata M, Kubo T. Positive effect on bone fusion by the combination of platelet-rich plasma and a gelatin β-tricalcium phosphate sponge: a study using a posterolateral fusion model of lumbar vertebrae in rats. *Tissue Eng Part A* 2012; **18**: 157-166 [PMID: 21819268 DOI: 10.1089/ten.TEA.2011.0283]
75 **Alden TD**, Pittman DD, Beres EJ, Hankins GR, Kallmes DF, Wisotsky BM, Kerns KM, Helm GA. Percutaneous spinal fusion using bone morphogenetic protein-2 gene therapy. *J Neurosurg* 1999; **90**: 109-114 [PMID: 10413134 DOI: 10.3171/spi.1999.90.1.0109]
76 **Helm GA**, Alden TD, Beres EJ, Hudson SB, Das S, Engh JA, Pittman DD, Kerns KM, Kallmes DF. Use of bone morphogenetic protein-9 gene therapy to induce spinal arthrodesis in the rodent. *J Neurosurg* 2000; **92**: 191-196 [PMID: 10763690 DOI: 10.3171/spi.2000.92.2.0191]
77 **Boden SD**, Titus L, Hair G, Liu Y, Viggeswarapu M, Nanes MS, Baranowski C. Lumbar spine fusion by local gene therapy with a cDNA encoding a novel osteoinductive protein (LMP-1). *Spine* (Phila Pa 1976) 1998; **23**: 2486-2492 [PMID: 9854747 DOI: 10.1097/00007632-199812010-00003]
78 **Viggeswarapu M**, Boden SD, Liu Y, Hair GA, Louis-Ugbo J, Murakami H, Kim HS, Mayr MT, Hutton WC, Titus L. Adenoviral delivery of LIM mineralization protein-1 induces new-bone formation in vitro and in vivo. *J Bone Joint Surg Am* 2001; **83-A**: 364-376 [PMID: 11263640]
79 **Wang JC**, Kanim LE, Yoo S, Campbell PA, Berk AJ, Lieberman JR. Effect of regional gene therapy with bone morphogenetic protein-2-producing bone marrow cells on spinal fusion in rats. *J Bone Joint Surg Am* 2003; **85-A**: 905-911 [PMID: 12728043]
80 **Dumont RJ**, Dayoub H, Li JZ, Dumont AS, Kallmes DF, Hankins GR, Helm GA. Ex vivo bone morphogenetic protein-9 gene therapy using human mesenchymal stem cells induces spinal fusion in rodents. *Neurosurgery* 2002; **51**: 1239-1244; discussion 1244-1245 [PMID: 12383369 DOI: 10.1097/00006123-200211000-00020]
81 **Zhu W**, Rawlins BA, Boachie-Adjei O, Myers ER, Arimizu J, Choi E, Lieberman JR, Crystal RG, Hidaka C. Combined bone morphogenetic protein-2 and -7 gene transfer enhances osteoblastic differentiation and spine fusion in a rodent model. *J Bone Miner Res* 2004; **19**: 2021-2032 [PMID: 15537446 DOI: 10.1359/jbmr.040821]
82 **Feeley BT**, Conduah AH, Sugiyama O, Krenek L, Chen IS, Lieberman JR. In vivo molecular imaging of adenoviral versus lentiviral gene therapy in two bone formation models. *J Orthop Res* 2006; **24**: 1709-1721 [PMID: 16788987 DOI: 10.1002/jor.20229]
83 **Mack CA**, Song WR, Carpenter H, Wickham TJ, Kovesdi I, Harvey BG, Magovern CJ, Isom OW, Rosengart T, Falck-Pedersen E, Hackett NR, Crystal RG, Mastrangeli A. Circumvention of anti-adenovirus neutralizing immunity by administration of an adenoviral vector of an alternate serotype. *Hum Gene Ther* 1997; **8**: 99-109 [PMID: 8989999 DOI: 10.1089/hum.1997.8.1-99]
84 **Miyazaki M**, Sugiyama O, Tow B, Zou J, Morishita Y, Wei F, Napoli A, Sintuu C, Lieberman JR, Wang JC. The effects of lentiviral gene therapy with bone morphogenetic protein-2-producing bone marrow cells on spinal fusion in rats. *J Spinal Disord Tech* 2008; **21**: 372-379 [PMID: 18600149 DOI: 10.1097/BSD.0b013e31814cf51d]
85 **Sugiyama O**, An DS, Kung SP, Feeley BT, Gamradt S, Liu NQ, Chen IS, Lieberman JR. Lentivirus-mediated gene transfer induces long-term transgene expression of BMP-2 in vitro and new bone formation in vivo. *Mol Ther* 2005; **11**: 390-398 [PMID: 15727935 DOI: 10.1016/j.ymthe.2004.10.019]

P- Reviewer: Lykissas MG, Schoeffl V **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i6.457

World J Orthop 2015 July 18; 6(6): 457-461
ISSN 2218-5836 (online)

MINIREVIEWS

Use of Teriparatide to improve fracture healing: What is the evidence?

Satish Babu, Nemandra A Sandiford, Mark Vrahas

Satish Babu, Core Surgical Trainee, St. George's Hospital, London SW17 0QT, United Kingdom

Nemandra A Sandiford, Lower Limb and Tumor Reconstruction Fellow, University of British Columbia, Vancouver V5Z 1M9, British Columbia, Canada

Mark Vrahas, Orthopaedic Trauma Service, Massachusetts General Hospital, Boston, MA 02114, United States

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: We, the authors of this scientific paper, do hereby state that we have no conflicts of interest to declare.

Correspondence to: Nemandra A Sandiford, FRCS (Trauma and Orthopaedics), Lower Limb and Tumor Reconstruction Fellow, University of British Columbia, 2329 West Mall, Vancouver V5Z 1M9, British Columbia, Canada. nemsandiford@hotmail.com
Telephone: +1-208-3069032

Received: February 12, 2015
Peer-review started: February 12, 2015
First decision: April 10, 2015
Revised: May 2, 2015
Accepted: June 1, 2015
Article in press: June 2, 2015
Published online: July 18, 2015

Abstract

Teriparatide is a recombinant form of the biologically active component of Parathyroid hormone. It has been shown to increase bone mass and prevent fractures in osteoporotic bone. It is licensed by the Food and Drug Administration for the treatment of Osteoporosis. Over the last decade, a growing body of evidence has accumulated suggesting a role for Teriparatide in the management of fractures. Studies in both normal and delayed healing models have shown improvement in callus volume and mineralisation, bone mineral content, rate of successful union and strength at fracture sites. However most of these results have been derived from animal studies. The majority of this research on humans has comprised low level evidence, with few randomised controlled trials, many case reports and case series. Nevertheless, the results from these studies seem to support research from animal models. This has led to a growing number of clinicians using Teriparatide "off license" to treat fractures and non-unions in their patients. This review presents a critical appraisal of the current evidence supporting the use of Teriparatide for fracture healing, delayed unions and non unions and in the setting of osteoporotic fractures, the studies producing this evidence and their transferability to human beings.

Key words: Teriparatide; Fractures; Healing; Bone; Osteoporosis

Core tip: Teriparatide contains the biologically active component of Parathyroid Hormone. It is utilised in osteoporosis for its ability to increase bone mass and prevent fractures. Research suggests Teriparatide may improve callus volume, callus mineralisation, bone mineral content and successful union. However most research come from animal models. Human research, whilst supporting Teriparatide use, mostly comprises low level evidence such as case series. Currently many United States physicians use Teriparatide "off license" for fractures and non-unions. We suggest more, well designed, human randomised controlled trials are

required before Teriparatide can become a mainstream option in the conservative management of fractures and non-unions.

Babu S, Sandiford NA, Vrahas M. Use of Teriparatide to improve fracture healing: What is the evidence? *World J Orthop* 2015; 6(6): 457-461 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/457.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.457

INTRODUCTION

Parathyroid hormone (PTH) is a naturally occurring 84 amino acid polypeptide. Its function is to increase serum calcium levels in response to systemic hypocalcaemia. This effect is achieved by a promotion in osteoclast related bone resorption. In addition to this classical effect, PTH and its amino-terminal fragments have been shown to increase bone mass, increase bone strength and reduce bone loss[1,2].

Structure-function studies of PTH have suggested that the N-terminal fragment of the PTH molecule [encompassing amino acids 1-34 and called PTH(1-34)] is the principal framework responsible for the observed biological activity[3,4]. Teriparatide is a recombinant form of these 34 amino-terminal residues of human PTH. It has a molecular mass of 4117.8 daltons[5]. It is manufactured using a genetically modified strain of *Escherichia coli* and supplied as a solution for subcutaneous injection[5].

It was licensed for use by the FDA in the treatment of patients with Osteoporosis in 2002. This licences encompasses postmenopausal females, individuals with glucocorticoid-induced osteoporosis and men with hypogonadal or idiopathic osteoporosis at high risk of fracture.

The current recommended dose is 20 μg once daily and treatment is not recommended for a duration exceeding 2 years. Apart from this recognised application, there is a growing body of evidence suggesting its ability to accelerate fracture healing and heal nonunions. The purpose of this review is to summarise the current evidence for the use of Teriparatide for fracture healing, delayed unions and non unions and in the setting of osteoporotic fractures, the studies producing this evidence and their transferability to human beings.

ANIMAL MODELS OF NORMAL FRACTURE HEALING

Numerous studies using small animal models have demonstrated that PTH enhances fracture healing. In 1999, Andreassen *et al*[6] showed that PTH increased callus formation and ultimate load to failure for tibial fractures in adult rats. Intermittent administration of PTH(1-34) at 60 and 200 μg doses produced increases in callus volume of 42% and 72% respectively and increased ultimate load to failure by 132% and 175% respectively after 40 d. In the same year, Holzer *et al*[7] found histological evidence of increased callus area and improved bone strength after daily PTH(1-34) administration in rats.

In 2004, Andreassen *et al*[8] also found that intermittent PTH increased fracture strength and callus volume 8 wk after fracture in rats. The following year Komatsubara *et al*[9] showed, amongst other things, that intermittent Teriparatide at 30 μg/kg before and after osteotomy accelerated the fracture healing process in rats up to 12 wk after osteotomy. In 2010 Mognetti *et al*[10] noted that 40 μg/kg per day of Teriparatide stimulated callus mineralization until day 18 of bone healing and after 15 d of treatment the callus hardness approximated normal bone in closed tibial fracture models in mice. They also found that the formation of callus was accelerated.

The beneficial effect from PTH is not only limited to the periods during which treatment is given. Alkhiary *et al*[11] administered daily Teriparatide at 5 or 30 μg/kg doses to rats with fractures and compared this to controls. After 35 d both doses produced significant increases in bone mineral content, density and total osseous tissue volume. Analysis 49 d after discontinuing treatment in the 30 μg/kg group showed a sustained increase in bone mineral density and torsional strength when compared to controls. This implies a sustained anabolic effect throughout the remodelling phase of fracture-healing[11]. No change in osteoclast density was seen possibly suggesting that treatment enhanced bone formation but not resorption[11]. A sustained increase in mechanical strength and bone density was also observed by Andreassen *et al*[8].

Several authors have also suggested that PTH used in conjunction with other therapies may be beneficial in fracture healing. Gardner *et al*[12] showed a symbiotic relationship between PTH and mechanical loading in mice. They divided mice into 4 groups: (1) a control who received sham loading and vehicle injection; (2) a group which received daily loading; (3) one which received daily subcutaneous PTH injections (30 μg/kg per day); and (4) a group which received loading and PTH.

After 2 wk group 4 showed increased osteoblast and osteoclast activity and was the only group with a significantly larger callus mineral density and bone volume fraction. In contrast the PTH only group had more osteoid in the callus compared to controls (indicating increased early osteoblast activity) and a significantly higher bone mineral content and total bone volume compared to controls. The loading only group exhibited greater osteoclast activity.

A major criticism of the above studies is that they were all carried out in rodents. These animals and humans metabolise PTH differently and therefore legitimate questions have arisen about the transferability

of these results to human beings. Studies in animals genetically closer to humans have also been performed. Manabe *et al*[13] examined the effect of intermittent Teriparatide on cynomolgus monkeys who have an intracortical remodelling system similar to humans. They used the relatively low doses of 0.75 μg/kg and 7.50 μg/kg in their studies. They found a higher ultimate stress and elastic modulus in the femora of the group receiving 7.50 μg/kg. They also observed lower total area and percent bone area of the femur in PTH treated monkeys as well as a dose dependent decrease in callus porosity with PTH treatment[13]. These actions potentially accelerate fracture healing by restoring the mechanical properties of osteotomised femur.

Barnes *et al*[14] have recommended a cautious approach to the use of PTH preparations in human subjects. Dosages used in many animal studies exceed the recommended equivalent human dosage for treatment of an equivocal condition[14]. Current recommended dosages of between 20 and 40 μg/kg per day for humans are much lower than dosages used in animals[14]. Other authors have found conflicting results. In addition to the results obtained by Manabe *et al*[13], Nakajima's group have found higher bone mineral content, bone mineral density and ultimate load to failure in rat models on days 28 and 42 after fracture using 10 μg/kg doses of Teriparatide[15]. Increases in bone mineral density, bone mineral content and osseous tissue volume have also been reported with doses of 5 μg/kg[11].

ANIMAL MODELS OF DELAYED HEALING

Arguably the most useful clinical application of Teriparatide would be in those situations where sub-optimal fracture repair mechanisms are expected such as, smoking, diabetes, corticosteroid treatment, metabolic bone disease and states of relative oestrogen deficiency as well as patient with osteoporosis. Between 5% and 20% of the 7.9 million fractures that occur every year in the United States exhibit some degree of impaired fracture healing[16].

As our population ages, the effect of PTH on aging bone has become increasingly relevant. Andreassen *et al*[17] analysed the effect of intermittent doses of 200 μg/kg of Teriparatide on callus formation and bone strength in aged rats at 3 and 8 wk post fracture. At 21 d after fracture, those treated with Teriparatide exhibited an ultimate load to failure increase of 160%. After 56 d this increased to 270%. External callus volume increased by 208% and 135% after 21 and 56 d respectively. Bone mineral content increased by 190% after 3 wk and 388% after 8. This group noted differences in the healing mechanism of these older rats compared to their younger counterparts. They observed callus production to be slower in older rats when comparing young and old controls. The callus volume in the older group at 56 d was similar to the young controls at 20 d[17]. However when comparing PTH-treated animals both young and old rats had similar callus volumes at 20 and 21 d respectively. Callus volume remained unchanged from day 21 to 56 in old PTH-treated rats but this volume declined after 20 d in younger rats. These results suggest that PTH improves rate of callus formation and bone strength even in older bone.

Investigators examining the role of PTH in osteoporotic bone have commonly used ovariectomised animals to mimic menopause and relative oestrogen deficiency. In 2008 Nozaka *et al*[18] examined the effects of hPTH(1-34) in 4 groups of rats which received a sham operation and vehicle, sham and human PTH(1-34), bilateral ovariectomy and vehicle and bilateral ovariectomy and hPTH(1-34). Recombinant hPTH(1-34) was administered once a week at a dose of 100 μg/kg.

They assessed the effect of each of these regimens on osteotomy and non-osteotomy cancellous bone in the tibia. They observed that ovariectomy caused a significant decrease in cancellousbone volume compared with the sham group (33.2% decrease). PTH treatment significantly increased cancellous bone volume and osteoid surface in the sham group (81.5% and 75.4% respectively) and ovariectomised cohort (81.1% and 57.3%) compared with respective vehicle groups[18]. In the ovariectomised group PTH supressed bone resorption parameters, including eroded surface, osteoclast surface and osteoclast number compared with vehicle. PTH treatment was shown to significantly increase the percentage of union in both sham (45.6% increase) and ovariectomised (59.0% increase) groups compared with respective vehicle groups[18].

Histological analysis revealed that PTH treatment was associated with decreased adipocyte volume and number in the bone marrow of ovariectomised animals compared to controls. These findings suggested that intermittent PTH administration promoted osteoblastogenesis and decreased adipogenesis at the site of cancellous bone osteotomy resulting in increased bone union in normal and ovariectomised rats[18]. Similar results have also been reported by Kim and Jahng[19].

Improvements in rates of fracture healing have also been demonstrated in animals receiving corticosteroid therapy. Bostrom *et al*[20] examined the effect of the PTHrP analog RS-66271 and hPTHrP [(1-34)-NH_2] on fracture healing in the ulnae of steroid treated rabbits. Experimental group animals received a dose of 0.01 mg/kg of hPTHrP. After 6 wk, nine of the ten ulnae from the PTHrP treated rabbits achieved radiographic union compared to two in the control group[20]. In another arm of the study 100% of treatment group rabbits achieved union by 6 wk compared to 20% of controls after 10 wk. The ulnae of PTHrP treated rabbits showed greater radiographic intensity, larger callus dimensions and volume, greater stiffness (64%) and mechanical strength[20].

STUDIES IN HUMANS

The effects of Teriparatide on normal fracture healing,

delayed union and non unions in human subjects have also been examined. Aspenberg *et al*[21] examined the effect of placebo compared to Teriparatide administered in 20 and 40 μg doses given daily to a population of female patients with distal radius fractures[21]. These patients were all between 45 and 85 years of age and their fractures were being treated conservatively. This was a well designed level 1 study. They found that median time to the first radiographic evidence of healing was 9.1 wk in the placebo group compared to 7.4 and 8.8 wk in the groups treated with 20 μg and 40 μg of Teriparatide respectively. This was not statistically significant (P = 0.15).

There was no significant difference between the placebo and 40 μg groups (P = 0.523). Post hoc analysis demonstrated a significant difference between the placebo group and those patients treated with 20 μg daily. The authors advised interpreting this result with caution however.

Peichl *et al*[22] evaluated the effect of PTH 1-84 on pelvic fracture healing and functional outcome in postmenopausal women. Sixty five patients were divided into two groups; one control and one which received once daily 100 μg of PTH 1-84 starting within two days after admission to hospital. All individuals received calcium and vitamin D supplementation. The median time from fracture to the first sign of complete cortical bridging of the pelvic fracture (verified with CT scanning) was 7.8 wk for the treatment group compared with 12.6 wk for controls.

At the primary end point (8 wk after commencement of the study) all fractures in the treatment group (100%) and four fractures in the control group (9.1%) had healed. Significant improvements in functional outcome (assessed by VAS score) in the treatment group (7.6 at the start of the study to 3.2 at week 8) compared with controls (7.7 at origin to 6.5 at week 8). Statistically significant improvements in timed up and go test times were also noted in the treatment group. The authors of this study noted that although this molecule is not identical to Teriparatide, the time frame to healing that has been noted is similar to that observed in the treatment of patient with pelvic fracture nonunions with Teriparatide at the standard dosage[22].

DELAYED UNION

Bukata *et al*[23] reported on a series of 145 patients with fractures of the spine or other extremities that were treated with 20 μg of Teriparatide. Half of the patients in this study demonstrated delayed fracture healing and 88% had failed a previous attempt at union, presented with a non-union, were elderly or had significant medical comorbidities. Regardless of fracture site, 141 people reported resolution of pain at the fracture site within 12 wk of starting Teriparatide and the fracture united in 93%[23]. Indicators of healing (pain resolution and bridging of the fracture site by radiograph or CT scan) were noted to occur sooner in fractures that were predominantly trabecular bone (vertebrae, sacral ala, metadiaphyseal long bones) compared with fractures of diaphyseal bone or fusion sites[23]. Cases have been reported of almost normal fracture healing in elderly patients with established osteoporosis after starting treatment with Teriparatide[24].

NON-UNIONS

Several published case reports have suggested a beneficial effect of Teriparatide on non-unions. Chintamaneni *et al*[25] reported on a 67-year-old male who sustained a fracture of the body of the sternum as a result of a motor vehicle accident. This subsequently failed to heal resulting in a painful atrophic non-union. A trial of 20 μg per day of Teriparatide was initiated and showed significant healing of the non-union within 3 mo and complete healing and symptomatic resolution after 9 mo[25].

Rubery and Bukata[26] have also report 3 cases of painful delayed unions of type Ⅲ odontoid fractures which united and led to resolution of pain after treatment with Teriparatide.

CONCLUSION

Teriparatide constitutes the active portion of the Parathyroid Hormone molecule and is a commercially available, Food and Drug Administration (FDA) approved agent for the treatment of Osteoporosis. Emerging research over the last decade has shown a potential application in fracture management. Widespread evidence obtained from studies utilising small and large animal models indicate Teriparatide can improve fracture healing. Significant improvements in callus volume, callus mineralisation, bone mineral content, strength and rate of successful union at the fracture site in both normal and delayed healing models has been demonstrated. Research in humans has been relatively sparse with only two randomised controlled trials having been conducted to date. These are interspersed within a sea of anecdotal case reports. However the results of the human studies are in line with their animal counterparts and it seems that inferences can therefore be made despite obvious differences in PTH metabolism between the species.

Currently Teriparatide is being used "off license" for the management of fractures and non-unions by physicians who are confident of its beneficial effect. Well designed randomised controlled trials are required to comprehensively analyse the actions of Teriparatide in human subjects (in both normal and delayed healing models). This will allow conclusive decisions to be made on whether or not to incorporate this product as a standard option for conservative management of fractures and non-unions.

REFERENCES

1 **Dempster DW**, Cosman F, Parisien M, Shen V, Lindsay R.

Anabolic actions of parathyroid hormone on bone. *Endocr Rev* 1993; **14**: 690-709 [PMID: 8119233 DOI: 10.1210/edrv-14-6-690]
2 **Turner CH**, Wang T, Hirano T, Burr DB, Hock JM, Hotchkiss CE, Brommage R and Jerome CP (1999). In primates, treatment with PTH (1-34), LY333334, increases bone strength at trabecular bone sites without compromising the strength of cortical bone. *J Bone Miner Res* 1999; **14** Suppl 1: S414 abstract
3 **Neer RM**, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344**: 1434-1441 [PMID: 11346808 DOI: 10.1056/NEJM200105103441904]
4 **Hodsman AB**, Bauer DC, Dempster DW, Dian L, Hanley DA, Harris ST, Kendler DL, McClung MR, Miller PD, Olszynski WP, Orwoll E, Yuen CK. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. *Endocr Rev* 2005; **26**: 688-703 [PMID: 15769903 DOI: 10.1210/er.2004-0006]
5 **Berg C**, Neumeyer K, Kirkpatrick P. Fresh from the Pipeline: Teriparatide. *Nat Rev Drug Discov* 2003; **2**: 257-258 [DOI: 10.1038/nrd1068]
6 **Andreassen TT**, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. *J Bone Miner Res* 1999; **14**: 960-968 [PMID: 10352105 DOI: 10.1359/jbmr.1999.14.6.960]
7 **Holzer G**, Majeska RJ, Lundy MW, Hartke JR, Einhorn TA. Parathyroid hormone enhances fracture healing. A preliminary report. *Clin Orthop Relat Res* 1999; **(366)**: 258-263 [PMID: 10627743 DOI: 10.1097/00003086-199909000-00033]
8 **Andreassen TT**, Willick GE, Morley P, Whitfield JF. Treatment with parathyroid hormone hPTH(1-34), hPTH(1-31), and monocyclic hPTH(1-31) enhances fracture strength and callus amount after withdrawal fracture strength and callus mechanical quality continue to increase. *Calcif Tissue Int* 2004; **74**: 351-356 [PMID: 15255072 DOI: 10.1007/s00223-003-0093-6]
9 **Komatsubara S**, Mori S, Mashiba T, Nonaka K, Seki A, Akiyama T, Miyamoto K, Cao Y, Manabe T, Norimatsu H. Human parathyroid hormone (1-34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora. *Bone* 2005; **36**: 678-687 [PMID: 15781006 DOI: 10.1016/j.bone.2005.02.002]
10 **Mognetti B**, Marino S, Barberis A, Martin AS, Bala Y, Di Carlo F, Boivin G, Barbos MP. Experimental stimulation of bone healing with teriparatide: histomorphometric and microhardness analysis in a mouse model of closed fracture. *Calcif Tissue Int* 2011; **89**: 163-171 [PMID: 21701938 DOI: 10.1007/s00223-011-9503-3]
11 **Alkhiary YM**, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, Einhorn TA. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). *J Bone Joint Surg Am* 2005; **87**: 731-741 [PMID: 15805200 DOI: 10.2106/JBJS.D.02115]
12 **Gardner MJ**, van der Meulen MC, Carson J, Zelken J, Ricciardi BF, Wright TM, Lane JM, Bostrom MP. Role of parathyroid hormone in the mechanosensitivity of fracture healing. *J Orthop Res* 2007; **25**: 1474-1480 [PMID: 17568439 DOI: 10.1002/jor.20427]
13 **Manabe T**, Mori S, Mashiba T, Kaji Y, Iwata K, Komatsubara S, Seki A, Sun YX, Yamamoto T. Human parathyroid hormone (1-34) accelerates natural fracture healing process in the femoral osteotomy model of cynomolgus monkeys. *Bone* 2007; **40**: 1475-1482 [PMID: 17369013 DOI: 10.1016/j.bone.2007.01.015]
14 **Barnes GL**, Kakar S, Vora S, Morgan EF, Gerstenfeld LC, Einhorn TA. Stimulation of fracture-healing with systemic intermittent parathyroid hormone treatment. *J Bone Joint Surg Am* 2008; **90** Suppl 1: 120-127 [PMID: 18292366 DOI: 10.2106/JBJS.G.01443]
15 **Nakajima A**, Shimoji N, Shiomi K, Shimizu S, Moriya H, Einhorn TA, Yamazaki M. Mechanisms for the enhancement of fracture healing in rats treated with intermittent low-dose human parathyroid hormone (1-34). *J Bone Miner Res* 2002; **17**: 2038-2047 [PMID: 12412812 DOI: 10.1359/jbmr.2002.17.11.2038]
16 **Bishop GB**, Einhorn TA. Current and future clinical applications of bone morphogenetic proteins in orthopaedic trauma surgery. *Int Orthop* 2007; **31**: 721-727 [PMID: 17668207 DOI: 10.1007/s00264-007-0424-8]
17 **Andreassen TT**, Fledelius C, Ejersted C, Oxlund H. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. *Acta Orthop Scand* 2001; **72**: 304-307 [PMID: 11480610 DOI: 10.1080/00016470152846673]
18 **Nozaka K**, Miyakoshi N, Kasukawa Y, Maekawa S, Noguchi H, Shimada Y. Intermittent administration of human parathyroid hormone enhances bone formation and union at the site of cancellous bone osteotomy in normal and ovariectomized rats. *Bone* 2008; **42**: 90-97 [PMID: 17997377 DOI: 10.1016/j.bone.2007.08.041]
19 **Kim HW**, Jahng JS. Effect of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. *Iowa Orthop J* 1999; **19**: 71-77 [PMID: 10847519]
20 **Bostrom MP**, Gamradt SC, Asnis P, Vickery BH, Hill E, Avnur Z, Waters RV. Parathyroid hormone-related protein analog RS-66271 is an effective therapy for impaired bone healing in rabbits on corticosteroid therapy. *Bone* 2000; **26**: 437-442 [PMID: 10773582 DOI: 10.1016/S8756-3282(00)00251-9]
21 **Aspenberg P**, Genant HK, Johansson T, Nino AJ, See K, Krohn K, García-Hernández PA, Recknor CP, Einhorn TA, Dalsky GP, Mitlak BH, Fierlinger A, Lakshmanan MC. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res* 2010; **25**: 404-414 [PMID: 19594305 DOI: 10.1359/jbmr.090731]
22 **Peichl P**, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. *J Bone Joint Surg Am* 2011; **93**: 1583-1587 [PMID: 21915572 DOI: 10.2106/JBJS.J.01379]
23 **Bukata SV**, Puzas JE. Orthopedic uses of teriparatide. *Curr Osteoporos Rep* 2010; **8**: 28-33 [PMID: 20425088 DOI: 10.1007/s11914-010-0006-3]
24 **Resmini G**, Iolascon G. 79-year-old post-menopausal woman with humerus fracture during teriparatide treatment. *Aging Clin Exp Res* 2007; **19**: 30-31 [PMID: 18182890]
25 **Chintamaneni S**, Finzel K, Gruber BL. Successful treatment of sternal fracture nonunion with teriparatide. *Osteoporos Int* 2010; **21**: 1059-1063 [PMID: 19859645 DOI: 10.1007/s00198-009-1061-4]
26 **Rubery PT**, Bukata SV. Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: a report of 3 cases. *J Spinal Disord Tech* 2010; **23**: 151-155 [PMID: 20051918 DOI: 10.1097/BSD.0b013e31819a8b7a]

P- Reviewer: Kovar FM, Madadi F **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

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DOI: 10.5312/wjo.v6.i6.462

World J Orthop 2015 July 18; 6(6): 462-468
ISSN 2218-5836 (online)

MINIREVIEWS

Use of bone marrow derived stem cells in trauma and orthopaedics: A review of current concepts

Philip S Pastides, Matthew J Welck, Wasim S Khan

Philip S Pastides, Wasim S Khan, University College London Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, Middlesex HA7 4LP, United Kingdom

Matthew J Welck, Wexham Park Hospital, Slough, West Berkshire SL2 4HL, United Kingdom

Author contributions: Pastides PS, Welck MJ and Khan WS all collected, wrote, edited and approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflicting interests attached to this article.

Correspondence to: Wasim S Khan, MBChB, MSc, PhD, FRCS (Tr and Orth), Orthopaedic Registrar, Clinical Lecturer, University College London Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex HA7 4LP, United Kingdom. wasimkhan@doctors.org.uk
Telephone: +44-20-889542300
Fax: +44-20-7679200

Received: February 8, 2015
Peer-review started: February 9, 2015
First decision: April 10, 2015
Revised: May 7, 2015
Accepted: May 27, 2015
Article in press: May 28, 2015
Published online: July 18, 2015

Abstract

There is a considerable amount of interest in the future role of bone marrow-derived stem cells (BMDSCs) and tissue engineering techniques to manage conditions within the musculoskeletal system. Repair of soft tissue and bone defects, in the early stages of injury, may lead to a reduction in progression of symptoms. Furthermore, troublesome soft tissue injuries that are notoriously fraught with problems either in healing or function, could be augmented with such techniques. The aim of this review paper is to look at the advances in such strategies to tackle these problems and assess how BMDSCs, with the aid of growth factors and scaffolds, are being used *in vitro*, animal and even human models to treat problems within the field of trauma and orthopaedics. There is plenty of evidence that the results are encouraging and thus gaining momentum toward their use in human studies.

Key words: Trauma; Orthopaedics; Bone marrow-derived stem cells; Scaffolds; Growth factors

Core tip: Tissue engineering techniques using bone marrow-derived stem cells is an attractive, promising and growing area of research within the field of trauma and orthopaedics. There are plenty of *in vitro* and animal studies showing the benefits of such treatments with a slow and steady growth of human *in vivo* studies emerging.

Pastides PS, Welck MJ, Khan WS. Use of bone marrow derived stem cells in trauma and orthopaedics: A review of current concepts. *World J Orthop* 2015; 6(6): 462-468 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/462.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.462

INTRODUCTION

The advances in modern medicine over the last century

have been dramatic. Life expectancy has risen as has patient expectation and demands. This has now led to a new target, that of not solely survival until an elderly age, but of a pain free, mobile and reduced co morbidity survival.

Tissue engineering strategies, in the context of musculoskeletal medicine, focus on repair and prevention of soft tissue and osseous structures. For successful tissue regeneration, it is necessary to have cells that are capable of high proliferation but also differentiation. These must be placed in a suitably created environment to allow for such regeneration to occur. In recent years, regenerative medicine has emerged as an attractive field for new cellular and non cellular approaches to tissue repair. Bone marrow-derived stem cells (BMDSCs) can be influenced by external factors and cause them to differentiate down a desired path. Growth factors are peptide signaling molecules whose role includes the regulation of several pathways regulating metabolism at a cellular level including extra-cellular matrix production growth and production. Another obstacle to overcome is how to adequately deliver and keep the BMDSCs at the injured or repaired site. This has led to the further interest in the development of appropriate scaffolds to act as a mould to keep the cells *in situ*. As such, the ideal scaffold must be of appropriate size, shape and porosity in order to allow the cells to move from the scaffold to the injured area and potentially proliferate and grow.

Musculoskeletal injury can involve tendons and ligament, bone, meniscus and cartilage. More long term complications can include large bone defects and non unions. All such injuries are painful, troublesome, limiting to patients and costly to society. The high incidence of such injuries highlights the need for novel, more effective treatments. Currently a lot of research is being carried out into this area. The use of BMDSCs is one such option[1] and the aim of this review is to present current studies within the field.

ROTATOR CUFF

The rotator cuff muscles comprise of a group of four muscles around the shoulder girdle that contribute to both stability and movement of the joint. Tears within the rotator cuff are associated with muscle pathology, such as weakness or impingement[2]. Injuries to the rotator cuff can be managed operatively, with either open or arthroscopic surgery with satisfactory outcomes, but are associated high re-rupture rates[3]. This is partly due to the poor healing capabilities of tendon. Supraspinatus biopsies, obtained from 24 patients who underwent an arthroscopic repair of partial or full-thickness supraspinatus tendon tears, were analysed at a cellular level. Those with full-thickness tears were found to have a reduction in the density of satellite cells, atrophy of MHC1+ and MHC2+ (major histocompatibility complex) myofibers and reduced MHC1 content. Histological analysis revealed that the tendons did not heal by the regeneration of normal fibrocartilage, but by forming scar tissue with a high content of type III collagen[4,5]. As a result, tissue engineering techniques could have a huge role in the augmentation of rotator cuff tears and is undergoing constant evaluation.

Yokoya *et al*[6] surgically created defects within the infraspinatus tendons of rabbits. They used two different materials to repair the defects; a polyglycolic acid (PGA) sheet alone (PGA group) and a PGA sheet seeded with autologously cultured BMDSCs. Performing a tendon defect with no graft created a control group. At 8 wk, the layers of fibrocartilage and Sharpey fibers in the BDMSCs group were regularly identified at the supraspinatus footprint compared with the PGA group. In the control group, thin membranes with many fibroblasts arranged in an irregular pattern were identified at the tendon-bone interface, lacking any evidence of Sharpey fibers or type Ⅰ collagen. An abundance of type Ⅰ collagen relative to type Ⅲ collagen was seen at 16 wk in the BDMSCs group, whereas type Ⅲ collagen was more prevalent than type Ⅰ in the PGA group. The tendon maturing score was the highest in the BMDSCs group at both 8 and 16 wk, with a statistically significant better tensile strength than in the PGA and control groups. Funakoshi *et al*[7] showed similar tendon regeneration and mechanical properties in rabbit infraspinatus defects using fibroblast seeded scaffold.

There is early evidence that this technology can be translated into humans. Mazzocca *et al*[8] showed that BMDSCs could safely be aspirated and cultured from the proximal humerus in 23 patients during arthroscopic rotator cuff repair. They later showed in a follow up study[9] that exposure of the harvested cells to a one-time physiologic dose of insulin is capable of differentiating BMDSCs into tenocytes. Another group of researches found that the implantation of BMDSCs, harvested from the iliac crest at the time of surgery, and injected into the repaired rotator cuff, led to a 100% radiological (MRI) intergrity of the rotator cuff at 12 mo[10].

However, there is also evidence to suggest that the use of tissue engineering strategies in rotator cuff defects is not always successful. Gulotta *et al*[11] used three groups of Lewis rats to investigate whether BMDSCs that with a fibrin carrier, no carrier or a non-augment repair altered the histological or biomechanical outcomes following rotator cuff repair. At no point in time, did they notice any significant differences in the amount of new cartilage formed, the collagen fibre organization or mechanical properties between the groups.

The potential benefits, or not, of biological approaches involving BMDSCs to improve the outcome of rotator cuff therapies and reduce rates of re injury as still very unclear. In fact, a recent systematic review focusing on such techniques found only 3 papers in their

initial literature review, forcing the authors to expand their search criteria[12]. This highlights the needs for further high level and targeted studies to evaluate the efficacy in human subjects.

TENDONS AND LIGAMENTS

Tendons and ligaments are critical to the musculoskeletal system in order to attach the force generating muscles to the solid skeleton of the body[13,14]. Tendon repair is a slow process that often results in structurally weaker and less functional properties compared to undamaged tissue[15]. The hypothesis at the centre of many researchers is that it may be possible to improve the reparative potential of tendons by implementing biological techniques.

An animal study to assess this was conducted by Adams *et al*[16] using 54 rat specimens. The 108 bilateral hind limbs underwent a transection of the Achilles tendon. Randomisation to repair with suture only (SO), suture plus injection (SI) of BDMSCs at the repair site or sutures loaded with BMDSCs (suture with stem cells SCS) was performed. At 14 and 28 d post surgery, 54 specimens were humanely killed and the tendons harvested and subsequently underwent a blinded histological examination and mechanical testing. Ultimate failure strength was significantly higher in the SI and SCS groups *vs* the SO group. Histology scores were best in the SCS group.

Biologically culturing of the BMDSCs can modify the outcome of such techniques. A study by Yao *et al*[17] used BMDSCs harvested from Sprague-Dawley rat femurs. Coated sutures (CS) with intercellular cell adhesion molecule 1 and poly-L-lysine and seeded with labelled BMDSCs formed the intervention group. Control (substrate-only) coated group sutures were coated with intercellular cell adhesion molecule 1 and poly-L-lysine only. The CS suture repairs were statistically stronger than SO repairs at 7 and 10 d, without any significant difference in strength 4, 14 and 28 d. Their findings suggest that suture repair augmented with biological substrates may kick start the repair process. Improved early strength might, in turn allow earlier unprotected mobilization and thus reduce the rate of early re-rupture rates. However in a similar study using the same animal model, but using recombinant human growth differentiation factor-5 (rhGDF-5) to culture the cells instead, Dines *et al*[18] came to a different outcome. Histological assessment at 3 wk showed improved healing in tendons repaired with coated suture *vs* a control group. By 6 wk, there were no significant differences in any mechanical property tested. At 3 wk, tendons repaired with rhGDF-5-coated sutures were found to have a significantly higher ultimate tensile load and stiffness.

The true benefits of augmentation in tendon and ligament repair with BMDSCs remains unclear. What is evident it that the stem cells can be cultures under various stimuli to produce a more beneficial outcome. Further studies, including human trials need to be conducted[15].

CARTILAGE

Undoubtedly, joint arthroplasty is a triumph of modern day orthopaedics. Osteoarthritis, the loss of articular cartilage, is a chronic disease effecting an increasingly aging population. Joint replacement arthroplasty has been a tremendous success in restoring independence to an otherwise frail group of patients. Cartilage loss, or damage, in the younger, more active patient still remains a challenge. Damage of cartilage is often asymptomatic and related to sporting activities. The decision to treat such lesions is related to the extent of symptoms the patient expresses, but growingly there is a trend to prophylactically address these defects because once damaged cartilage becomes vulnerable to further degradation due to its poor ability to heal[19]. Thus even small defects may degenerate over time, ultimately causing osteoarthritis[20]. While arthroplasty remains a successful treatment option, performing such procedures in this population group will mean further revision surgery in the future[21,22]. It is this area that tissue engineering is focusing its attention[23,24].

Current treatments such as arthroscopic debridement and microfracture, autologous osteochondral transfer and autologous chondrocyte implantation, all of which have been shown to produce positive results[25]. BMDSCs are a good cell source for regeneration of cartilage as they can migrate directly to the site of cartilage injury and differentiate into articular chondrocytes[26,27]. There is a plethora of publications showing how under different stimulation, scaffolds and gene therapy, BMDSCs can lead to regeneration and/or an increase rate of regeneration of damaged articular cartilage[28]. The vast majority of these studies are either *in vitro* or make use of animal studies. Zhu *et al*[29] reported on a combined technique of articular cartilage repair, consisting of BMDSCs transfected with connective tissue growth factor (*CTGF*) gene and NaOH-treated poly(lactic-co-glycolic) acid (PLGA) scaffolds. Full-thickness cartilage defects were created unilaterally in the patellar grooves of rabbits. Defects were either left empty, implanted with BMDSCs/PLGA, BMDSCs/NaOH-treated PLGA or CTGF-modified BMDSCs/NaOH-treated PLGA. Overall, the CTGF-modified BMDSCs/NaOH-treated PLGA group showed successful hyaline-like cartilage regeneration similar to normal cartilage, which was superior to the other groups in all histological and mechanical assessments.

The effect of other growth factors on chondrocyte differentiation is also being investigated. Reyes *et al*[30] showed that the addition of bone morphogenetic protein (BMP) 2 to BMDSCs with a alginate/PLGA osteochondral scaffold was just as efficient at repairing an osteochondral defect in rabbit knees. Equally good results have been reported by Guo *et al*[31] who investigated the effects of transforming growth factor

(*TGF*)-*β(1*) gene modified BMDSCs and a biodegradable poly-L-lysine coated polylactide biomimetic scaffolds, cultured *in vitro*, and then allografted into full-thickness articular cartilage defects in 18 New Zealand rabbits. They found that hyaline cartilage began to infill within the chondral defects, whilst at 24 wk, the subchondral region contained a mix of both compact and trabecular bone.

Likewise, the choice of scaffold to further augment repair has been the subject of many investigations. For example, Deng *et al*[32] showed that the addition of a silk fibrion/chitosan scaffold in combination with BMDSCs augmented osteochondral defects in rabbit knee better than no scaffold at all. They found that the scaffold resulted in near complete repair of the defect and scaffold degradation at 12 wk.

Significantly, there is a slow and steady growth in the body of evidence of such studies involving human patients. A systematic review was conducted by the authors looking at the outcome of studies reporting on BMDSCs treatment in human subjects. Our findings were that there is early and promising data but more high level studies, with extensive and robust validated reporting methods, should be conducted to evaluate the true effect of such techniques in human cartilage defect repairs as well as the effects of scaffolds and growth factors to improve the quality and timing to repair[33].

MENISCUS

Meniscal injuries are a very frequent sport related injuries. Removal of an extensive area of meniscus can alter the knee biomechanics and thus predispose patients to osteoarthritis. Thus tissue engineering poses an attractive reparative option to attempt meniscal tissue repair and avoid the long-term sequelae[34,35].

Studies have shown that growth factor differentiation and the use of scaffolds can result in good outcomes in animal models. Steinert *et al*[36] investigated the use of a scaffold seeded with genetically modified meniscal cells or BMDSCs isolated from bovine calves were transduced with adenoviral vectors encoding green fluorescent protein, luciferase or TGF-β1 complementary deoxyribonucleic acid (cDNA). These cells were then germinated within type Ⅰ collagen-glycosaminoglycan matrices and transplanted into the avascular zone of injured bovine menisci. At 3 wk, recombinant adenovirus readily transduced meniscal cells and MSCs, and transgene expression remained high after the cells were incorporated into collagen-glycosaminoglycan matrices. Transfer of TGF-β1 cDNA resulted in an increased cellularity and cell synthesis.

Yamasaki *et al*[37] assessed the transplantation of regenerated menisci using scaffolds from normal allogeneic menisci and BMDSCs in rats. After 4 wk, the tissues were transplanted to a defect within the menisci. Repopulation of BMDSCs and expression of extracellular matrices were observed in the transplanted tissues at 4 wk after surgery. At 8 wk, articular cartilage in the cell-free group appeared to be more damaged compared to the other groups.

Hatsushika *et al*[38] showed a very promising study that may be useful for the management of acute, massive meniscal injuries which tend to affect young patients. They investigated how repetitive intraarticular injections of synovial BMDSCs effected meniscal regeneration in porcine knees that two weeks prior had undergone partial anterior menisectomies. BMDSCs were injected into the right knee at 0, 2, and 4 wk and assessed prospectively with serial MRI. Regeneration was significantly better both histologically and radiologically in the BMDSCs group compared to the control group. Macroscopically, the meniscal defect already appeared to be filled with synovial tissue at 2 wk.

Although promising, the use of BMDSCs and tissue engineering strategies for meniscal repair are still in their infancy and require further evaluation to establish the benefits or not of such methods[39].

BONE DEFECTS

Reconstruction of bony defects remains a challenge in modern day trauma and orthopaedic cases. Treatment options such as the Masquelet[40,41] technique are gaining in popularity. Henrich *et al*[42] investigated the cellular, histological, growth factor expression and biochemical make-up of the membranes induced around femoral defects during this technique. They found that the membranes formed around bone defects were similar to those formed in subcutaneous pockets; however, both were significantly different from periosteum with regard to structural characteristics, location of blood vessels and overall thickness. Membranes induced at the femoral defect at 2 wk and in periosteum contain mesenchymal stem cells (MSCs; STRO-1^{+}) which were not found in membranes induced subcutaneously. BMP-2, TGFβ and vascular endothelial growth factor were significantly elevated in membranes induced around femur defects. This raises the question of whether BMDSCs can be used to repair bone defects.

A recent systematic review and metaanalysis was conducted by Liao *et al*[43] to assess the treatment outcomes for bone repair using BMDSCs. The combined findings of the 20 included preclinical studies showed statistically significant beneficial effect of stem cell therapy by increasing new bone formation and bone mineral density. Stratified analysis showed that predictors of new bone formation included the number of cells and that the addition of a scaffold was more effective than isolated direct cell injection. The results appeared to be sustainable at 12 wk.

Furthermore there is evidence that augmenting bone allograft with BMDSCs has beneficial outcomes in revision surgery. In a case-control study, Hernigou *et al*[44] treated 60 patients with aseptic failure of a cemented acetabular implant with bone allograft with

or without BDMSCs incorporation. Both groups of 30 patients were matched for the size of the periacetabular osteolytic areas. They compared the evolution of the allografts and evaluated cup migration and revision of the hips as end points at a minimum of 12 years or until failure. Better radiographic graft union rates and less allograft resorption were observed with allografts loaded with stem cells. Allograft resorption was significantly decreased in the group with allograft loaded with BMDSCs. The rate of mechanical failure was highest (P = 0.01) among the 30 patients with allograft without stem cells (9/30; 30%) compared with no failures for patients with allograft loaded with stem cells. Revision of the cup was necessary in nine patients in the control group. No revision was performed in the 30 patients of the study group with BMDSCs. This leads to an encouraging hypothesis that the addition of BMDSCs to these bone graft may restore the osteogenic capacity of an allogenic dead bone and therefore enhance incorporation of allografts with the host bone and decrease the number of failures related to the allograft.

OSSEOUS NON-UNIONS

Osseous non-unions represent a significant and troublesome problem with a high patient morbidity rate, despite surgical advances[45]. As such, tissue engineering could be an attractive addition to the traditional approaches implemented in the treatment of fracture non-unions[46-48].

Giannotti *et al*[49] investigated the long-term outcomes of *in vitro* expanded BMDSCs, embedded in autologous fibrin clots, for the healing of atrophic pseudarthrosis of the upper limb. Tissue-engineered constructs designed to embed the BMDSCs from 8 patients in autologous fibrin clots were locally implanted with bone grafts. Radiographic healing was evaluated at a mean of 6.7 and 76.0 mo. All patients recovered limb function, with no evidence of tissue overgrowth or tumour formation. Successful results have also been reported in lower limb non-unions. Fernandez-Bances *et al*[50] successfully treated 7 patients with long bone non-unions with autologous BMDSCs from iliac crest combined with frozen allogenic cancellous bone graft. All patients showed complete bone consolidation at a mean of around 5 mo. Moreover, limb pain disappeared in all of them. At a mean follow-up of 36 mo there was no recurrence of pain or limitations of function. Bajada *et al*[51] successfully treated a nine-year old tibial non union, that had undergone six previous operative attempts to treat it, using BMDSCs and a calcium sulphate scaffold. Applying the concept of growth factor stimulation, Grgurevic *et al*[52] showed that exposure of BMDSCs to growth factor such as BMP1-3, increased the expression of collagen type I and osteocalcin in MC3T3-E(1) osteoblast like cells, and enhanced the formation of mineralised bone nodules in rat long bone non unions.

CONCLUSION

There has been a remarkable progression during the past two decades in the development of tissue engineering techniques and strategies. Large amounts of attention are being focussed on the development of suitable scaffolds to deliver the cells, as well as the positive influence of growth factors on isolated BMDSCs. A huge obstacle in the application of such techniques is the ethical issues surrounding the trials of such products in humans. There is an ever increasing move to perform studies within the human population but more work and resources are needed to assess the safety and efficacy of treatments. Although in the infancy, there is no doubt that the use of BMDSCs and tissue engineering techniques represents an attractive, feasible and exciting prospect that may hold to future key to repairing rather than replacing within the Trauma and Orthopaedic setting.

REFERENCES

1 **Tucker BA**, Karamsadkar SS, Khan WS, Pastides P. The role of bone marrow derived mesenchymal stem cells in sports injuries. *J Stem Cells* 2010; **5**: 155-166 [PMID: 22314864]

2 **Lundgreen K**, Lian OB, Engebretsen L, Scott A. Lower muscle regenerative potential in full-thickness supraspinatus tears compared to partial-thickness tears. *Acta Orthop* 2013; **84**: 565-570 [PMID: 24171689 DOI: 10.3109/17453674.2013.858289]

3 **Bollier M**, Shea K. Systematic review: what surgical technique provides the best outcome for symptomatic partial articular-sided rotator cuff tears? *Iowa Orthop J* 2012; **32**: 164-172 [PMID: 23576937]

4 **Galatz LM**, Sandell LJ, Rothermich SY, Das R, Mastny A, Havlioglu N, Silva MJ, Thomopoulos S. Characteristics of the rat supraspinatus tendon during tendon-to-bone healing after acute injury. *J Orthop Res* 2006; **24**: 541-550 [PMID: 16456829]

5 **Rodeo SA**, Arnoczky SP, Torzilli PA, Hidaka C, Warren RF. Tendon-healing in a bone tunnel. A biomechanical and histological study in the dog. *J Bone Joint Surg Am* 1993; **75**: 1795-1803 [PMID: 8258550]

6 **Yokoya S**, Mochizuki Y, Natsu K, Omae H, Nagata Y, Ochi M. Rotator cuff regeneration using a bioabsorbable material with bone marrow-derived mesenchymal stem cells in a rabbit model. *Am J Sports Med* 2012; **40**: 1259-1268 [PMID: 22491821 DOI: 10.1177/0363546512442343]

7 **Funakoshi T**, Majima T, Iwasaki N, Suenaga N, Sawaguchi N, Shimode K, Minami A, Harada K, Nishimura S. Application of tissue engineering techniques for rotator cuff regeneration using a chitosan-based hyaluronan hybrid fiber scaffold. *Am J Sports Med* 2005; **33**: 1193-1201 [PMID: 16000663]

8 **Mazzocca AD**, McCarthy MB, Chowaniec DM, Cote MP, Arciero RA, Drissi H. Rapid isolation of human stem cells (connective tissue progenitor cells) from the proximal humerus during arthroscopic rotator cuff surgery. *Am J Sports Med* 2010; **38**: 1438-1447 [PMID: 20375368 DOI: 10.1177/0363546509360924]

9 **Mazzocca AD**, McCarthy MB, Chowaniec D, Cote MP, Judson CH, Apostolakos J, Solovyova O, Beitzel K, Arciero RA. Bone marrow-derived mesenchymal stem cells obtained during arthroscopic rotator cuff repair surgery show potential for tendon cell differentiation after treatment with insulin. *Arthroscopy* 2011; **27**: 1459-1471 [PMID: 21978434 DOI: 10.1016/j.arthro.2011.06.029]

10 **Ellera Gomes JL**, da Silva RC, Silla LM, Abreu MR, Pellanda R. Conventional rotator cuff repair complemented by the aid of mononuclear autologous stem cells. *Knee Surg Sports Traumatol Arthrosc* 2012; **20**: 373-377 [PMID: 21773831 DOI: 10.1007/

s00167-011-1607-9]
11 **Gulotta LV**, Kovacevic D, Ehteshami JR, Dagher E, Packer JD, Rodeo SA. Application of bone marrow-derived mesenchymal stem cells in a rotator cuff repair model. *Am J Sports Med* 2009; **37**: 2126-2133 [PMID: 19684297 DOI: 10.1177/0363546509339582]
12 **Isaac C**, Gharaibeh B, Witt M, Wright VJ, Huard J. Biologic approaches to enhance rotator cuff healing after injury. *J Shoulder Elbow Surg* 2012; **21**: 181-190 [PMID: 22244061 DOI: 10.1016/j.jse.2011.10.004]
13 **Schweitzer R**, Zelzer E, Volk T. Connecting muscles to tendons: tendons and musculoskeletal development in flies and vertebrates. *Development* 2010; **137**: 2807-2817 [PMID: 20699295 DOI: 10.1242/dev.047498]
14 **Hasson P**. "Soft" tissue patterning: muscles and tendons of the limb take their form. *Dev Dyn* 2011; **240**: 1100-1107 [PMID: 21438070 DOI: 10.1002/dvdy.22608]
15 **Davies BM**, Morrey ME, Mouthuy PA, Baboldashti NZ, Hakimi O, Snelling S, Price A, Carr A. Repairing damaged tendon and muscle: are mesenchymal stem cells and scaffolds the answer? *Regen Med* 2013; **8**: 613-630 [PMID: 23998754 DOI: 10.2217/rme.13.55]
16 **Adams SB**, Thorpe MA, Parks BG, Aghazarian G, Allen E, Schon LC. Stem cell-bearing suture improves Achilles tendon healing in a rat model. *Foot Ankle Int* 2014; **35**: 293-299 [PMID: 24403347 DOI: 10.1177/1071100713519078]
17 **Yao J**, Woon CY, Behn A, Korotkova T, Park DY, Gajendran V, Smith RL. The effect of suture coated with mesenchymal stem cells and bioactive substrate on tendon repair strength in a rat model. *J Hand Surg Am* 2012; **37**: 1639-1645 [PMID: 22727924 DOI: 10.1016/j.jhsa.2012.04.038]
18 **Dines JS**, Weber L, Razzano P, Prajapati R, Timmer M, Bowman S, Bonasser L, Dines DM, Grande DP. The effect of growth differentiation factor-5-coated sutures on tendon repair in a rat model. *J Shoulder Elbow Surg* 2007; **16**: S215-S221 [PMID: 17507245]
19 **Frank RM**, Cole BJ. Complex cartilage cases in the athletic patient: advances in malalignment, instability, articular defects, and meniscal insufficiency. *Phys Sportsmed* 2013; **41**: 41-52 [PMID: 24231596 DOI: 10.3810/psm.2013.11.2035]
20 **Grenier S**, Bhargava MM, Torzilli PA. An in vitro model for the pathological degradation of articular cartilage in osteoarthritis. *J Biomech* 2014; **47**: 645-652 [PMID: 24360770 DOI: 10.1016/j.jbiomech.2013.11.050]
21 **Ravi B**, Croxford R, Reichmann WM, Losina E, Katz JN, Hawker GA. The changing demographics of total joint arthroplasty recipients in the United States and Ontario from 2001 to 2007. *Best Pract Res Clin Rheumatol* 2012; **26**: 637-647 [PMID: 23218428 DOI: 10.1016/j.berh.2012.07.014]
22 **Kurtz S**, Mowat F, Ong K, Chan N, Lau E, Halpern M. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *J Bone Joint Surg Am* 2005; **87**: 1487-1497 [PMID: 15995115]
23 **Punwar S**, Khan WS. Mesenchymal stem cells and articular cartilage repair: clinical studies and future direction. *Open Orthop J* 2011; **5** Suppl **2**: 296-301 [PMID: 21886696 DOI: 10.2174/1874325001105010029]
24 **Oragui E**, Nannaparaju M, Khan WS. The role of bioreactors in tissue engineering for musculoskeletal applications. *Open Orthop J* 2011; **5** Suppl **2**: 267-270 [PMID: 21886691]
25 **Gopal K**, Amirhamed HA, Kamarul T. Advances of human bone marrow-derived mesenchymal stem cells in the treatment of cartilage defects: a systematic review. *Exp Biol Med* (Maywood) 2014; **239**: 663-669 [PMID: 24764239]
26 **Diaz-Flores L**, Gutierrez R, Madrid JF, Acosta E, Avila J, Diaz-Flores L, Martin-Vasallo P. Cell sources for cartilage repair; contribution of the mesenchymal perivascular niche. *Front Biosci* (Schol Ed) 2012; **4**: 1275-1294 [PMID: 22652871]
27 **Murray IR**, West CC, Hardy WR, James AW, Park TS, Nguyen A, Tawonsawatruk T, Lazzari L, Soo C, Péault B. Natural history of mesenchymal stem cells, from vessel walls to culture vessels. *Cell Mol Life Sci* 2014; **71**: 1353-1374 [PMID: 24158496 DOI: 10.1007/s00018-013-1462-6]
28 **de Windt TS**, Hendriks JA, Zhao X, Vonk LA, Creemers LB, Dhert WJ, Randolph MA, Saris DB. Concise review: unraveling stem cell cocultures in regenerative medicine: which cell interactions steer cartilage regeneration and how? *Stem Cells Transl Med* 2014; **3**: 723-733 [PMID: 24763684 DOI: 10.5966/sctm.2013-020]
29 **Zhu S**, Zhang B, Man C, Ma Y, Liu X, Hu J. Combined effects of connective tissue growth factor-modified bone marrow-derived mesenchymal stem cells and NaOH-treated PLGA scaffolds on the repair of articular cartilage defect in rabbits. *Cell Transplant* 2014; **23**: 715-727 [PMID: 24763260 DOI: 10.3727/096368913X669770]
30 **Reyes R**, Pec MK, Sánchez E, del Rosario C, Delgado A, Évora C. Comparative, osteochondral defect repair: stem cells versus chondrocytes versus bone morphogenetic protein-2, solely or in combination. *Eur Cell Mater* 2013; **25**: 351-365; discussion 365 [PMID: 23832688]
31 **Guo X**, Zheng Q, Yang S, Shao Z, Yuan Q, Pan Z, Tang S, Liu K, Quan D. Repair of full-thickness articular cartilage defects by cultured mesenchymal stem cells transfected with the transforming growth factor beta1 gene. *Biomed Mater* 2006; **1**: 206-215 [PMID: 18458408 DOI: 10.1088/1748-6041/1/4/006]
32 **Deng J**, She R, Huang W, Dong Z, Mo G, Liu B. A silk fibroin/chitosan scaffold in combination with bone marrow-derived mesenchymal stem cells to repair cartilage defects in the rabbit knee. *J Mater Sci Mater Med* 2013; **24**: 2037-2046 [PMID: 23677433 DOI: 10.1007/s10856-013-4944-z]
33 **Pastides P**, Chimutengwende-Gordon M, Maffulli N, Khan W. Stem cell therapy for human cartilage defects: a systematic review. *Osteoarthritis Cartilage* 2013; **21**: 646-654 [PMID: 23485933 DOI: 10.1016/j.joca.2013.02.008]
34 **Malvankar SM**, Khan WS. An overview of the different approaches used in the development of meniscal tissue engineering. *Curr Stem Cell Res Ther* 2012; **7**: 157-163 [PMID: 22023637]
35 **Khan WS**, Malik AA, Hardingham TE. Stem cell applications and tissue engineering approaches in surgical practice. *J Perioper Pract* 2009; **19**: 130-135 [PMID: 19472685]
36 **Steinert AF**, Palmer GD, Capito R, Hofstaetter JG, Pilapil C, Ghivizzani SC, Spector M, Evans CH. Genetically enhanced engineering of meniscus tissue using ex vivo delivery of transforming growth factor-beta 1 complementary deoxyribonucleic acid. *Tissue Eng* 2007; **13**: 2227-2237 [PMID: 17561802]
37 **Yamasaki T**, Deie M, Shinomiya R, Yasunaga Y, Yanada S, Ochi M. Transplantation of meniscus regenerated by tissue engineering with a scaffold derived from a rat meniscus and mesenchymal stromal cells derived from rat bone marrow. *Artif Organs* 2008; **32**: 519-524 [PMID: 18638305 DOI: 10.1111/j.1525-1594.2008.00580]
38 **Hatsushika D**, Muneta T, Nakamura T, Horie M, Koga H, Nakagawa Y, Tsuji K, Hishikawa S, Kobayashi E, Sekiya I. Repetitive allogeneic intraarticular injections of synovial mesenchymal stem cells promote meniscus regeneration in a porcine massive meniscus defect model. *Osteoarthritis Cartilage* 2014; **22**: 941-950 [PMID: 24795274 DOI: 10.1016/j.joca.2014.04.028]
39 **Haddad B**, Pakravan AH, Konan S, Adesida A, Khan W. A systematic review of tissue engineered meniscus: cell-based preclinical models. *Curr Stem Cell Res Ther* 2013; **8**: 222-231 [PMID: 23317471]
40 **Masquelet AC**, Begue T. The concept of induced membrane for reconstruction of long bone defects. *Orthop Clin North Am* 2010; **41**: 27-37; table of contents [PMID: 19931050 DOI: 10.1016/j.ocl.2009.07.011]
41 **Masquelet AC**, Fitoussi F, Begue T, Muller GP. Reconstruction of the long bones by the induced membrane and spongy autograft. *Ann Chir Plast Esthet* 2000; **45**: 346-353 [PMID: 10929461]
42 **Henrich D**, Seebach C, Nau C, Basan S, Relja B, Wilhelm K, Schaible A, Frank J, Barker J, Marzi I. Establishment and characterization of the Masquelet induced membrane technique in a rat femur critical-sized defect model. *J Tissue Eng Regen Med* 2013 Nov 8; Epub ahead of print [PMID: 24668794 DOI: 10.1002/term.1826]
43 **Liao Y**, Zhang XL, Li L, Shen FM, Zhong MK. Stem cell therapy

for bone repair: a systematic review and meta-analysis of preclinical studies with large animal models. *Br J Clin Pharmacol* 2014; **78**: 718-726 [PMID: 24645974 DOI: 10.1111/bcp.12382]

44 **Hernigou P**, Pariat J, Queinnec S, Homma Y, Flouzat Lachaniette CH, Chevallier N, Rouard H. Supercharging irradiated allografts with mesenchymal stem cells improves acetabular bone grafting in revision arthroplasty. *Int Orthop* 2014; **38**: 1913-1921 [PMID: 24509980 DOI: 10.1007/s00264-014-2285-2]

45 **Hak DJ**. Management of aseptic tibial nonunion. *J Am Acad Orthop Surg* 2011; **19**: 563-573 [PMID: 21885702]

46 **Giannoudis PV**, Einhorn TA, Marsh D. Fracture healing: the diamond concept. *Injury* 2007; **38** Suppl 4: S3-S6 [PMID: 18224731]

47 **Chimutengwende-Gordon M**, Khan WS. Advances in the use of stem cells and tissue engineering applications in bone repair. *Curr Stem Cell Res Ther* 2012; **7**: 122-126 [PMID: 22023632]

48 **Shekkeris AS**, Jaiswal PK, Khan WS. Clinical applications of mesenchymal stem cells in the treatment of fracture non-union and bone defects. *Curr Stem Cell Res Ther* 2012; **7**: 127-133 [PMID: 22023633]

49 **Giannotti S**, Trombi L, Bottai V, Ghilardi M, D'Alessandro D, Danti S, Dell'Osso G, Guido G, Petrini M. Use of autologous human mesenchymal stromal cell/fibrin clot constructs in upper limb non-unions: long-term assessment. *PLoS One* 2013; **8**: e73893 [PMID: 24023694 DOI: 10.1371/journal.pone.0073893]

50 **Fernandez-Bances I**, Perez-Basterrechea M, Perez-Lopez S, Nuñez Batalla D, Fernandez Rodriguez MA, Alvarez-Viejo M, Ferrero-Gutierrez A, Menendez-Menendez Y, Garcia-Gala JM, Escudero D, Paz Aparicio J, Carnero Lopez S, Lopez Fernandez P, Gonzalez Suarez D, Otero Hernandez J. Repair of long-bone pseudoarthrosis with autologous bone marrow mononuclear cells combined with allogenic bone graft. *Cytotherapy* 2013; **15**: 571-577 [PMID: 23415918 DOI: 10.1016/j.jcyt.2013.01.004]

51 **Bajada S**, Harrison PE, Ashton BA, Cassar-Pullicino VN, Asham-makhi N, Richardson JB. Successful treatment of refractory tibial nonunion using calcium sulphate and bone marrow stromal cell implantation. *J Bone Joint Surg Br* 2007; **89**: 1382-1386 [PMID: 17957083]

52 **Grgurevic L**, Macek B, Mercep M, Jelic M, Smoljanovic T, Erjavec I, Dumic-Cule I, Prgomet S, Durdevic D, Vnuk D, Lipar M, Stejskal M, Kufner V, Brkljacic J, Maticic D, Vukicevic S. Bone morphogenetic protein (BMP)1-3 enhances bone repair. *Biochem Biophys Res Commun* 2011; **408**: 25-31 [PMID: 21453682 DOI: 10.1016/j.bbrc.2011.03.109]

P- Reviewer: Colak T, Foss B, Jeschke MG **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

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DOI: 10.5312/wjo.v6.i6.469

World J Orthop 2015 July 18; 6(6): 469-482
ISSN 2218-5836 (online)

MINIREVIEWS

Current surgical strategies for total arthroplasty in valgus knee

Dimitrios Nikolopoulos, Ioannis Michos, George Safos, Petros Safos

Dimitrios Nikolopoulos, George Safos, Orthopaedic Department, Central Clinic of Athens, 10680 Athens, Greece

Ioannis Michos, D' Orthopaedic Department, Asklepeion Voulas General Hospital, 16673 Voul, Greece

Petros Safos, Orthopaedic Department, Ikaria General Hospital, 83300 Ikaria, Greece

Author contributions: Nikolopoulos D and Michos I contributed equally to conception and design of the research; Nikolopoulos D, Safos G and Safos P designed the research on PubMed and analyzed the data; Nikolopoulos D and Michos I drafted the article and revised it critically; all authors approved the final version so as to be published.

Conflict-of-interest statement: We declare that there is no conflict of interest of any of the authors.

Correspondence to: Dimitrios Nikolopoulos, PhD, Consultant, Orthopaedic Department, Central Clinic of Athens, Asklepiou 31 str., 10680 Athens, Greece. drdnikol@hotmail.com
Telephone: +30-210-3674064
Fax: + 30-210-3605110

Received: March 28, 2015
Peer-review started: March 28, 2015
First decision: April 10, 2015
Revised: April 23, 2015
Accepted: May 16, 2015
Article in press: May 18, 2015
Published online: July 18, 2015

Abstract

The majority of orthopaedic surgeons even currently agree that primary total arthroplasty in valgus knees with a deformity of more than ten degrees may prove challenging. The unique sets of bone and soft tissue abnormalities that must be addressed at the time of the operation make accurate axis restoration, component orientation and joint stability attainment a difficult task. Understanding the specific pathologic anatomic changes associated with the valgus knee is a prerequisite so as to select the proper surgical method, to optimize component position and restore soft-tissue balance. The purpose of this article is to review the valgus knee anatomical variations, to assess the best pre-operative planning and to evaluate how to choose the grade of constraint of the implant. It will also be underlying the up-to-date main approaches and surgical techniques be proposed in the English literature both for bone cuts and soft tissue management of valgus knees.

Key words: Valgus knee; Arthroplasty; Balancing soft tissue; Knee surgical approaches; Tibial tubercle osteotomy

Core tip: Knee arthroplasty in valgus deformity more than 10° is an orthopaedic challenge. During the operation, due to the deformities of the bone and soft tissue, there are many difficulties for the surgeon, such as the restoration of the mechanical axis, the orientation of the component and the stability of the knee joint. Our aim is to review the valgus knee anatomical variations, to assess the best approach and surgical technique for bone cuts and soft tissue management of valgus knees so as to succeed the best result.

Nikolopoulos D, Michos I, Safos G, Safos P. Current surgical strategies for total arthroplasty in valgus knee. *World J Orthop* 2015; 6(6): 469-482 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/469.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.469

INTRODUCTION

Of the patients requiring a primary total knee arthroplasty (TKA), 10% to 15% present with valgus deformity (VD), the inaccurate correction of which continues to be a challenge for the orthopedics even currently[1]. Excessive pre-operative malalignment predisposes to a greater risk of failure compared to well-aligned knees[2]. It is observed that the restoration of the correct lower limb mechanical axis postoperatively; as also the normal balance of the soft tissues are important for the final outcome of these joint replacement operations[2-5]. Thus, the severely valgus deformed knees are related with a worse outcome *vs* their varus counterparts[5].

There are different and multifactorial etiologic parameters of knee VD, from congenital to secondary such as primary osteoarthritis. To be more specific, in adults VD is commonly associated with inflammatory arthritis (rheumatic diseases) as well as with primary osteoarthritis, posttraumatic arthritis (as a result of a tibial malunion, physeal arrest, or tibial plateau fracture), or even overcorrection from a proximal tibial osteotomy performed to correct a preexisting varus deformity[2,6]. Nevertheless, a significant percentage of adults with lateral compartment osteoarthritis and associated VD represent unresolved physiologic valgus deformity. Occasionally, persistence of genu valgum from childhood may exist secondary to metabolic disorders, such as rickets and renal osteodystrophy[7]. Overwhelmingly, the most common etiology of VD is primary osteoarthritis with a smaller number of patients having rheumatoid arthritis and posttraumatic arthritis; whereas other inflammatory disorders and osteonecrosis are scarce etiologies based on the main clinical series that utilized TKA in patients with knee VD the last two decades[1-5,8-16].

The valgus knee may have any combination of primary or secondary abnormalities even osseous (acquired or preexisting bony anatomic deficiencies) or soft-tissue (lateral and medial). These include on the one hand contraction of the lateral capsule and lateral soft tissues and ligaments; and on the other hand lax medial structures. This constellation of pathology makes attaining soft-tissue balance when the knee is returned to physiologic alignment extremely difficult[2,4,6]. More specifically, the contracted structures are the lateral collateral ligament (LCL), the posterolateral capsule (PLC), the iliotibial band (ITB) and lastly the popliteus tendon. Rarely, there are also affected the long head of the biceps femoralis in addition to the lateral head of the gastrocnemius muscle. Some authors also further described a posterior cruciate ligament (PCL) alteration in valgus knees, but in the literature its influence in maintaining the deformity is not universally accepted[2]. Thus, the knee medial side of the stabilising structures is attenuated. Unlike its varus counterpart, most of the bone defects are found on the lateral femoral condyle, consisting of cartilage erosion, or hypoplasia of the lateral condyle and remodeling of the femur metaphysis, while the plateau of the tibia is generally less affected[2,3,8-10]. The described deformities can lead to a tibial external rotation and to patellar lateral subluxation tendency[11].

In 2005, Ranawat *et al*[1] described three grades of VD. More specifically, Grade-Ⅰ occurs in 80% of the patients, whereas the mechanical axis deviation is less than 10° and it is passively correctable. In Grade-Ⅰ the medial collateral ligament (MCL) is intact. Grade-Ⅱ accounts for 15%; is characterized by a range of axis deviation 10° to 20°, whereas the MCL is functional thought elongated. Grade-Ⅲ is seen in the remaining 5% of the patients having axis deviation more than 20°. The medial stabilising elements are typically not functional so a constrained implant is often required[1,10] (Figure 1).

To understand the important anatomic changes in valgus deformed knees is absolutely helpful so as to choose the best surgical method, to optimize correct component position and restore gap and soft-tissue balancing. Over the last 25 years, different approaches and soft-tissue procedures have been proposed for TKA with VD, having the purpose to restore the limb's mechanical axis. The objective of this article is to give an overview of the most common approaches, to analyze the different techniques of succeeding anatomical or mechanical axis restoration, soft tissue and gap balance and lastly to present the literature up-to-date long term results.

CLINICAL EXAMINATION AND PRE-OPERATING PLANNING

Knee physical examination

During standard physical examination for end-stage degenerative knee disease the orthopaedic physician should observe the patient's gait, in order to identify other dynamic instabilities and assess the lower limb alignment both in the supine and weight-bearing positions. Any sagittal deformity, such as fixed flexion contracture or recurvatum, as well as any rotational deformity, should be attended. It should also be measured the range of motion; and further evaluated the status of the extensor mechanism and the patello-femoral articulation[2,6,11,17].

Furthermore, clinical examination plays a major role for the surgeon so as to determine even if the deformity is correctable or fixed, and whether the knee is stable or unstable. The knee should be further evaluated for anteroposterior laxity, coronal and sagittal deformity, and mediolateral instability[3]. It is very crucial to assess if VD is fixed (Ranawat Grade Ⅲ) or still reducible (Ranawat Grade Ⅱ or Ⅰ). In a fixed deformity, the lateral structures are tight and require release. In cases with non-functional MCL and when the release of the lateral structures has fulfilled, the use of a constrained prosthesis may be necessary. If the deformity is reducible, soft tissue release will be less invasive, and a

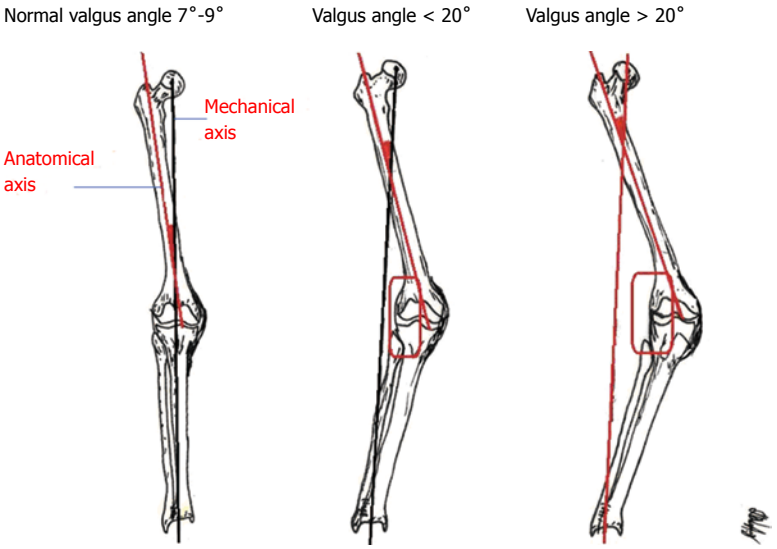

Figure 1 Mechanical and anatomical axis of the normal and valgus knee with deformity less or more of 20°.

standard unconstrained prosthesis could be sufficient. The orthopaedic surgeon would lastly perform a neurovascular examination to differentiate a possible lumbosacral or vascular disease[2,9-11].

Radiographic evaluation

After the clinical assessment, the mandatory preoperative planning radiographs that should be included are: (1) a weight-bearing knee anteroposterior view; (2) a lateral; and (3) a patella merchant view. Furthermore, the limb axis deviation measurement with long standing film views or CT-scan with anterior orientation of the patella is also often needed[3]. It has been shown that rotation up to 20° has little effect on the measurement of the femorotibial axis deviation[18].

Based to our experience, in cases of serious bone stock deficiency a knee computer tomography will be helpful. Attention should be focused on the hypoplastic lateral femoral condyle, the eroded posterior femoral condyle and the remodeled femoris or tibial metaphysis that can lead to malaligned or malrotated positioned component on the femur. The patellofemoral joint may also be partially dislocated. A precise profile X-ray of the knee will help to assess the tibial slope, and the patellar height (alta or baja) according to the Insall-Salvati ratio. Besides, the patellofemoral view at 30° will add to the evaluation of patellar centering by classifying three states (centered, subluxation, luxation)[2,11,19].

A weight-bearing long leg view is fundamental for the evaluation of lower limb alignment (mechanical and anatomical axis), measure the VD level and plan the amount of correction (templating). In order to determine the amount of VD knee medial instability stress radiographs could be also used[2]. A electromyogram should be made in any case of lower limb dysesthesias that may be attributed to lumbosacral disease[2,11] (Figure 2).

Component selection

The implant selection should be carried out pre-operatively, based on the radiological and clinical evaluation, but the final decision should be taken after the bone cuts and knee soft-tissue balancing. There will always be plane A and plane B in the selected prosthesis with regard to the degree of component constraint, especially in severe VD total knee arthroplasties.

Ideally, if proper soft-tissue balance is restored, a minimally constrained component can be implanted. Although most surgeons agree that a posteriorly stabilized (PS) component should be used if significant deformity necessitates PCL sacrifice for soft-tissue balancing, it is not universally accepted[6]. PS-TKA prosthesis provides some degree of posterior stabilization as well as protection against posteromedial and posterolateral translation, but it will not protect against residual medial laxity, which is one of the major considerations in achieving proper balance in VD knees[9,10,17].

The debate in VD, PS *vs* cruciate-retaining (CR) implants has to do with the PCL, which is not rarely contracted and it possibly will limit the VD correction[10,20]. In some cases it may be more difficult to obtain the deformity correction with an intact PCL, since the PCL presence contributes to the deformity on frontal level[21,22]. Besides, on the one hand the PS design is more stable than a CR one, due to the post-cam mechanism; and on the other hand the PS allows greater lateralization of the knee arthroplasty components, which improves patellar tracking[1,2]. For these reasons some surgeons suggest in VD knees to substitute a contracted PCL with a PS design as simplest as to stabilize it by using a CR implant[6].

Besides McAuley *et al*[23] presented that CR implants may possibly be used in different variations of VD arthritic knees in which the implant survival is improved when the LCL and/or the popliteus tendon (POP) are preserved. The likelihood of revision is POP increased by 19.9 times, when release of both the LCL and POP is performed, because of more mediolateral laxity.

Another debated issue is the amount of constraint

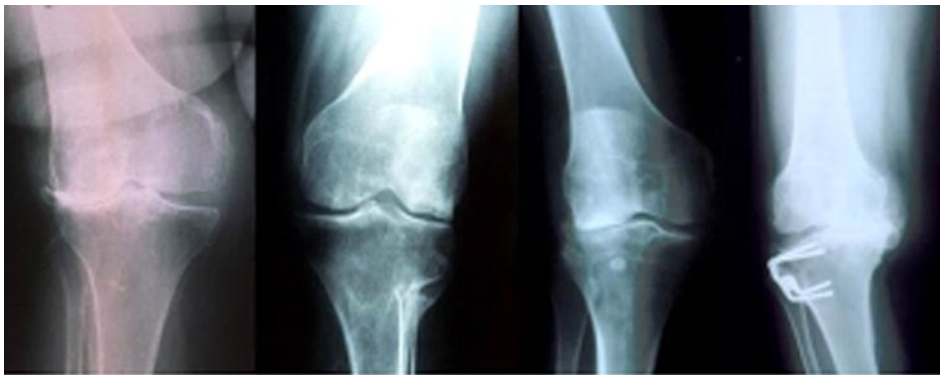

Figure 2 Pre-operative images of different valgus knees.

needed to balance a valgus knee. Favorito *et al*[6] proposed that the surgeon should resist the temptation, when possible, to move to a more highly constrained prosthesis, such as a totally stabilized prosthesis, to compensate for shortcomings in achievable soft-tissue balancing. Although highly constrained components may be necessary in difficult revision cases, they are infrequently necessary for primary TKA. The problem is that in severe VD knees the PCL may be stretched or elongated, which means nonfunctional and these knees require either an ultra-congruent (VVC or hinged) or PC component.

Furthermore, in valgus knees with extreme deficiencies of the lateral femoral condyle, the usage of component augmentation blocks may be required. In cases that the lateral femoral condyle has very little or no distal femoral bone resection or, likewise, from the chamfer and posterior cuts; then these cuts might require component augmentation[4,6]. Though, if the femoral component is being press-fit, then as long as native bone is resting on one of the chamfer cuts (as is usually the case for the posterior bevel or chamfer cut), then the remaining defect can be filled with autograft bone taken from the other cut bone in the procedure[1,6].

SURGICAL APPROACH AND TECHNIQUE

To understand the "typical" operative procedure in valgus knee, it should be considered that the lateral stabilizers, which may hinder reduction, are of two types. On the one hand, those inserting near the flexion-extension axis (LCL and popliteal tendon), acting in both extension and flexion of the knee; and on the other hand those inserting remotely with respect to the axis (fascia lata, posterolateral articular capsule, biceps and external gastrocnemius muscles), acting only in extension[24].

The sequencing of lateral release is controversial, with many and various protocols of progressive stepwise release. Based on the SOO classification presented in 2003 (Societe d'Orthopedie de l'Ouest - Western France Orthopedics Society), four types of valgus knee of increasing surgical difficulty has been distinguished. Type Ⅰ, can be completely reduced, without medial laxity, posing no particular problem and a medial approach is possible; but in case of patellar dislocation, it is recommended a lateral approach. Type Ⅱ is totally or partially irreducible, but without medial laxity, and is the most frequent; lateral release is required, whereas Type Ⅲ is reducible, but with medial distension laxity, and may require management of the medial laxity. Lastly, Type Ⅳ is irreducible, with medial distension laxity, combining the problems of types Ⅱ and Ⅲ[24] (Figure 3).

Anterolateral approach

Keblish[11] was the first, in 1991, to recommend a lateral capsular approach for valgus knee arthroplasty, in addition to Buechel[25] who refined the technique. It has been proved unpopular due to the technical difficulties and demands of the elevation of the tibial tubercle. Nevertheless, Whiteside[26], in 1993, and Burki *et al*[27] in 1999, showed their outcome in valgus deformed knees after lateral approach and tibial tubercle osteotomy (TTO). A disadvantage of this approach is the osteotomy of the tibial tuberosity which is necessary for patellar eversion. Fiddian *et al*[28] presented in 1998 a modified lateral capsular approach with repositioning of vastus lateralis in valgus knee arthroplasties with very good results.

Keblish[11] described a lateral incision along the lateral quadriceps border, taking care to leave 1 cm of the lateral retinaculum, from the junction between the vastus lateralis and the quadriceps tendon to the patella, through 50% of the tendon. During lateral closure, if there were difficulties, he proposed two different tricks to facilitate it: (1) approximation of the infrapatellar fat pad to the patella ligament; and (2) separation of the vastus lateralis from the rectus femoris, followed by suturing together the two tendons in a staggered position[11].

In the anterolateral approach, as detailed described by Nikolopoulos *et al*[4], a straight 8-10 cm midline skin incision is performed and a lateral parapatellar capsulotomy follows. The ITB is elevated carefully from Gerdy's tubercle. In order to medially displace the patella, TTO is performed laterally, leaving the soft tissues intact medially. The osteotomy length measures 5 to 6 cm; whereas proximally, at the upper part of the patellar tendon insertion, the oblique proximal part of

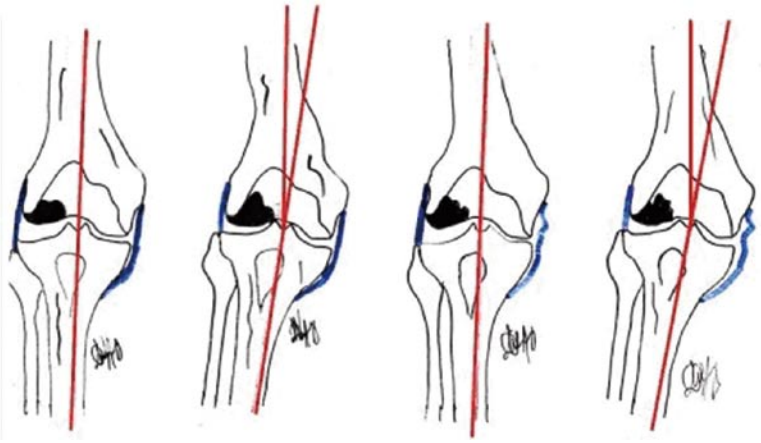

Figure 3 Societe d'Orthopedie de l'Ouest valgus knee classification. SOO: Societe d'Orthopedie de l'Ouest.

the osteotomy prevents proximal migration. The tibial tubercle is medially hinged hence the knee joint surface is widely exposed (Figure 4).

Tibial cut is done - directing the level of the resection perpendicular to its longitudinal axis. The resection should be from 6 to 8 mm in the medial compartment and always has to be performed after having removed all the osteophytes, especially in the lateral side of the tibial plateau. In cases that the bone in the tibial plateau is severely deformed, then almost no bone is resected on the lateral side to avoid medial over-resection or malaligned cuts[2].

The distal femoral cut is performed in 3° of valgus in relation to the femoral axis. The distal femoral cut at 3° only, instead of 5° to 7° that applies in varus knees, protects against under-correction. During TKA for VD, it is proposed to put the prosthesis a slightly more varus so as to counteract any tendency for valgus recurrence[11]. Caution is taken not to over-resect the lateral femoral condyle to avoid marked elevation of the joint line[4]. Rossi *et al*[2] proposed minimal (1-2 mm) or absent of lateral condyle distal femoral resection in severe valgus deformity of the distal femur. Femoral resection should be no more than 10 mm in the medial condyle (usually 7-8 mm). The surgeon has to pay also attention to the lateral condylar hypoplasia that can determine a great intra-rotation of the components if a posterior reference is used[2]. In order to perform the femoral cut in a correct orientation the Whiteside AP axis and the epicondyle axis are used[3,4]. Considering this aspect, Arima *et al*[29] support the utility of using the anteroposterior axis in order to give the proper femoral rotation in valgus anatomy. In cases of severe trochlear dysplasia, where the Whiteside line can be extremely difficult to identify, then the epicondylar axis or parallel to the tibial cut technique should be used to assess a correct femoral rotation[2].

At this stage, sub-periosteal elevation of the POP and LCL from the epicondyle is performed in stages, namely for knees be tight in flexion. The PLC release can be performed in cases of tightness both in flexion and extension. During closure, the tibial tuberosity as a rule is fixed to its original position; or slightly more medially in cases that the patella tends to track laterally and dislocate, so tibial tubercle transfer is necessary for satisfactory alignment. Tibial tubercle fixation can be performed with three wire loops (preferred) or with 2 cortical screws (4.5 mm). Oblique direction of the wire loops offers better resistance to proximal directed forces[4]. Patellar tracking was finally checked with the "no-thumb" test.

According to the surgeons[1-4] preferring the antero-lateral procedure, the main reasons and advantages are: (1) the lateral release, most usually necessary in valgus knees, is part of the approach. In the alternative case of medial arthrotomy, the vascular supply of the extensor mechanism is seriously impaired; (2) the lateral approach facilitates the release of the lateral contracted elements, offering better surgical view; and (3) the possibility to medicalize the tubercle, if required, improving this way the patellar tracking[2,4].

Anteromedial approach

The standard approach performed by the majority of orthopaedic surgeons even in the valgus knee and without contraindications is the anteromedial[1,4,25,30]. A straight midline incision with a medial parapatellar arthrotomy is made. The tibial and femoral bone cuts followed the same technique as the one described in the anterolateral approach. In order to achieve optimal soft tissue balancing, in knee extension the contracted ITB is released even by elevating it form Gerdy's tubercle or by ITB lengthening with multiple stab wounds. If additional release is needed, then the LCL and popliteus is slightly released or lengthened from the distal part of the femur[4]. In most cases with mild to severe VD, the PLC is further released. If the PLC is released, that is done either in flexed knee from the distal part of the femur, by using a curved osteotome; or in fully extended knee by fractionally lengthening with multiple stabs punctures ("pie crust" technique)[1,30]. Finally, the patellofemoral tracking is improved with lateral retinacular release. Tracking of the extensor mechanism is again evaluated with use of the appropriate lift-off test[3,4].

The medialis approach main disadvantage is the

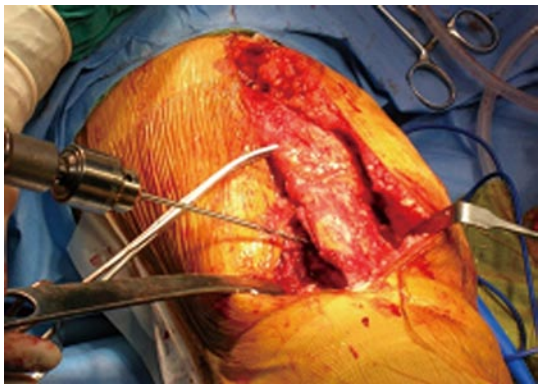

Figure 4 Anterolateral approach with tibial tubercle osteotomy.

difficulty to reach the PLC during the lateral soft tissue release. In addition, patellar vascular damage has been described when a medial parapatellar approach is combined with a lateral release[25].

Soft tissue balancing

Lateral soft tissue: Despite the agreement in the literature that lateral structure release is necessary in VD, there is an open debate on which are the best sequence and the best technique to perform those releases. In the abovementioned part it was presented our experience - based on our publications on the subject of valgus knee arthroplasty[3,4] - in accordance with the main ideas of other researchers[11,25-28,31-33]. In that part it would be analyzed more detailed the literature different proposals for soft tissue balancing of the retracted lateral structures of valgus deformed knees.

The releases should be performed in fully extended knee by using lamina spreaders to check the tension of the medial and lateral compartments. After each release the surgeon should evaluate the alignment and the stability of the knee, in order to achieve a symmetrical rectangular extension and flexion gaps with the spacer block *in situ*[2,34].

Krackow *et al*[10] presented firstly the release of the ITB and the LCL in the type Ⅰ valgus knee, followed by the PLC, POP and the gastrocnemius muscle lateral head, when necessary, while in type Ⅱ valgus deformities a medial ligamentous reconstruction was also proposed, which consisted of either proximal or distal advancement of the medial ligament mechanism according to the surgeon's preference. The same period Buechel[25] presented a sequential three-step lateral release during TKA, for correcting fixed valgus deformed knee which included elevation: (1) the ITT from Gerdy's tubercle; (2) the LCL and PT; and (3) the entire periosteum of the fibular head.

Ranawat *et al*[1] described a stepwise technique in which the first structure to be released is the PCL; and thereafter a PLC intra-articular release by using an electrocautery at the level of the tibial cut surface. When necessary the ITB is released with multiple "inside-out" stab incisions, as well as the LCL. These multiple transverse stab incisions a few centimeters proximal to the joint line of the ITB with a no. 15 surgical blade, lengthens as necessary the lateral side from the inside with the so-called "pie-crusting" technique. On the contrary the POP is normally preserved[1]. Pie-crust technique has also been performed by Clarke *et al*[35] and Aglietti *et al*[36] with excellent results. It is believed that the pie-crust is a reliable technique to correct moderate to severe fixed valgus deformed knees with excellent results and limited complications. The multiple punctures have the following advantages: (1) allow gradual stretching of the lateral soft tissues; (2) reduce the risk of PLC instability; and (3) Maintain the POP tendon[36]. Lastly, one of the disadvantages of this technique is the potential risk of peroneal nerve lesion[1,35,36].

Bruzzone *et al*[37], in a cadaveric study, concluded that the nerve is at risk during the PLC release, in the triangle defined by the POP, the surface of the tibial cut and the ITB posterior fibres ("danger zone"), but not during the ITB pie-crust technique ("safe zone").

Favorito *et al*[6] proposed that due to the fact that the LCL is the tightest structure more commonly, then it is the first structure to be released. The next sequential release follows is the POP (an important structure for rotational and valgus stability in flexion), the PLC, the femoral insertion of the LHG and, finally, the ITB.

Whiteside LA described a soft tissue release sequence based on the anatomic function of ligaments in flexion and extension consistently. A ligament attached to the femur near the epicondyles, so near the axis through which the tibia rotates and the knee flexes and extends, has an important role in flexion stability. On the other hand, a ligament attached far away from the epicondyle is more important for the extension knee stability. Thus, more specifically, for tight knees both in flexion and extension, the LCL and POP tendon are released. For those knees that tightness remains in extension ITB release is needed. Posterior capsular release is performed only when necessary for persistent lateral ligament tightness[38].

Krackow *et al*[39] published a cadaveric study, in 1999, in which it was studied the correction amount achieved in each step of release of two different sequences, comparing it in flexion and extension. The sequences were on the one hand ITB, POP, LCL and LHG; and on the other hand LCL, POP, ITB and LHG. They evaluated the amount of correction at 0°, 45° and 90° of flexion. The results showed that the greatest varus rotation occurred once all structures were released, with the LHG origin last in both groups. Moreover, the largest increase occurred after the release of the LCL. It was concluded that in severe VD, the LCL should be released first; whereas POP and ITB should be released step-by-step according to the soft tissue balancing needs[39].

Boyer *et al*[40] give emphasis to the fact that the lateral approach in valgus TKA allows the ITB elevation from the Gerdy's tubercle in continuity with the anterior

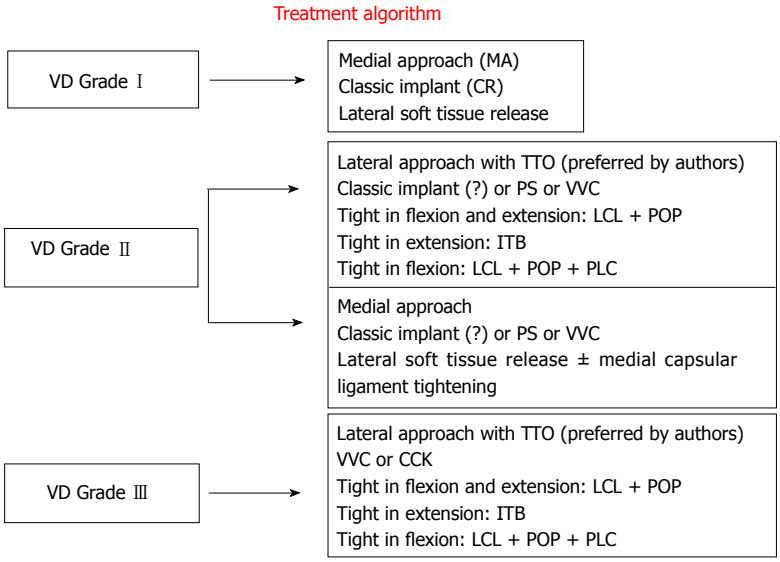

Figure 5 Treatment algorithm in valgus knee arthroplasty. MA: Medial approach; CR: Cruciate retaining; TTO: Tibial tubercle osteotomy; PS: Posterior stabilize; VVC: Varus-valgus constrained; CCK: Constrained condylar knee; ITB: Iliotibial band; LCL: Lateral collateral ligament; POP: Popliteus tendon; PLC: Posterolateral corner.

compartment fascia, and the release of the lateral part of the femur attachments. Was the knee tight in extension after ITB release, then additional releases was performed? If PLC was tight, it was detached from the posterior condyles or transected at the tibial cut level from PCL insertion to the PLC. If this was insufficient, gastrocnemius and biceps tendon release could be considered[40].

An alternative technique for lateral structure release has been described by Brilhault *et al*[41] associated with a lateral parapatellar approach. A sliding osteotomy of the femoral LCL and POP insertions is done and the resulting bone block is mobilized and placed more distally. This procedure produces a rectangular space and had great results in Bremer *et al*[42]'s study, as there was no need for semi-constrained or constrained prosthesis. Mullaji *et al*[43] described a similar technique in which, after the release of the PLC and the ITB, they performed a computer navigated lateral epicondylar osteotomy, with a more accurate repositioning of the epicondyle. With the computer navigated lateral femoral epicondylar osteotomy is fulfilled precise, absolutely controlled, quantitative lengthening of lateral structures and restoration of optimum soft tissue balance and alignment[43].

Medial soft tissue: As described by Krackow *et al*[44] in grade Ⅱ valgus deformities the MCL may not be completely functional and a residual medial laxity is poorly tolerated if VD still exists post-operatively. In these conditions the authors suggested tightening of the medial structures, particularly if the PCL is retained. The advancement of the MCL from the epicondyle or a division and imbrication in order to tighten it can be performed along with the use of constrained condylar implant prosthesis[6] (Figure 5).

CLINICAL RESULTS (TABLE 1)

In the last three decades, a number of different surgical techniques have been described for TKA, in severe valgus deformed knees[1-6,9-11,17,31-33]. As already mentioned, with the aim of correcting the mechanical axis in valgus knees and achieving soft tissue stability, proper bony alignment and ligament balancing are critical. The distal femoral cut at 3° only, instead of 5° to 7° that applies in varus knees, protects against under-correction. In order the mechanical axis after operation not to shift back into valgus, a slightly more varus result has been proposed during TKA for VD[30]. Miyasaka *et al*[30] in their 10 to 20-year follow-up study presented 75% successful bony alignment by having a postoperative valgus alignment 2° to 7°.

Above and beyond, on the subject of ligament balancing in valgus knee there is no consensus on the subject of the correct sequence in which the lateral elements should be released. Starting with Insall *et al*[45], in 1979, who described soft-tissue balancing by transverse division of the ITB above the joint line, and hereafter the lateral aspect of the capsule, the LCL and the POP were detached from the lateral femoral condyle[9,45]. Insall referred 93% of excellent or good results with almost 3% posterior subluxation and 3.6% reoperation rate in 5 years[45] and 6.7% in 12 years[46].

Later on, Keblish[11], Buechel[25] and Fiddian *et al*[28] suggested a lateral capsular approach with or without TTO. More specifically, Keblish[11] presented lateral approach in valgus knees as a "direct, anatomical, more physiologic surgical technique that maintained soft-tissue integrity". By performing "lateral release" as part of the main approach in these 79 cases, Keblish[11] presented on the one hand improvement on the limb alignment, and patellofemoral stability and tracking; whereas on the other hand preserved the medial blood supply. Clinical experience also showed a more aesthetic approach and with results objectively superior. Due to that the lateral approach was recommended as the "approach of choice" for fixed VD in TKA. Scores was good to excellent in 94.3% of cases; whereas knee stability was enhanced with the use of non-constrained

prostheses in that difficult group of patients[11].

Buechel[25] suggested that lateral release with TTO allows the surgeon firstly to regain neutral alignment in valgus deformities of up to 90° and secondly to correct the fixed external tibial rotation deformity. Furthermore, Fiddian *et al*[28] used a lateral capsular approach with repositioning of vastus lateralis at closure. It was presented good to excellent results in all the 25 cases on the knee ROM and the VD restoration; apart from 2 cases which developed 10° and 15° of fixed flexion deformity. Repositioning of vastus lateralis offered also consistent restoration of the normal patellofemoral tracking[28].

Meanwhile, Whiteside recommended sequential releases of the ITB, POP, LCL and lateral head of gastrocnemius[26]. It was also performed TTO and transfer when the Q angle was > 20°. Whiteside presented mean valgus angle after surgery at 7°; but without alignment or varus-valgus stability deterioration during the 6-year follow-up period. Nevertheless, the deformed knees over 25° had a tendency to increase posterior laxity. Lastly, patellar subluxation and dislocation occurred in less than 1% of the cases[26].

On the other hand, Krackow *et al*[10,39,44] and Healy *et al*[47] mentioned medial soft-tissue advancement or reconstruction in combination with lateral release. To be more specific Krackow *et al*[39] studied in cadavers the flexion-extension joint gap change after lateral structure release for VD correction in TKA, and concluded that in severe VD, it should be considered firstly the LCL release and afterwards gradually release of the POP and ITB to be performed. In the 99 knees reported Grade Ⅰ VD knees (according to Ranawat scale) were treated with lateral soft-tissue release, and Grade Ⅱ patients were treated with medial capsular ligament tightening (ligament reconstruction procedures on the medial side). The results were 72% excellent, 17.5% good, 8.25% fair, and 2.25% poor. Ligament stability was satisfactorily established by lateral release in Grade Ⅰ and with the combined medial plication in the Grade Ⅱ patients[44]. Healy *et al*[47] presented on the one hand the lateral ITB release at the level of the tibial osteotomy, and on the other hand proximal MCL advancement with bone plug recession in Grade Ⅱ VD knees. The researchers concluded that all the knees were stable with a functional ROM at the time of the last follow-up in 4 to 9 years.

Apart from Krackow cadaveric study, extremely interesting results published in 2001 by Peters *et al*[48] who studied the flexion-extension gap symmetry in the valgus knee TKA during sequenced release of lateral structures. They concluded that the ITB complete release at the joint line had a more profound effect on the extension than the flexion gap. On the contrary, complete release from the femur of the LCL/POP affected more profoundly the flexion *vs* the extension gap; both of these release steps produced gap increases that were significant (7-12 mm). Consequently, selective release even of the ITB (fractional lengthening), PLC, and POP tendons alone produced smaller magnitudes of correction, and then more symmetrically affected flexion-extension gaps[48].

Besides, Politi *et al*[49] presented in 2004, good-to-excellent results by achieving soft tissue balancing in TKAs with VD > 15°, by using a lateral cruciform retinacular (LCR) release, while the LCL and POP are not released. In 3 only cases out of 35, extension gap balancing could not be achieved by using only the LCR release; and so the LCL and POP were partially released to balance the knee. No further constraint prosthesis was necessary after these releases, whereas the stability of these knees remained stable at the latest mean 3.4-year follow-up[49].

Stern *et al*[31] achieved good-to-excellent results in 91% of his patients in knees with VD > 10°, by accomplishing ligamentous balancing in TKA with sequential releases from the lateral side of the femur and without MCL reconstruction. The postoperative axis alignment was 5° to 9° valgus. Likewise, Laurencin *et al*[50] succeeded excellent results and achieved postoperative anatomic alignment between 0° and 10° valgus in 96% of TKAs with 25° VD, by releasing lateral retinacular with sequential lateral release.

Chalidis *et al*[51] in 2014 presented the outcome of 57 valgus knees Grade Ⅱ according to the Ranawat classification that underwent a primary TKA *via* lateral parapatellar approach with a global step-cut "coffin" type TTO over a 10-year period. Post-operatively, the knee extension, flexion, Knee Society Pain and Function Scores and WOMAC Osteoarthritis Index were significantly improved. In all cases the patellar tracking observed to be congruent. The researchers concluded that "lateral parapatellar approach along with TTO is an effective technique for addressing non-correctable valgus knee deformity during TKA"[51].

Another interesting way to balance the VD knee is the one proposed in 2002 by Brilhault *et al*[41]. The surgeons' treated 13 patients with fixed knee VD by implanting a semi-constrained TKA along with advancement of the LCL by performing a lateral femoral condylar sliding osteotomy. At follow-up of mean 4.6 years, it was improvement of the mean Knee Society score from 32 to 88 and of the functional score from 45 to 73. The mean anatomical axis was corrected from 191 degrees to 180 degrees. There were no postoperative complications as tibiofemoral or patellar instability or distal transposition of the lateral femoral condyle osteotomy[41].

Likewise, Hadjicostas *et al*[52] presented excellent mid-term results of 15 TKAs with VD over 20° by using an osteotomy of the lateral femoral condyle and computer navigation. Before the final fixation of the lateral femoral condyle, the correct mediolateral balancing of the extension gap was confirmed by the navigation system. All the knees were corrected between 0° to 2° valgus. There were also post-operative statistical significant improvement of the knee flexion to a mean of 105° (90° to 130°) and to the mean Knee

Society score from 37 (30 to 44) to 90 points (86 to 94)[53].

Consequently, the "inside-out" or the "outside-in" technique has been proposed by different many surgeons, as Keblish[11], Murray *et al*[8], Stern *et al*[31], Buechel[25] and with similar results. Likewise, the "pie crust" technique by Clarke *et al*[35] and Bruzzone *et al*[37] through the taut PLC or ITB with the knee fully extended has also be proposed as an alternative, having the orthopaedic surgeon always the same expectation, the knee balance[53]. If the lateral release does not sufficiently stabilize flexion and extension gaps, then the medial side of the joint should be addressed, in an effort to limit the degree of lateral soft-tissue release[4,6]. Several techniques have been also described for successfully and safely "tightening" the incompetent MCL[10,39,47] (Table 1).

ADVANTAGES OF THE ANTEROLATERAL APPROACH AND THE LATERAL BALANCING *VS* HAZARDS OF ANTEROMEDIAL APPROACH

The medial parapatellar arthrotomy although recommended as a standard procedure in a varus knee, does not represent the optimal approach in a severe and technically demanding VD knee[4]. More specifically, release of lateral patellar retinaculae is necessitated in most cases, in order to prevent patellar instability. The latter in combination with medial capsulotomy results in significant impairment of the extensor (quadriceps-patellar tendon) mechanism's blood supply[54]. However if the knee joint is approached *via* a lateral parapatellar arthrotomy, release of the lateral retinaculae is integrated in the approach. Patella vascularity is also preserved, as the medial side stays undisturbed[4,10,54]. Laurencin *et al*[50] reported 12% rate of the patella avascular necrosis in TKA by performing medial approach with an extensive lateral release. Miyasaka *et al*[30] reported only one case out of 108, in which a patella fracture occurred 3 years after surgery that was thought to be secondary due to avascular necrosis. In Apostolopoulos *et al*[3] and Nikolopoulos *et al*[4] series, no patella fracture or avascular necrosis was observed.

Moreover, in the medial approach, the lateral displacement of the extensor mechanism increases the external tibial rotation, pushing the contracted PLC away from the operative field[11]. In the lateral capsulotomy the surgeon succeeds better viewing of the contracted lateral structures, as the extensor mechanism is displaced medially, and the tibia rotates internally. As a consequence the hazard of unnecessary steps that may create instability is limited[4,11].

Moreover, in cases that patella's eversion may be compromised by scar tissue - for instance previous tibial osteotomy - the patellar ligament may be particularly prone to avulsion by forceful intraoperative retraction. Therefore, in order to protect the knee extensor mechanism, additional surgical steps are needed either proximally (V-Y quadricepsplasty or "quadriceps snip")[55,56], or distally to the patella (with TTO)[4,6,27,33,57-60].

Analyzing the literature on the subject of TTO, it is considered as a highly advantageous and safe procedure in achieving gentle eversion of the patella without avulsion[1,4,6,27,33,57-60]. Besides, it prevents tibia internal rotation during patellar eversion, which may simplify the correct positioning of the tibial component in severe valgus knees[4,10,60]. It is true that when a TTO is added to the lateral approach in primary TKA in severe deformed valgus knees, the eversion of the patella is easily performed, offering excellent view[4].

Additionally, with a medial capsulotomy, patella tracking is less than optimum and postoperative patellar problems are more common[10,11,26]. Conversely, with a lateral approach patellar tracking is assured with the self-centering movement of the quadriceps-patellar tendon mechanism[1,11,26]. In cases where lateral capsulotomy is combined with TTO, alignment of the extensor mechanism can be improved or adjusted when required, as osteotomy allows transfer of the patellar tendon insertion medially, eliminating the postoperative hazard for patellar maltracking[4,11]. In our series, no patellar instability was observed post-operatively in the Group of lateral parapatellar arthrotomy combined with TTO, as we had the chance to release the soft tissues easily and to transfer the tuberosity medially in two cases; succeeding the optimal quadriceps-patella tendon balance[4].

Burki *et al*[27] applied TTO as a part of their lateral approach in revision valgus TKAs, observing good results in 88%. No complications from the osteotomy side were reported; apart from one case complicated with anterior tibial compartment syndrome. Apostolopoulos *et al*[3] also presented one case in their series. Burki *et al*[27] believed that the TTO may traumatize the anterior tibial compartment; that's why it was recommended release of the anterior tibial fascia with several longitudinal incisions. The length of the osteotomized tubercle in Burki approach was 7 cm, while Apostolopoulos *et al*[3] and Nikolopoulos *et al*[4] shorten it to 5 cm, in order to avoid tibial fractures. Piedade had TTO fractures and tibial plateau fissures in 8.7%[58]. Consequently, consideration needs to be given to the size of the osteotomized bone fragment and the quality of the internal fixation so as to be stable[4].

The results of TKA in valgus knees with conventional medial parapatellar capsulotomy have been inferior to those of varus knees with significant deformity[5]. Karachalios *et al*[5] mentioned the residual VD in these total knee arthroplasties did not result in early component failure, but was associated with a worse clinical outcome, due to patellofemoral malalignment. The literature refers full restoration of the anatomical axis in 70%-78% of valgus knees[2,5,6,9]. Incomplete axis restoration has been linked with impaired clinical outcome[4,5]. Conversely, authors using lateral para-

Table 1 Results reported in the literature on total knee arthroplasty in valgus knee

Ref.	No knees	Valgus deformity	Technique	Implant Selection	Results	Follow-up
Ranawat *et al*[1]	85	> 10°	Inside-out soft-tissue release of PLC with pie-crusting of the ITB Resection of proximal part of tibia and distal part of femur to provide a balanced, rectangular space	PS	Knee Society Score improved from 30 to 93 points; mean functional score improved from 34 to 81 points; mean ROM 110° 3 patients underwent revision No cases of delayed instability	10 yr
Apostolopoulos *et al*[3]	33	> 10°	Lateral parapatellar arthrotomy, in combination with TTO ITB is elevated from Gerdy's tubercle Pie-crust technique in LCL and PLC if needed	CR, PS, VVC or CCK (> 20 °)	Mean IKS score improved from 44 points preoperatively, to 91 points postoperatively, at the last follow-up In terms of alignment parameter, only 2 knees had a residual valgus deviation greater than 7°	11.5 yr
Karachalios *et al*[5]	51	> 20°	Medial or lateral parapatellar arthrotomy; balancing non referred	CR or PS	Bristol knee score 84.3% excellent to good results; 15.7% fair to poor Some deformity persisted in 14/51 patients. These patients had a significantly poorer mean clinical outcome Lateral dislocation or subluxation of the patella was found in 4 knees, with VD > 30°	5.5 yr
Elkus *et al*[9]	85	> 10°	Inside-out soft-tissue release of PCL with pie-crusting of the ITB and resection of the proximal part of the tibia and distal part of the femur to provide a balanced, rectangular space	PS	The mean modified Knee Society clinical score improved from 30 points preoperatively to 93 points postoperatively and the mean functional score improved from 34 to 81 points. The mean post- ROM was 110° No cases of delayed instability	5 yr
Krackow *et al*[10]	99	Type I and II Ranawat	Type I: Lateral soft tissue release Type II: Medial capsular ligament tightening	CR	Knee Society post-operative knee score was 87.6 (± 10.6) and mean post-operative functional score was 52.3	2 yr
Keblish[11]	79	Type 2 and 3 Ranawat	Lateral approach ITB, PLC release	Non-constrained	Scores have been good/excellent in 94.3% of cases	> 2 yr
Whiteside[26]	135	91: 8°-15° 25: 16°-25° 19: > 25°	Lateral approach < 15°: LCL release < 25°: + ITB > 25 °: + POP + Lat. Head gastrocnemius	CR	Neither alignment nor varus-valgus stability deteriorated during the six-year follow-up period, but the knees with greater than 25 degrees deformity had a tendency to increase posterior laxity Patellar subluxation and dislocation occurred in less than 1% of the cases	6 yr
Burki *et al*[27]	61	> 10°	Lateral approach with TTO LCL release	CR	Good or excellent in 45 (88%) patients, fair in four (8%), and poor in two (4%) No postoperative tibial fractures, no delayed unions, and no nonunions at the site of the osteotomy were seen	1 yr
Stern *et al*[31]	134	> 10°	Medial approach and lateral release	118 PS, 8 VVC, 4 KSS, 4 CR	95 knees (71%) rated as excellent, 27 knees (20%) as good, eight knees (6%) as fair, and four knees (3%) as poor Postoperatively, 76% of the knees had a tibiofemoral alignment between 5 degrees and 9 degrees valgus with an overall average of 7 degrees valgus	2-10 yr (mean 4.5 yr)
Miyasaka *et al*[30]	108	> 10°	Medial approach Releasing the lateral retinaculum and ITB, followed when necessary by detaching the PCL and POP tendon from the femur	PS	Mean Knee Society knee score was 88.7 and the mean functional score was 69.2. Postoperative knee alignment averaged 4.5 degrees with 75% of the knees corrected to between 2 degrees and 7 degrees valgus. Postoperative flexion averaged 101 degrees	10-20 yr

Sekiya *et al*[32]	47	6°-24°	All cases required ITB release at Gerdy's tubercle, 83% ITB at joint level, 21% LCL, 17% POP in medial approach group, and 88% ITB at Gerdy's tubercle, 46% ITB at joint level, 13% LCL, 4% POP in lateral approach group	PS	Pre/postoperative alignment, surgical time, lateral laxity, and preoperative ROM had no significant in two groups; however, postoperative flexion was superior in lateral approach group 123.8°, 109° in medial approach group	43 mo
Chalidis *et al*[51]	57	Type II Ranawat	Lateral approach and TTO	PS	Significant improvement in knee extension (P = 0.002), flexion (P = 0.006), Knee Society Pain and Function Scores (P < 0.001) and WOMAC Osteoarthritis Index (P < 0.001) The tibiofemoral angle changed from a preoperative median value of 11° (10 to 17) to a postoperative value of 3.75° (0 to 9)	20-98 mo
Hadjicostas *et al*[52]	15	17°-24°	Osteotomy of the lateral femoral condyle and computer navigation	CR	All the knees were corrected to a mean of 0.5° of valgus (0 to 2) Flexion of the knee had been limited to a mean of 85° (75 to 110) pre-operatively and improved to a mean of 105° (90 to 130) after operation The mean Knee Society score improved from 37 (30 to 44) to 90 points (86 to 94)	24-60 mo

CR: Cruciate retaining; TTO: Tibial tubercle osteotomy; PS: Posterior stabilize; VVC: Varus-valgus constrained; CCK: Constrained condylar knee; ITB: Iliotibial band; LCL: Lateral collateral ligament; POP: Popliteus tendon; PLC: Posterolateral corner.

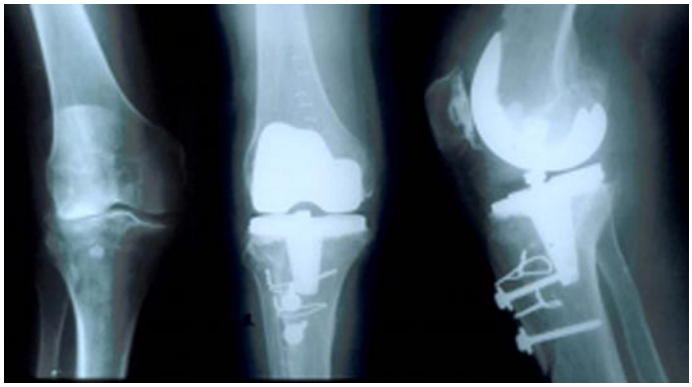

Figure 6 Pre- and Post-operative X-rays in valgus knee (18˚) with lateral approach and tibial tubercle osteotomy.

patellar capsulotomy have reported better results in terms of anatomical axis correction and also in terms of clinical performance[11,25]. Besides, Krackow *et al*[10] by using a PCL-sparing prosthesis presented in 90% of cases good results; as the PCL is not usually contracted in VD knees. However, in severe VD the mechanical axis correction is performed with PCL release. A PCL release or a PCL-substituting prosthesis should be selected in severe valgus deformed knees[25,61].

Lastly, it is important to be mentioned the results of the open debate about which approach leads to better outcome. The recent studies of comparison of a standard medial parapatellar approach in contrast to lateral parapatellar with TTO showed the following. Nikolopoulos *et al*[4] presented no statistically significant differences in terms of clinical results, on the groups of lateral approach with TTO and in the second one of a standard medial approach (Figure 6). Nevertheless in the lateral approach group a valgus deviation occurred in 9% of the patients, compared to 32% in the medial approach one[4]. A similar study has been published by Hirschmann *et al*[33] concluding that the lateral approach combined with TTO leads to comparable functional results and reduced pain at 2 years follow-up. The question that easily arises for the researchers however remained if these results can outweigh the higher risk of early complications and revisions. Moreover, by studying the results in two randomized groups of valgus TKAs, Sekiya *et al*[32] found no significant differences in range of movement (ROM), but better post-operative flexion in the group of lateral approach without TTO *vs* the group of medial parapatellar approach.

Hay *et al*[62] randomly divided 32 patients in two groups, the one in which lateral subvastus approach combined with a TTO was performed and the other with classic medial approach. Between the two groups no significant differences were found in the parameters of clinical outcome (ROM, VAS score, Western Ontario

McMasters University Osteoarthritis index, and KSS) at 2 years follow-up. Better patellar tracking was observed in the group of lateral subvastus approach combined with TTO. Nevertheless the researchers did not support its routine use, because of the complications related with TTO and the longer surgical time (10-15 min). It is not indicated in patients in whom problems with patellar tracking is anticipated[62].

COMPLICATIONS

Favorito *et al*[6] presented in his review article the several complications that have been reported more frequently in this subset of patients. The most commonly reported complications in patients with VD who undergo TKA are tibiofemoral instability (2% to 70%), recurrent valgus deformity (4% to 38%), postoperative motion deficits which requires manipulation under anesthesia (1% to 20%), wound problems (superficial or deep infection) (4% to 13%), patellar stress fracture or osteonecrosis (1% to 12%), patellar tracking problems (2% to 10%), and peroneal nerve palsy (1% to 4%)[1,2,4,8,10,13,37]. In cases with arthrofibrosis and limited flexion < 90° an arthroscopic arthrolysis can be successfully performed[13,33].

Other complications often referred in the English literature are proximal migration of the osteotomized fragment in TTO. In our cases a 5 mm proximal migration was occurred due to breakage of one of the two screws being used to stabilize the osteotomized fragment in one patient[3]. In other cases there is breakage of the wire loops or local infection of the material even early postoperatively, or after the osteotomy fusion[2,27,32,51].

Deep venous thrombosis has also been detected, or superficial or deep infections. Often hematomas, bruises and skin blisters are seen, as in Apostolopoulos *et al*[3] and Nikolopoulos *et al*[4] patients that was treated conservatively. Other researchers referred skin necrosis. Chalidis *et al*[51] published a case of TKA in a patient suffering from rheumatoid arthritis that had as a complication poor wound healing and breakdown, and which was addressed with a gastrocnemius flap. Non-union of the tibial osteotomy was also displayed with migration of the bone fragment.

Very often, especially in cases of TTO, there are operative or post-operative proximal tibial stress fractures. These fractures can be treated surgically or conservative including application of functional knee brace and toe-touch weight bearing of the affected leg till the fracture heals[27,31-33,51].

Peroneal nerve palsy has been cited as an important complication after TKA for VD. The elongation of the lateral side stretches the nerve and places it at risk for indirect injury, *via* traction or induced ischemia[4,6,22]. Other indirect mechanisms of injury may include compression or crushing from tight dressings[63]. When using the "pie crust" technique as part of the lateral release, there is greater deal of concern regarding peroneal nerve safety[27,35,37]. Idusuyi *et al*[64] reported 32 postoperative peroneal nerve palsies in more than ten thousand consecutive TKAs. Of the 32 palsies, 10 knees had 12 degrees of preoperative VD or more. This problem presumably is caused by lengthening the lateral aspect of the knee during lateral stabilizer release and subsequent traction to the peroneal nerve. It is generally recommended that patients be evaluated carefully for symptoms postoperatively. If peroneal nerve palsy type symptoms are discovered, the knee should be flexed to relax the tension that is effectively being placed on the nerve. There are no objective guidelines or data to support the efficacy of any immediate surgical intervention[64].

CONCLUSION

TKA is the gold standard procedure with excellent results for the treatment of advanced knee arthritis. Nevertheless, the long-term results in valgus deformed knee were relatively inferior to those of varus deformation. One of the main reasons of poor prognosis may be the difficulty to acquire good soft-tissue balance during the surgery. That's the reason the valgus knee presents a challenge to the joint replacement surgeon. By taking into account the pre-existing anatomic deformities and by using the AP axis for femoral component placement may help prevent postoperative patello-femoral maltracking and instability. This article is an up-to-date review of the valgus knee philosophy, the approaches and surgical techniques proposed so as to fulfill the lower limb mechanical axis correction; analyzing in detail the pros and cons of each proposed technique. The surgeon in valgus knee should more confidently achieve soft tissue balancing, resulting in better load distribution and enhancing component stability and longevity.

REFERENCES

1 **Ranawat AS**, Ranawat CS, Elkus M, Rasquinha VJ, Rossi R, Babhulkar S. Total knee arthroplasty for severe valgus deformity. *J Bone Joint Surg Am* 2005; **87** Suppl 1: 271-284 [PMID: 16140800 DOI: 10.2106/JBJS.E.00308]

2 **Rossi R**, Rosso F, Cottino U, Dettoni F, Bonasia DE, Bruzzone M. Total knee arthroplasty in the valgus knee. *Int Orthop* 2014; **38**: 273-283 [PMID: 24366186 DOI: 10.1007/s00264-013-2227-4]

3 **Apostolopoulos AP**, Nikolopoulos DD, Polyzois I, Nakos A, Liarokapis S, Stefanakis G, Michos IV. Total knee arthroplasty in severe valgus deformity: interest of combining a lateral approach with a tibial tubercle osteotomy. *Orthop Traumatol Surg Res* 2010; **96**: 777-784 [PMID: 20934399 DOI: 10.1016/j.otsr.2010.06.008]

4 **Nikolopoulos DD**, Polyzois I, Apostolopoulos AP, Rossas C, Moutsios-Rentzos A, Michos IV. Total knee arthroplasty in severe valgus knee deformity: comparison of a standard medial parapatellar approach combined with tibial tubercle osteotomy. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1834-1842 [PMID: 21484391 DOI: 10.1007/s00167-011-1474-4]

5 **Karachalios T**, Sarangi PP, Newman JH. Severe varus and valgus deformities treated by total knee arthroplasty. *J Bone Joint Surg Br* 1994; **76**: 938-942 [PMID: 7983123]

6 **Favorito PJ**, Mihalko WM, Krackow KA. Total knee arthroplasty in the valgus knee. *J Am Acad Orthop Surg* 2002; **10**: 16-24 [PMID: 11809047]

7 **White GR**, Mencio GA. Genu Valgum in Children: Diagnostic and Therapeutic Alternatives. *J Am Acad Orthop Surg* 1995; **3**: 275-283 [PMID: 10795033]

8 **Murray PB**, Rand JA. Symptomatic Valgus Knee: The Surgical Options. *J Am Acad Orthop Surg* 1993; **1**: 1-9 [PMID: 10675850]

9 **Elkus M**, Ranawat CS, Rasquinha VJ, Babhulkar S, Rossi R, Ranawat AS. Total knee arthroplasty for severe valgus deformity. Five to fourteen-year follow-up. *J Bone Joint Surg Am* 2004; **86-A**: 2671-2676 [PMID: 15590852]

10 **Krackow KA**, Jones MM, Teeny SM, Hungerford DS. Primary total knee arthroplasty in patients with fixed valgus deformity. *Clin Orthop Relat Res* 1991; **(273)**: 9-18 [PMID: 1959292 DOI: 10.1097/00003086-199112000-00004]

11 **Keblish PA**. The lateral approach to the valgus knee. Surgical technique and analysis of 53 cases with over two-year follow-up evaluation. *Clin Orthop Relat Res* 1991; **(271)**: 52-62 [PMID: 1914314 DOI: 10.1097/00003086-199110000-00008]

12 **Satish BR**, Ganesan JC, Chandran P, Basanagoudar PL, Balachandar D. Efficacy and mid term results of lateral parapatellar approach without tibial tubercle osteotomy for primary total knee arthroplasty in fixed valgus knees. *J Arthroplasty* 2013; **28**: 1751-1756 [PMID: 23702269 DOI: 10.1016/j.arth.2013.04.037]

13 **Rajgopal A**, Dahiya V, Vasdev A, Kochhar H, Tyagi V. Long-term results of total knee arthroplasty for valgus knees: soft-tissue release technique and implant selection. *J Orthop Surg* (Hong Kong) 2011; **19**: 60-63 [PMID: 21519079]

14 **Radulescu R**, Badila A, Japie I, Ciobanu T, Manolescu R. Primary total knee arthroplasty in severe valgus knee. *J Med Life* 2013; **6**: 395-398 [PMID: 24868248]

15 **Girard J**, Amzallag M, Pasquier G, Mulliez A, Brosset T, Gougeon F, Duhamel A, Migaud H. Total knee arthroplasty in valgus knees: predictive preoperative parameters influencing a constrained design selection. *Orthop Traumatol Surg Res* 2009; **95**: 260-266 [PMID: 19481514 DOI: 10.1016/j.otsr.2009.04.005]

16 **Ang CL**, Fook S, Chia SL, Chin PL, Lo NN, Yeo SJ. Unconstrained arthroplasty in type II valgus knees: posterior stabilized or cruciate retaining? *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 666-673 [PMID: 24057422 DOI: 10.1007/s00167-013-2677-7]

17 **Lombardi AV**, Dodds KL, Berend KR, Mallory TH, Adams JB. An algorithmic approach to total knee arthroplasty in the valgus knee. *J Bone Joint Surg Am* 2004; **86-A** Suppl 2: 62-71 [PMID: 15691110]

18 **Swanson KE**, Stocks GW, Warren PD, Hazel MR, Janssen HF. Does axial limb rotation affect the alignment measurements in deformed limbs? *Clin Orthop Relat Res* 2000; **(371)**: 246-252 [PMID: 10693572 DOI: 10.1097/00003086-200002000-00029]

19 **Robbins GM**, Masri BA, Garbuz DS, Duncan CP. Preoperative planning to prevent instability in total knee arthroplasty. *Orthop Clin North Am* 2001; **32**: 611-626, viii [PMID: 11689374 DOI: 10.1016/S0030-5898(05)70231-5]

20 **Mihalko WM**, Miller C, Krackow KA. Total knee arthroplasty ligament balancing and gap kinematics with posterior cruciate ligament retention and sacrifice. *Am J Orthop* (Belle Mead NJ) 2000; **29**: 610-616 [PMID: 10955465]

21 **Matsuda Y**, Ishii Y, Noguchi H, Ishii R. Varus-valgus balance and range of movement after total knee arthroplasty. *J Bone Joint Surg Br* 2005; **87**: 804-808 [PMID: 15911663 DOI: 10.1302/0301-620X.87B6.15256]

22 **Mihalko WM**, Krackow KA. Anatomic and biomechanical aspects of pie crusting posterolateral structures for valgus deformity correction in total knee arthroplasty: a cadaveric study. *J Arthroplasty* 2000; **15**: 347-353 [PMID: 10794231 DOI: 10.1016/S0883-5403(00)90716-2]

23 **McAuley JP**, Collier MB, Hamilton WG, Tabaraee E, Engh GA. Posterior cruciate-retaining total knee arthroplasty for valgus osteoarthritis. *Clin Orthop Relat Res* 2008; **466**: 2644-2649 [PMID: 18712454 DOI: 10.1007/s11999-008-0436-8]

24 **Williot A**, Rosset P, Favard L, Brilhault J, Burdin P. Total knee arthroplasty in valgus knee. *Orthop Traumatol Surg Res* 2010 May 4; Epub ahead of print [PMID: 20447887 DOI: 10.1016/j.otsr.2010.03.009]

25 **Buechel FF**. A sequential three-step lateral release for correcting fixed valgus knee deformities during total knee arthroplasty. *Clin Orthop Relat Res* 1990; **(260)**: 170-175 [PMID: 2225620]

26 **Whiteside LA**. Correction of ligament and bone defects in total arthroplasty of the severely valgus knee. *Clin Orthop Relat Res* 1993; **(288)**: 234-245 [PMID: 8458139 DOI: 10.1097/00003086-199303000-00030]

27 **Burki H**, von Knoch M, Heiss C, Drobny T, Munzinger U. Lateral approach with osteotomy of the tibial tubercle in primary total knee arthroplasty. *Clin Orthop Relat Res* 1999; **(362)**: 156-161 [PMID: 10335294]

28 **Fiddian NJ**, Blakeway C, Kumar A. Replacement arthroplasty of the valgus knee. A modified lateral capsular approach with repositioning of vastus lateralis. *J Bone Joint Surg Br* 1998; **80**: 859-861 [PMID: 9768898 DOI: 10.1302/0301-620X.80B5.7626]

29 **Arima J**, Whiteside LA, McCarthy DS, White SE. Femoral rotational alignment, based on the anteroposterior axis, in total knee arthroplasty in a valgus knee. A technical note. *J Bone Joint Surg Am* 1995; **77**: 1331-1334 [PMID: 7673281]

30 **Miyasaka KC**, Ranawat CS, Mullaji A. 10- to 20-year followup of total knee arthroplasty for valgus deformities. *Clin Orthop Relat Res* 1997; **(345)**: 29-37 [PMID: 9418618]

31 **Stern SH**, Moeckel BH, Insall JN. Total knee arthroplasty in valgus knees. *Clin Orthop Relat Res* 1991; **(273)**: 5-8 [PMID: 1959286 DOI: 10.1097/00003086-199112000-00003]

32 **Sekiya H**, Takatoku K, Takada H, Sugimoto N, Hoshino Y. Lateral approach is advantageous in total knee arthroplasty for valgus deformed knee. *Eur J Orthop Surg Traumatol* 2014; **24**: 111-115 [PMID: 23412262 DOI: 10.1007/s00590-012-1137-2]

33 **Hirschmann MT**, Hoffmann M, Krause R, Jenabzadeh RA, Arnold MP, Friederich NF. Anterolateral approach with tibial tubercle osteotomy versus standard medial approach for primary total knee arthroplasty: does it matter? *BMC Musculoskelet Disord* 2010; **11**: 167 [PMID: 20649966 DOI: 10.1186/1471-2474-11-167]

34 **Matsueda M**, Gengerke TR, Murphy M, Lew WD, Gustilo RB. Soft tissue release in total knee arthroplasty. Cadaver study using knees without deformities. *Clin Orthop Relat Res* 1999; **(366)**: 264-273 [PMID: 10627744 DOI: 10.1097/00003086-199909000-00034]

35 **Clarke HD**, Fuchs R, Scuderi GR, Scott WN, Insall JN. Clinical results in valgus total knee arthroplasty with the "pie crust" technique of lateral soft tissue releases. *J Arthroplasty* 2005; **20**: 1010-1014 [PMID: 16376256 DOI: 10.1016/j.arth.2005.03.036]

36 **Aglietti P**, Lup D, Cuomo P, Baldini A, De Luca L. Total knee arthroplasty using a pie-crusting technique for valgus deformity. *Clin Orthop Relat Res* 2007; **464**: 73-77 [PMID: 17975373]

37 **Bruzzone M**, Ranawat A, Castoldi F, Dettoni F, Rossi P, Rossi R. The risk of direct peroneal nerve injury using the Ranawat "inside-out" lateral release technique in valgus total knee arthroplasty. *J Arthroplasty* 2010; **25**: 161-165 [PMID: 19056220 DOI: 10.1016/j.arth.2008.08.016]

38 **Whiteside LA**. Selective ligament release in total knee arthroplasty of the knee in valgus. *Clin Orthop Relat Res* 1999; **(367)**: 130-140 [PMID: 10546607 DOI: 10.1097/00003086-199910000-00016]

39 **Krackow KA**, Mihalko WM. Flexion-extension joint gap changes after lateral structure release for valgus deformity correction in total knee arthroplasty: a cadaveric study. *J Arthroplasty* 1999; **14**: 994-1004 [PMID: 10614893 DOI: 10.1016/S0883-5403(99)90016-5]

40 **Boyer P**, Boublil D, Magrino B, Massin P, Huten D. Total knee replacement in the fixed valgus deformity using a lateral approach: role of the automatic iliotibial band release for a successful balancing. *Int Orthop* 2009; **33**: 1577-1583 [PMID: 19066890 DOI: 10.1007/s00264-008-0698-5]

41 **Brilhault J**, Lautman S, Favard L, Burdin P. Lateral femoral sliding osteotomy lateral release in total knee arthroplasty for a fixed valgus deformity. *J Bone Joint Surg Br* 2002; **84**: 1131-1137 [PMID: 12463657 DOI: 10.1302/0301-620X.84B8.12824]

42 **Bremer D**, Orth BC, Fitzek JG, Knutsen A. [Briard's sagittal sliding osteotomy of the lateral condyle in total knee arthoplasty of the severe valgus knee]. *Oper Orthop Traumatol* 2012; **24**: 95-108 [PMID: 22526171 DOI: 10.1007/s00064-011-0064-4]

43 **Mullaji AB**, Shetty GM. Lateral epicondylar osteotomy using

computer navigation in total knee arthroplasty for rigid valgus deformities. *J Arthroplasty* 2010; **25**: 166-169 [PMID: 19679436 DOI: 10.1016/j.arth.2009.06.013]
44 **Krackow KA**, Holtgrewe JL. Experience with a new technique for managing severely overcorrected valgus high tibial osteotomy at total knee arthroplasty. *Clin Orthop Relat Res* 1990; **(258)**: 213-224 [PMID: 2394048 DOI: 10.1097/00003086-199009000-00027]
45 **Insall J**, Scott WN, Ranawat CS. The total condylar knee prosthesis. A report of two hundred and twenty cases. *J Bone Joint Surg Am* 1979; **61**: 173-180 [PMID: 422602]
46 **Vince KG**, Insall JN, Kelly MA. The total condylar prosthesis. 10- to 12-year results of a cemented knee replacement. *J Bone Joint Surg Br* 1989; **71**: 793-797 [PMID: 2584249]
47 **Healy WL**, Iorio R, Lemos DW. Medial reconstruction during total knee arthroplasty for severe valgus deformity. *Clin Orthop Relat Res* 1998; **(356)**: 161-169 [PMID: 9917681 DOI: 10.1097/00003086-199811000-00023]
48 **Peters CL**, Mohr RA, Bachus KN. Primary total knee arthroplasty in the valgus knee: creating a balanced soft tissue envelope. *J Arthroplasty* 2001; **16**: 721-729 [PMID: 11547370 DOI: 10.1054/arth.2001.25504]
49 **Politi J**, Scott R. Balancing severe valgus deformity in total knee arthroplasty using a lateral cruciform retinacular release. *J Arthroplasty* 2004; **19**: 553-557 [PMID: 15284974 DOI: 10.1016/j.arth.2003.12.083]
50 **Laurencin CT**, Scott RD, Volatile TB, Gebhardt EM. Total knee replacement in severe valgus deformity. *Am J Knee Surg* 1992; **5**: 135-139
51 **Chalidis BE**, Ye K, Sachinis NP, Hawdon G, McMahon S. Lateral parapatellar approach with tibial tubercle osteotomy for the treatment of non-correctable valgus knee osteoarthritis: a retrospective clinical study. *Knee* 2014; **21**: 204-208 [PMID: 23796619 DOI: 10.1016/j.knee.2013.05.008]
52 **Hadjicostas PT**, Soucacos PN, Thielemann FW. Computer-assisted osteotomy of the lateral femoral condyle with non-constrained total knee replacement in severe valgus knees. *J Bone Joint Surg Br* 2008; **90**: 1441-1445 [PMID: 18978262 DOI: 10.1302/0301-620X.90B11.20092]
53 **McNabb DC**, Kim RH, Springer BD. Instability after total knee arthroplasty. *J Knee Surg* 2015; **28**: 97-104 [PMID: 25518877 DOI: 10.1055/s-0034-1396080]
54 **Wetzner SM**, Bezreh JS, Scott RD, Bierbaum BE, Newberg AH. Bone scanning in the assessment of patellar viability following knee replacement. *Clin Orthop Relat Res* 1985; **(199)**: 215-219 [PMID: 4042481]
55 **Coonse K**, Adams JD. A new operative approach to the knee joint. *Surg Gynecol Obstet* 1943; **77**: 344–347
56 **Garvin KL**, Scuderi G, Insall JN. Evolution of the quadriceps snip. *Clin Orthop Relat Res* 1995; **(321)**: 131-137 [PMID: 7497658 DOI: 10.1097/00003086-199512000-00020]
57 **Dolin MG**. Osteotomy of the tibial tubercle in total knee replacement. A technical note. *J Bone Joint Surg Am* 1983; **65**: 704-706 [PMID: 6853581]
58 **Whiteside LA**, Ohl MD. Tibial tubercle osteotomy for exposure of the difficult total knee arthroplasty. *Clin Orthop Relat Res* 1990; **(260)**: 6-9 [PMID: 2225644 DOI: 10.1097/00003086-199011000-00003]
59 **Wolff AM**, Hungerford DS, Krackow KA, Jacobs MA. Osteotomy of the tibial tubercle during total knee replacement. A report of twenty-six cases. *J Bone Joint Surg Am* 1989; **71**: 848-852 [PMID: 2745481]
60 **Piedade SR**, Pinaroli A, Servien E, Neyret P. Tibial tubercle osteotomy in primary total knee arthroplasty: a safe procedure or not? *Knee* 2008; **15**: 439-446 [PMID: 18771928 DOI: 10.1016/j.knee.2008.06.006]
61 **Insall JN**, Easley ME. Surgical techniques and instrumentation in total knee arthroplasty. In: Insall JN, Scott WN, editors. Surgery of the Knee. 3rd ed. New York NY: Churchill Livingstone, 2001: 1717-1738
62 **Hay GC**, Kampshoff J, Kuster MS. Lateral subvastus approach with osteotomy of the tibial tubercle for total knee replacement: a two-year prospective, randomised, blinded controlled trial. *J Bone Joint Surg Br* 2010; **92**: 862-866 [PMID: 20513886 DOI: 10.1302/0301-620X.92B6.24027]
63 **Rose HA**, Hood RW, Otis JC, Ranawat CS, Insall JN. Peroneal-nerve palsy following total knee arthroplasty. A review of The Hospital for Special Surgery experience. *J Bone Joint Surg Am* 1982; **64**: 347-351 [PMID: 7061551]
64 **Idusuyi OB**, Morrey BF. Peroneal nerve palsy after total knee arthroplasty. Assessment of predisposing and prognostic factors. *J Bone Joint Surg Am* 1996; **78**: 177-184 [PMID: 8609107]

P- Reviewer: Canavese F, Colak T, Kovar MF **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wu HL

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i6.483

World J Orthop 2015 July 18; 6(6): 483-490
ISSN 2218-5836 (online)

Evaluation of current surgeon practice for patients undergoing lumbar spinal fusion surgery in the United Kingdom

Alison Rushton, Louise White, Alison Heap, Nicola Heneghan

Alison Rushton, Nicola Heneghan, School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom

Louise White, Alison Heap, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Birmingham B15 2TH, United Kingdom

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: There are no conflicts of interest arising from this work.

Data sharing statement: No further data are available.

Correspondence to: Dr. Alison Rushton, Senior Lecturer of Physiotherapy, School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom. a.b.rushton@bham.ac.uk
Telephone: +44-121-4158597

Received: February 26, 2015
Peer-review started: February 27, 2015
First decision: April 27, 2015
Revised: May 20, 2015
Accepted: June 1, 2015
Article in press: June 2, 2015
Published online: July 18, 2015

Abstract

AIM: To ascertain current surgeon practice in the United Kingdom National Health Service for the management of patients undergoing lumbar spinal fusion surgery.

METHODS: Descriptive survey methodology utilised an online questionnaire administered through SurveyMonkey. Eligible participants were all surgeons currently carrying out lumbar spinal fusion surgery in the National Health Service. Two previous surveys and a recent systematic review informed questions. Statistical analyses included responder characteristics and pre-planned descriptive analyses. Open question data were interpreted using thematic analysis.

RESULTS: The response rate was 73.8%. Most surgeons (84%) were orthopaedic surgeons. Range of surgeon experience (1-15 years), number of operations performed in the previous 12 mo (4-250), and range of information used to predict outcome was broad. There was some consistency of practice: most patients were seen preoperatively; all surgeons ensured patients are mobile within 3 d of surgery; and there was agreement for the value of post-operative physiotherapy. However, there was considerable variability of practice: variability of protocols, duration of hospital stay, use of discharge criteria, frequency and timing of outpatient follow up, use of written patient information and outcome measures. Much variability was explained through patient-centred care, for example, 62% surgeons tailored functional advice to individual patients.

CONCLUSION: Current United Kingdom surgeon practice for lumbar spinal fusion is described. The surgical procedure and patient population is diverse, and it is therefore understandable that management varies. It is evident that care should be patient-centred. However with high costs and documented patient dissatisfaction

it is important that further research evaluates optimal management.

Key words: Lumbar spinal fusion; Spinal surgery; Surgeon practice; Management; Fusion

Core tip: This study surveyed all surgeons carrying out lumbar spinal fusions in the United Kingdom (response rate 73.8%) to ascertain current practice. Eighty-four percent of participants were orthopaedic surgeons and their experience of lumbar spinal fusion ranged from 1-15 years, each performing 4-250 operations in the previous 12 mo. Surgeons consistently saw patients preoperatively, ensured patients are mobile within 3 d of surgery, and valued post-operative physiotherapy. However, variability of protocols, duration of hospital stay, use of discharge criteria, frequency and timing of outpatient follow up, use of written patient information and outcome measures was considerable. Much variability was explained through patient-centred care.

Rushton A, White L, Heap A, Heneghan N. Evaluation of current surgeon practice for patients undergoing lumbar spinal fusion surgery in the United Kingdom. *World J Orthop* 2015; 6(6): 483-490 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/483.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.483

INTRODUCTION

In the United Kingdom, the largest single component of expenditure for the management of low back pain is surgery[1]. Lumbar spinal fusion accounted for 14% of United States back surgery expenditure in 1992, increasing to 47% by 2003[2]. Recent data evidences a worldwide increase in lumbar spinal fusion, illustrated by > 4036 operations within the United Kingdom National Health Service[1] in 2009/10[3]; representing a 14% increase on the previous year. The United States reported an increased spinal surgical rate of 220% from 1990-2001[4,5] followed by a reduction between 2002-2007, although during the same period the rate of lumbar fusion surgery increased from 1.3 to 10.9 operations for every 100000 patients[6]. The increased rates are partly explained by technological advances, including the United States Food and Drug Administration's approval in 1996 of intervertebral cage implants and in 1998 of pedicle screws. Data also reveals considerable variation in fusion rates between regions within and between countries[2,7], suggesting poor surgeon consensus and/or a range of indications for surgery. A recent survey found a lack of consensus between 62 surgeons (Netherlands) regarding both prognostic factors and predictive tests for patient selection for surgery[8].

The primary indication for lumbar fusion is back and/or leg pain as a result of degenerative disease, as it can potentially help to stabilise the spine[9]. It is acknowledged that fusion could be beneficial in some patients but it remains a controversial procedure[8]. The updated Cochrane review investigating effectiveness of surgery for lumbar spondylosis of degenerative causes found conflicting results[1], and in the more recent United Kingdom spine stabilisation trial, there was no evidence that fusion was more beneficial at 2 years follow up compared to an intensive rehabilitation programme[10]. The trial also identified a higher complication rate than previous trials, and evidence of less cost-effectiveness for surgery when compared with intensive rehabilitation[10]. Swedish National Spine Register data illustrate that 40% patients communicated dissatisfaction regarding their outcome at 12 mo, and 25% patients had no change or described worsened pain (back and/or leg) following their surgery[11].

Synthesising existing literature, the increasing rate of surgery, lack of data supporting effectiveness of surgery, the high reported patient dissatisfaction, continued level of patient disability, documented high revision rate (in the United Kingdom > 200/year)[3], and 13% re-hospitalisation rate (United States)[6], evidence two problems. Firstly, research needs to investigate the effectiveness of fusion surgery in specific populations of patients, and, secondly, that optimal outcomes of surgery through post-operative management/rehabilitation requires investigation. Our recent systematic review[12] found only two trials, providing inconclusive evidence of very low quality for the effectiveness of physiotherapy rehabilitation for patients after lumbar spinal fusion surgery.

An initial evaluation of current practice by surgeons is necessary to ensure the appropriate focus and parameters of future trials. No evaluation of surgeon practice has specifically focused on lumbar spinal fusion. McGregor *et al*[13] did evaluate post-operative practice of spinal surgeons in the United Kingdom across the range of their surgical procedures; finding considerable variation in practice, inconsistent advice regarding functional restrictions following surgery, and limited referral for rehabilitation.

MATERIALS AND METHODS

Objective

To ascertain current surgeon practice in the United Kingdom National Health Service for the management of patients undergoing lumbar spinal fusion surgery.

Setting, design and sample size

A descriptive United Kingdom survey[14] was conducted. Target settings were all units within United Kingdom NHS Trusts in which surgeons perform spinal fusion surgery; and, the aim was to obtain data from all surgeons who currently conduct lumbar spinal fusion

surgery.

Methods for data collection and distribution

Data were collected through an on-line SurveyMonkey questionnaire to ensure participants' cost effectiveness (ease of questionnaire return, response time), ease of administration (no paperwork, easy tracking of reminders and returns), and ease of data management[15]. At 3 and 6 wk, reminders were sent to participants.

Development of the questionnaire

A team consisting of a spinal surgeon, physiotherapists, and research methodologists developed the range of closed and open questions; informed by the findings from our recent systematic review[12], and previous surveys on spinal surgery[13] and lumbar discectomy[16]. The questionnaire consisted of 4 sections: surgeons' backgrounds, surgical procedures, and pre- and post-operative practice. There were 2 phases to the pilot of the questionnaire. Phase Ⅰ recruited student physiotherapists (n = 15). Surgeons were not used as it was predicted that the potential sample for the main study was limited. Phase Ⅱ recruited physiotherapists working in spinal surgery and surgeons who would, then, not participate in the survey (n = 5). Sequencing and wording of questions were amended to enhance the questionnaire's reliability and validity.

Statistical analysis

Data were downloaded to SPSS (version 19), and to ensure integrity were checked. None of these data were traceable to individual respondents. All analyses were pre-planned and comprised summaries across respondents, to ensure anonymity of findings. Statistical analyses incorporated a combination of simple graphical, tabular and numerical descriptive summaries of: characteristics of surgeons, variation in routine surgical practice pre-operatively and post-operatively. Open question data responses were analysed through thematic analysis.

Participants and recruitment

The target population comprised surgeons currently performing spinal fusion surgery within NHS Trusts and major surgery centres. Recognised registers of surgeons (*e.g.*, register of the British Association of Spinal Surgeons), and contact with all NHS Trusts, Health Authorities and specialist orthopaedic centres in the United Kingdom enabled the identification of surgeons. Cross-referencing of these sources created a listing of potentially eligible surgeons. Invitations to participate were sent through email accompanied by a Participant Information Sheet. This approach for recruitment was verbally approved by the local Research and Development office. Ethical approval was provided by the University of Birmingham. Questionnaire completion was taken as informed consent. To ensure that it was not possible to link data to individuals, IP addresses were not saved. The questionnaires were distributed to 42 eligible participants.

RESULTS

Participants

Thirty-one out of 42 questionnaires were returned giving a response rate of 73.8%. Twenty (64%) surgeons worked in a teaching/University hospital, 8 (26%) in a District General Hospital and 3 (10%) in a Specialist Centre. Of these, 1 surgeon worked across both a teaching/University hospital and Specialist Centre. Five (16%) surgeons who worked in a University/teaching hospital specialised in neurosurgery, whilst all others (n = 26, 84%) specialised in orthopaedic surgery. Experience in lumbar spinal fusion surgery ranged 1-15 years (median 10, inter-quartile range 4-17 years). The surgeons had conducted 4-250 fusion operations in the previous 12 mo = (median 23, inter-quartile range 20-40 operations). Nineteen (61%) surgeons reported no change in the rate of surgery based on their experience over the previous 5 years, whilst 7 (23%) reported an increase and 5 (16%) a decrease.

Management of patients pre-operatively

Of the surgeons reporting on pre-operative management (n = 30, 94%), their patients were seen pre-operatively by nurses (n = 21, 70%), anaesthetists (n = 19, 63%), physiotherapists (n = 13, 43%), occupational therapists (n = 2, 7%) and other healthcare professionals (5, 17%) (*e.g.*, pain specialist). All surgeons discuss expected post-surgery outcomes with patients. One surgeon's patients underwent a spinal rehabilitation programme pre-operatively. Surgeons reported a range of indications for surgery, that management should be tailored to the individual patient, and that patient factors (motivation, pre-operative fitness, weight) influence management decisions. Surgeons used a range of information to predict expected outcome (Table 1). Thirteen surgeons (43%) provided written information sheets/booklets for patients pre-operatively.

Spinal fusion operation

Twenty nine (91%) surgeons provided information regarding operations. Instability, leg and back pain were the most frequently reported indicators (Table 2). Reported ages of patients undergoing operation ranged 14-100 years (Figure 1), with variation in reports for the youngest (14-50 years) and oldest (55-100 years). Twenty four (83%) surgeons reported that the mean patient age had not changed over the last five years.

All surgeons (n = 29) reported using instrumentation for some operations, with 11 (38%) performing operations without instrumentation. Other variations, used by over half of the responding surgeons, included: open procedures (n = 26), posterior lumbar interbody fusion (n = 20), transforaminal lumbar interbody fusion (n = 20), anterior lumbar interbody fusion (n =

Table 1 Information used to predict post surgery outcomes

Patient characteristics and history
Patient personality and expectations[1], including motivation
Age, occupation/unemployment, social issues, smoking, weight
Presence or absence of personal injury or yellow flags
Diabetes, other medical co-morbidities
Clinical information including patient history, *e.g.*, symptoms duration
Use of outcome data, *e.g.*, DRAM, GAD7, ODI, PHQ9, SF36, SRS, VAS pain, walking
Response to previous approaches, *e.g.*, physiotherapy, facet joint injections, discogram, disc block
Pathology or degree of deformity
Number of levels predominant leg pain; more leg than back pain
Performance based outcome measures
Neurological examination
Imaging: CT scans, CT with 3D reconstruction, discography, MRI scans, X-ray
Evidence
Audit of data from past patients
Literature or empirical evidence
Experiential clinical experience
Other
Pathology: segmental instability, single level, spondylolisthesis, central disc protrusion
Pain mechanism: no features of chronic regional pain syndrome (allodynia, non-anatomical pain), stenosis

[1]Realistic expectations (VAS 4/10 end result would be satisfactory). DRAM: Distress Risk Assessment Method; GAD7: Generalized Anxiety Disorder 7-item scale; ODI: Oswestry Disability Index; PHQ9: Patient health questionnaire - depression component; VAS: Visual analogue scale; SRS: Session rating scale.

Table 2 Key indicators for performing spinal fusion (*n* = 29 responders)

Key indicator for surgery	Surgeons *n* (%)
Instability	25 (86)
Leg pain	21 (72)
Back pain	18 (62)
Failed conservative treatment	17 (59)
Failed previous surgery	16 (55)
Degenerative disc disease	15 (52)
Neurological changes	13 (48)
Other[1]	12 (41)

[1]Other indicators included: deformity stabilisation ± degenerate scoliosis (*n* = 4), infection (*n* = 2), tumours (*n* = 2), trauma (*n* = 1), degenerative spondylolisthesis or spondylolysis (*n* = 7), recurrent disc prolapse (*n* = 2), stenosis (*n* = 3).

Table 3 Complications of lumbar spinal fusion surgery reported by surgeons (*n* = 29 surgeons)

Complications of lumbar spinal fusion surgery	Surgeons *n* (%)
Persistent symptoms	18 (62)
Dislodged instrumentation/implant failure	14 (48)
Infection	9 (31)
Failure of fusion	7 (24)
Dural tear	6 (21)
Nerve injury	5 (17)
Failure at adjacent level	4 (14)
No improvement	3 (10)
Other[1]	8 (28)

[1]Epidural hematoma, cauda equina, DVT/PE, pain at donor site, wound problems, respiratory problems, urinary tract infection, and pseudo bowel obstruction.

15), transforaminal lumbar interbody fusion (*n* = 20), combined anterior and posterior fusion (*n* = 13), and minimally invasive procedures (*n* = 15). Five surgeons reported other procedures that included: posterolateral fusion; posterolateral fusion with pedicle screws; posterior spinal fusion with instrumentation without anterior interbody fusion and posterolateral graft; transforaminal lumbar interbody; fusion cage inserted by posterior lumbar interbody fusion approach; and lateral interbody fusion. Surgeons reported that during the previous 5 years, 30%-90% of patients required fusion at 1 level, 10%-40% 2 levels and 10%-30% ⩾ 3 levels.

Inpatient management

Twenty two (76% of 29) surgeons used post-operative protocols/pathway/discharge criteria. Nine surgeons reported that the protocol varied according to type of surgical procedure, with 5 reporting influence for anterior *vs* posterior lumbar interbody fusion, or instrumented *vs* non-instrumented procedures. Thirteen surgeons reported that the protocol was not influenced by procedure. Other reported factors influencing protocols included presence of co-morbidities, patient factors (fitness, weight), and speed of mobilisation. Written instructions/advice were provided post-operatively by 16 surgeons (55%). Post-operative physiotherapy was provided routinely to patients of 27 surgeons (93%); the remaining 2 surgeons would never provide physiotherapy. More than half of surgeons (*n* = 15, 52%) did not employ discharge criteria. Of the 14 (48%) who did, there was no consensus of medical and functional criteria being used (Figure 2).

A range of post-operative complications were reported by surgeons with persistent symptoms (*n* = 18, 62%) and dislodged instrumentation/implant failure (*n* = 14, 48%) most commonly reported (Table 3). In the absence of complications, all surgeons (*n* = 29) reported that patients are mobilised within 3 d of surgery, with the majority (*n* = 24, 83%) mobilised on the same or first day post-operation. Patient reported outcome measures are rarely used, with only 2 surgeons (5%) routinely using pain Visual Analogue Scale and Oswestry Disability Index, and 1 of these surgeons additionally using SF-12. No surgeons use performance based outcomes measures.

Advice on return to function was tailored to individual patients by 18 surgeons (62%); dependent upon patient factors (age, fitness, occupation, expectations, compliance, motivation, anxiety levels), surgical factors (bone quality, quality of fixation), presence co-morbidities (obesity), complications and pain levels. Surgeons' advice on when to return to sitting varied from immediately to 6 wk; return to driving, sex and work from 1 wk to 6 mo; and sport, contact sports, jogging/running, outer-range lumbar movements,

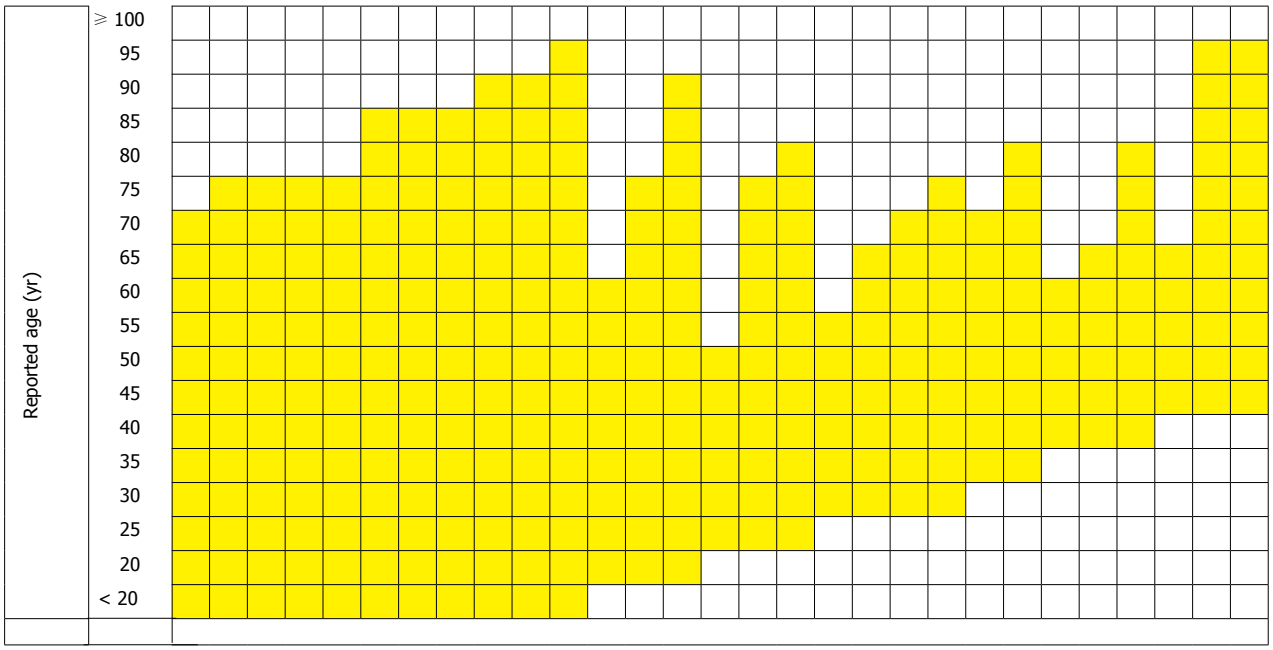

Figure 1 Reported age ranges for patients undergoing spinal fusion (*n* = 29). Ages rounded to nearest 5 years; youngest reported age 14 years; oldest age reported as "over 100".

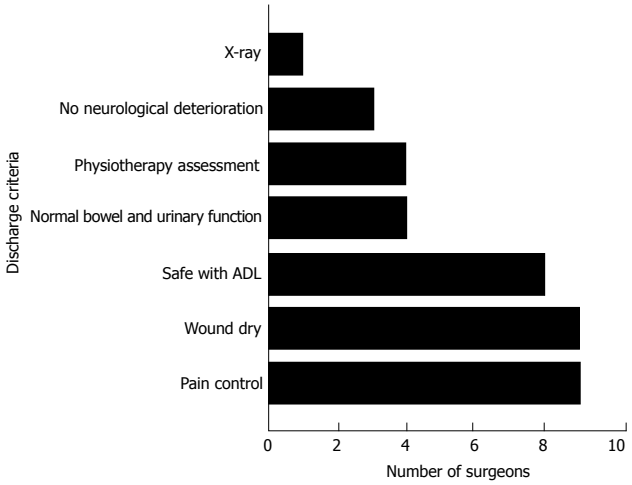

Figure 2 Criteria for discharge post lumbar spinal fusion surgery (*n* = 14 responders).

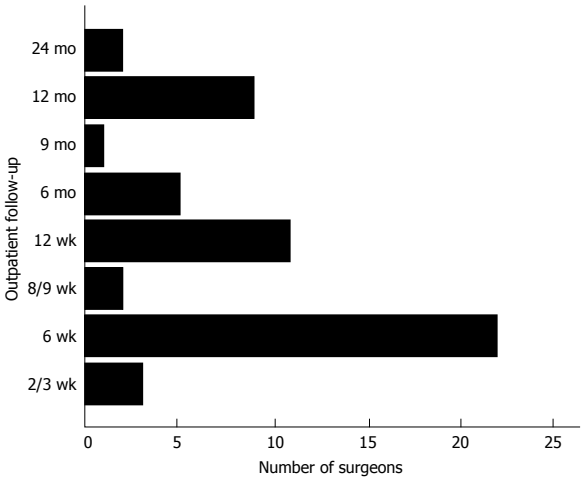

Figure 3 Outpatient follow up appointments (*n* = 29 surgeons).

heavy lifting and weight training from 2 wk to 9 mo (Table 4). Use of corsets was infrequent with 2 surgeons (7%) recommending, and 7 (24%) occasionally recommending use. Reason for corset use related to pain (*n* = 4), compliance with protecting back (*n* = 2), bone problems (*n* = 2), anterior lumbar interbody fusion (*n* = 1), multilevel surgery (*n* = 1), and in one instance it was standard practice to encourage mobilisation.

Surgeons reported variability of duration of hospital stay for elderly patients, multilevel surgery, or different types of surgery. The majority (*n* = 20, 69%) reported that patients remain in hospital 1-4 d, with 8 (28%) reporting stays of 3-4 to 6-7 d and one surgeon reporting hospitalisation of 3-10 d.

Outpatient management

All surgeons (*n* = 29) followed up patients as outpatients although frequency and timing varied considerably from once at 3-6 wk (*n* = 15) to a maximum of five visits in once instance (at 6, 12, 24, 52 wk and 2 years) (Figure 3). Written information sheets/booklets were provided to outpatients by nine (31%) surgeons, with 20 (69%) not using standardised information sheets.

There was wide variation in use of patient reported outcome measures, ranging from no measures (*n* = 10, 34%) to 8 surgeons using ⩾ 3 tools; and routine use by 19 (66%) surgeons. The ODI, SF-36 and a pain rating scale were most frequently used, with ODI and VAS most frequently used in combination. There was a diverse range of additional measures (Table

Table 4 Pre-discharge advice on time (weeks post discharge) to return to functional activities

Functional activity	No. (%) of surgeons								
	Weeks[1]						Months[1]		
	1	2	3	4	6	8	3	6	9
Sitting	22 (85)	2 (8)	1 (4)	0	1 (4)	0	0	0	0
Driving	0	4 (15)	3 (12)	10 (39)	10 (39)	2 (8)	0	0	0
Sex	2 (10)	3 (15)	2 (10)	6 (30)	9 (45)	2 (10)	1 (5)	0	0
Work	0	2 (8)	3 (12)	2 (8)	13 (50)	4 (15)	9 (35)	1 (4)	0
Sport	0	1 (4)	0	1 (4)	4 (17)	0	10 (42)	6 (25)	2 (8)
Contact sports	0	0	0	0	0	0	5 (21)	8 (33)	2 (8)
Jogging/running	0	0	0	1 (4)	6 (25)	1 (4)	5 (21)	10 (42)	1 (4)
Weight training	0	0	0	0	1 (5)	0	5 (21)	9 (41)	3 (14)
Heavy lifting	0	0	0	0	2 (8)	0	5 (21)	10 (42)	1 (4)
Extreme range of lumbar movements	0	1 (5)	0	0	0	0	8 (36)	6 (27)	2 (9)

[1]Time (in weeks post discharge) at which patients were advised to return to each functional activity.

Table 5 Post-operative outpatient use of patient reported outcome measures (*n* = 29 surgeons)

Domain	Questionnaire	Surgeons *n* (%)
Disability	ODI	17 (90)
Pain	VAS or NPRS	14 (74)
	MSP	1 (5)
	Pain drawing	1 (5)
Health	SF-26	6 (32)
	SF-12	1 (5)
	PHQ-9	1 (5)
	EQ-5D	1 (5)
Depression	Zung Depression Index	2 (10)
	Hospital Depression Scale	1 (10)
Anxiety	Hospital Anxiety Scale	1 (10)
	GAD-7	1 (10)
Other[1]		2 (10)

[1]GPOS: Global Patient Outcome System, own questionnaire. GAD: Generalized Anxiety Disorder; NPRS: Numerical Pain Rating Scale; ODI: Oswestry Disability Index; PHQ: Patient Health Questionnaire; VAS: Visual analogue scale; MSP: Multidimensional scale of pain.

5). Performance based measures were only used occasionally by 2 (7%) surgeons. From open question data (*n* = 3) the need to monitor outcomes appears to be a current priority for implementation.

Outpatient physiotherapy is used routinely by 14 (48%) surgeons, or when required by 15 (52%). Indications varied based on medical or personal factors: ongoing pain or stiffness (*n* = 8), requirement for education or confidence building (*n* = 7), lack of progress linked to function (*n* = 4), poor trunk control (*n* = 3), on patient's request (*n* = 1), following previous surgery, elderly patients, or patients finding rehabilitation difficult. One surgeon reported standardised care including 6 wk of hydrotherapy followed by gym exercise.

Surgeons reported a small percentage of patients requiring further invasive procedures: < 5% (*n* = 13, 49%), 10%-15% (*n* = 11, 38%), and 20%-25% (*n* = 1, 8%) of cases, with 1 reporting no patients based on their past 5 years of experience. Procedures included: adjacent level surgery (*n* = 20, 69%), removal of metal-ware (*n* = 17, 59%), same level surgery (*n* = 13, 45%), and injection at adjacent level (*n* = 19, 66%). Reported reasons from 6 (21%) surgeons included other spinal problems or symptoms, unrelated back pain or implant failure.

DISCUSSION

The 73.8% response rate was good. Most surgeons (84%) were orthopaedic surgeons, perhaps reflecting the mechanical nature of patient presentations. This contrasted our previous survey findings when investigating lumbar discectomy, where patients were managed equally by neurosurgeons and orthopaedic surgeons[16]. The range of surgeon experience (1-15 years) was broad, as was the number of operations performed in the previous 12 mo (4-250), and range of information used to predict outcome (Table 1); perhaps reflecting regional variation[2,7] and poor surgeon consensus and/or a range of indications for surgery and outcome[8]. In contrast to international data[1-6] surgeons reported no increase in surgical rates over the previous 5 years.

The findings illustrate some consistency of practice as most patients were seen preoperatively (94%) and the importance of this encounter was clear. All surgeons ensured that patients are mobile within 3 d of surgery, with most being mobile by day 1 (83%). There was also agreement for the value of post-operative physiotherapy that was provided routinely for inpatients of 93% surgeons, and for outpatients of 48% surgeons. Surgeons were consistent in reporting a small percentage of patients requiring further invasive procedures (0%-15% cases), in contrast to existing data[3,6].

Overall, there was considerable variability of practice in managing patients. Although most surgeons used protocols to guide management, there was disagreement regarding variability of post-operative protocols according to surgical procedure, but recognition that co-morbidities, patient factors, and speed of mobilisation did contribute to variation. Fifty-two percent

of surgeons did not have specific discharge criteria, and there was no consensus for criteria when used. Sixty-two percent of surgeons tailored advice on return to function to individual patients, and surgeons reported variability of duration of hospital stay for different patients. All surgeons followed up patients as outpatients, but frequency and timing varied considerably. Surprisingly, in the current context of needing to evidence outcomes, use of patient reported outcome measures was limited and variable, and use of performance based outcomes measures minimal. It was not clear from the data whether surgeons see a distinction between patient reported and performance based outcomes, which considering the emphasis on function post recovery is an important consideration. Written support for patients was variable for inpatients and outpatients. This range of written support for patients can be improved to enhance patient care.

Several reasons perhaps explain the variability of practice. Firstly patient-centred practice was clear, with most surgeons advocating tailoring management to the individual patient. Secondly, the range of indications for lumbar spinal fusion was emphasised and this was also reflected in the range of surgical procedures, and number of levels fused, again dependent on the individual patient's presentation. Thirdly patient factors were felt to influence management (motivation, pre-operative fitness, weight).

The strengths of this survey are its good response rate from a United Kingdom wide population. A key limitation is that the survey structure did not provide further information on clinical decision making from surgeons to manage the obvious variability of surgical indication and patient presentations.

A description of current United Kingdom current surgeon practice has been provided by this survey for managing patients both pre- and post-operatively when undergoing lumbar spinal fusion surgery. The surgical procedure takes many forms, and combined with the diversity (and possible complexity) of this patient population it is understandable that protocols and management approaches vary. It is evident that care should be tailored to the individual through patient-centred care. However with high costs and documented patient dissatisfaction[3,6,11], it is important that further research evaluates optimal management.

ACKNOWLEDGMENTS

The Musculoskeletal Association of Chartered Physiotherapists for small funding to enable participant identification and access to SurveyMonkey software.

COMMENTS

Background

The increasing rate of lumbar spinal fusion surgery, lack of data supporting effectiveness of surgery, high level of patient dissatisfaction, continued level of patient disability, high revision and re-hospitalisation rate, evidence two problems. Firstly, research needs to investigate the effectiveness of fusion surgery in specific populations of patients, and, secondly, that optimal outcomes of surgery through post-operative management/rehabilitation requires investigation.

Research frontiers

No evaluation of surgeon practice has specifically focused on lumbar spinal fusion. The objective of this study was to ascertain current surgeon practice for the management of patients undergoing lumbar spinal fusion in the United Kingdom National Health Service.

Innovations and breakthroughs

Current United Kingdom surgeon practice for lumbar spinal fusion is described. This study surveyed all surgeons carrying out lumbar spinal fusions in the United Kingdom to ascertain current practice. Eighty-four percent of participants were orthopaedic surgeons and their experience of lumbar spinal fusion ranged from 1-15 years, each performing 4-250 operations in the previous 12 mo. The surgical procedure and patient population is diverse, and it is therefore understandable that management varies. It is evident that care should be patient-centred.

Applications

Surgeons consistently saw patients preoperatively, ensured patients are mobile within 3 d of surgery, and valued post-operative physiotherapy. However, variability of protocols, duration of hospital stay, use of discharge criteria, frequency and timing of outpatient follow up, use of written patient information and outcome measures was considerable. Much variability was explained through patient-centred care.

Terminology

Lumbar spinal fusion surgery aims to fuse two or more vertebrae in the lumbar region using bone or metal implants. The primary indication for lumbar fusion is pain (back and/or leg pain) as a consequence of degenerative disease, where it can potentially stabilise the spine.

Peer-review

It is a well written manuscript concerning survey in the surgical option in lumbar degenerative disorder treated with /without fusion and with/without instruments.

REFERENCES

1 **Gibson JN**, Waddell G. Surgery for degenerative lumbar spondylosis. *Cochrane Database Syst Rev* 2005; **(4)**: CD001352 [PMID: 16235281 DOI: 10.1002/14651858.CD001352.pub3]
2 **Weinstein JN**, Lurie JD, Olson PR, Bronner KK, Fisher ES. United States' trends and regional variations in lumbar spine surgery: 1992-2003. *Spine* (Phila Pa 1976) 2006; **31**: 2707-2714 [PMID: 17077740 DOI: 10.1097/01.brs.0000248132.15231.fe]
3 **The Health and Social Care Information Centre.** HES online. Primary Diagnosis: 3 character tables [accessed 2011 Oct 20]. Available from: URL: http://www.hesonline.nhs.uk
4 **Deyo RA**, Gray DT, Kreuter W, Mirza S, Martin BI. United States trends in lumbar fusion surgery for degenerative conditions. *Spine* (Phila Pa 1976) 2005; **30**: 1441-1445; discussion 1441-1445 [PMID: 15959375 DOI: 10.1097/01.brs.0000166503.37969.8a]
5 **Gray DT**, Deyo RA, Kreuter W, Mirza SK, Heagerty PJ, Comstock BA, Chan L. Population-based trends in volumes and rates of ambulatory lumbar spine surgery. *Spine* (Phila Pa 1976) 2006; **31**: 1957-1963; discussion 1964 [PMID: 16924213 DOI: 10.1097/01.brs.0000229148.63418.c1]
6 **Deyo RA**, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA* 2010; **303**: 1259-1265 [PMID: 20371784 DOI: 10.1001/jama.2010.338]
7 **Katz JN**. Lumbar spinal fusion. Surgical rates, costs, and complications. *Spine* (Phila Pa 1976) 1995; **20**: 78S-83S [PMID: 8747260]
8 **Willems P**, de Bie R, Oner C, Castelein R, de Kleuver M. Clinical decision making in spinal fusion for chronic low back pain. Results of a nationwide survey among spine surgeons. *BMJ Open* 2011; **1**: e000391 [PMID: 22189352 DOI: 10.1136/bmjopen-2011-000391]

9 **Martin BI**, Mirza SK, Comstock BA, Gray DT, Kreuter W, Deyo RA. Reoperation rates following lumbar spine surgery and the influence of spinal fusion procedures. *Spine* (Phila Pa 1976) 2007; **32**: 382-387 [PMID: 17268274 DOI: 10.1097/01.brs.0000254104.55716.46]
10 **Fairbank J**, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R. Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. *BMJ* 2005; **330**: 1233 [PMID: 15911537 DOI: 10.1136/bmj.38441.620417.BF]
11 **Stromqvist B**, Fritzell P, Hagg O, Jonsson B, Sanden B. Follow-up of Lumbar Surgery in Sweden 2007, The Swedish National Spine Register. The Swedish Spinal Surgery Society, 2007 [accessed 2011 Sept 26]. Available from: URL: http://www.4s.nu/pdf/Ryggregisterrapport_2008_eng_version.pdf
12 **Rushton A**, Wright C, Goodwin P, Calvert M, Freemantle N. Physiotherapy rehabilitation post first lumbar discectomy: a systematic review and meta-analysis of randomized controlled trials. *Spine* (Phila Pa 1976) 2011; **36**: E961-E972 [PMID: 21224754 DOI: 10.1097/BRS.0b013e3181f0e8f8]
13 **McGregor AH**, Dicken B, Jamrozik K. National audit of post-operative management in spinal surgery. *BMC Musculoskelet Disord* 2006; **7**: 47 [PMID: 16737522 DOI: 10.1186/1471-2474-7-47]
14 **Sim J**, Wright C. Research in Health Care: Concepts, Designs and Methods. Stanley Thornes. *Cheltenham* 2000 [DOI: 10.1002/pri.233]
15 **Wright K**. Researching internet-based populations: advantages and disadvantages of online survey research, online questionnaire authoring software packages, and Web survey services. *JCMC* 2005; **10** [DOI: 10.1111/j.1083-6101.2005.tb00259.x]
16 **Williamson E**, White L, Rushton A. A survey of post-operative management for patients following first time lumbar discectomy. *Eur Spine J* 2007; **16**: 795-802 [PMID: 16944223 DOI: 10.1007/s00586-006-0207-8]

P- Reviewer: Pan HC, Wang Y **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Wu HL

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i6.491

World J Orthop 2015 July 18; 6(6): 491-497
ISSN 2218-5836 (online)

Analysing the outcome of surgery for chronic Achilles tendinopathy over the last 50 years

Wasim S Khan, Seema Malvankar, Jagmeet S Bhamra, Ioannis Pengas

Wasim S Khan, Seema Malvankar, Jagmeet S Bhamra, Ioannis Pengas, University College London Institute of Orthopaedics and Musculoskeletal Science, Royal National Orthopaedic Hospital, Stanmore, Middlesex, London HA7 4LP, United Kingdom

Author contributions: Khan WS and Malvankar S analysed the literature; Malvankar S wrote the preliminary draft of the manuscript and Khan WS revised the paper; Bhamra JS and Pengas I supervised the project and critically reviewed the draft; all authors approved the final submitted version of the manuscript.

Conflict-of-interest statement: None.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository.

Correspondence to: Dr. Wasim S Khan, Clinical Lecturer, University College London Institute of Orthopaedics and Musculoskeletal Science, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, London HA7 4LP, United Kingdom. wasimkhan@doctors.org.uk
Telephone: +44-79-71190720
Fax: +44-20-85703864

Received: February 23, 2015
Peer-review started: February 25, 2015
First decision: April 10, 2015
Revised: May 6, 2015
Accepted: May 16, 2015
Article in press: May 18, 2015
Published online: July 18, 2015

Abstract

AIM: To determine an association between when the study was performed, the robustness of the study and the outcomes for insertional and non-insertional Achilles tendinopathy surgery.

METHODS: We performed a systematic review in accordance with the PRISMA guidelines to assess the methodology of studies investigating the outcome of surgery in chronic Achilles tendinopathy over the last 50 years to identify any trends that would account for the variable results. The Coleman Methodology Scores were correlated with the reported percentage success rates and with the publication year to determine any trends using Pearson's correlation.

RESULTS: We identified 62 studies published between 1964 and 2014 reporting on a total of 2923 surgically treated Achilles tendinopathies. The average follow-up time was 40 mo (range 5-204 mo), and the mean reported success rate was 83.5% (range 36%-100%). The Coleman Methodology Scores were highly reproducible (r = 0.99, P < 0.01), with a mean of 40.1 (SD 18.9, range 2-79). We found a negative correlation between reported success rate and overall methodology scores (r = -0.40, P < 0.001), and a positive correlation between year of publication and overall methodology scores (r = 0.46, P < 0.001).

CONCLUSION: We conclude that although the success rate of surgery for chronic Acilles tendinopathy described in the literature has fallen over the last 50 years, this is probably due to a more rigorous methodology of the studies.

Key words: Achilles tendon; Surgery; Methodology; Outcome; Tendinopathy

Core tip: Although the success rate of surgery for chronic Acilles tendinopathy described in the literature has fallen over the last 50 years, this is probably due to a more rigorous methodology of the studies. Future studies with more robust methodologies will hopefully address some of the unanswered questions in the surgical management of this difficult condition.

Khan WS, Malvankar S, Bhamra JS, Pengas I. Analysing the outcome of surgery for chronic Achilles tendinopathy over the last 50 years. *World J Orthop* 2015; 6(6): 491-497 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/491.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.491

INTRODUCTION

Overuse injuries of the Achilles tendon are becoming increasingly common. Its manifestation used to be more associated with male athletes[1], however the rise in the incidence of Achilles tendon disorders is considered to be due to more females participating in recreational and competitive sporting activities[1]. Even though injuries of the Achilles tendon are on the rise, little is known regarding the long-term outcome of their surgical management due to a lack of reliable outcome studies[2]. Subjectively there is evidence that the surgical outcomes reported in the literature are worse than those described historically[3].

In addition to the lack of reliable research on the management of insertional and non-insertional Achilles tendinopathy, there is also a poor understanding of its pathogenesis, and its aetiology is unknown[4]. Even though Achilles tendinopathy has been linked to overuse, one study found that 31% of 58 patients who had Achilles tendinopathy did not participate in vigorous activity[5]. Other suggested Achilles tendinopathy caused by a mixture of intrinsic and extrinsic factors such as poor vascularity, genetic make-up, quinolone antibiotics, change of training regime or a change of foot wear[5]. The term "tendinitis" is incorrect as Achilles tendinopathy is not an inflammatory reaction[6]. Puddu *et al*[7] stated that "tendinosis" is a better term as this describes the collagen degeneration that occurs in tendinopathy, however this can only be conclusively demonstrated after histopathological confirmation[7]. Puddu *et al*[7] also further classified Achilles tendon disease based on his histological findings into peritendinitis and tendinosis, that could coexist and also develop into each other[7]. We therefore advocate the use of the term "tendinopathy" as a generic descriptor of the clinical conditions in and around tendons arising from overuse, eliminating the need for histopathological confirmation[3].

The lack of understanding of this condition and the poor use of terminology leave many questions to be answered, regarding the management of Achilles tendinopathy[3]. It has been stated generally that conservative treatment is not successful for patients with chronic Achilles tendinopathy and that surgical intervention is needed for 25% of patients[4]. Research has showed that the historical short-term results of surgical treatment are frequently very good but these studies are generally unreliable and fail to record the long term outcome of surgical management[4].

We therefore performed a systematic review of the available published literature over the last 50 years to analyse the studies and identify any explanations for these observations.

MATERIALS AND METHODS

This review was carried out following Institutional Review Board approval in accordance to PRISMA guidelines to analyse the quality of studies investigating the outcome of surgery for chronic Achilles tendinopathy from 1964-2014. The eligibility criterion for this systematic review was any study that investigated the surgical outcome for Achilles tendinopathy as its primary goal and that had its full text available in the English language. The eligibility criteria were not limiting as the aim of this study was to critically analyse the quality of the methodologies. A MEDLINE search covering the years 1964 to 2014 was performed. The search was first carried out on 10 September 2014 and the date last searched was 28 January 2015. Keywords used in the search were "Achilles tendon", "tendinitis", "tendon", "surgery", "postoperative complications", "tendon injuries" and "tendinopathy". All journals were considered and all relevant articles were retrieved. A hand search was also conducted and all relevant articles were also included in the study. The study selection process involved screening the study titles to check their relevance to Achilles tendinopathy, and then subsequently their abstracts were screened to check that the primary goal of each included study was investigating the surgical outcome of chronic Achilles tendinopathy. Studies that investigated the surgical outcome of Achilles tendon ruptures were excluded as even though these can develop as a result of chronic Achilles tendinopathy, this is not always the case and ruptures are Achilles tendinopathy, this is not always the case and ruptures are appropriately a separate medical condition in itself. The data collection involved examining all the studies for their reported surgical outcomes. We used the functional classification described by Nelen *et al*[8] (Table 1) to compare the outcome of the studies. We defined "success rate" as the sum of excellent and good outcomes expressed as a percentage of the total outcomes. A methods assessment for risk of bias in individual studies was carried out by using the criteria developed by Coleman *et al*[9] (Table 2) to blindly assess the methods of each article twice. Where previous Coleman Methodology Scores were available for studies in the literature, the scores were checked to ensure

Table 1 Functional classification of postsurgical outcome for Achilles tendinopathy[8]

Rating	Result
Excellent	No residual symptoms, sports performance unlimited
Good	Full return to the same sport as preoperatively; some stiffness after strenuous activities
Fair	Improvement with regard to the preoperative situation; still stiffness and aching relating to sports
Poor	No improvement at all

Table 2 Coleman Methodology Score criteria for studies reporting the outcomes of surgery for Achilles tendinopathy[9]

Section	Number or factor	Score
Part A - only one score to be given for each of the seven sections		
Study size - number of tendons (N) (if multiple follow-up, multiply N by number of times subjects followed up)	> 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. More than one surgical technique may be assessed but separate outcomes should be reported	One surgical procedure only	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
Type of study	Randomized control trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
Diagnostic certainty (use of preoperative ultrasound, MRI, or postoperative histopathology to confirm diagnosis)	In all	5
	In > 80%	3
	In < 80%, not stated, or unclear	0
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
Description of postoperative rehabilitation	Well described with > 80% of patients complying	10
	Well described with 60%-80% of patients complying	5
	Protocol not reported or < 60%-80% of patients complying	0
Part B - scores may be given for each option in each of the three sections if applicable		
Outcome criteria (if outcome criteria is vague and does not specify subjects' sporting capacity, score is automatically 0 for this section)	Outcome measures clearly defined	2
	Timing of outcome assessment clearly stated (*e.g.*, at best outcome after surgery or at follow-up)	2
	Use of outcome criteria that has reported good reliability	3
	Use of outcome with good sensitivity	3
Procedure for assessing outcomes	Subjects recruited (results not taken from surgeons' file)	5
	Investigator independent of surgeon	4
	Written assessment	3
	Completion of assessment by subjects themselves with minimal investigator assistance	3
Description of subject selection process	Selection criteria reported and unbiased	5
	Recruitment rate reported: > 80% or < 80%	5
	Eligible subjects not included in the study satisfactorily accounted for or 100% recruitment	5

they corresponded. Each study was given a Coleman Methodology Score of between 0 and 100 after scoring for 10 criteria. The Coleman Methodology Scores were correlated with the reported percentage success rates and with the publication year to determine any trends using Pearson's correlation (r). A statistical review of the study was performed by a biomedical statistician.

RESULTS

We identified 62[2,4-6,8,10-66] studies published between 1964 and 2014 reporting on a total of 2923 surgically treated Achilles tendinopathies. The average follow-up time was 40 mo (range 5-204 mo), and the mean reported success rate was 83.5% (range 36%-100%). The mean Coleman Methodology Scores for each of the 10 criteria for the included studies are summarised in Table 3. The methodology of each study was blindly assessed twice, and the Coleman Methodology Scores were highly reproducible (r = 0.99, P < 0.01), with a mean of 40.1 (SD 18.9, range 2-79). The Coleman Methodology Scores for the individual studies are shown in Table 4. The Table also includes data on year of publication, mean follow-up period, number of tendons and percentage success.

The Coleman Methodology Scores were correlated with the reported success rate and year of publication to determine any trends. For the 62 studies, the

Table 3 Mean Scores for each of the 10 Coleman Methodology Score criteria for all included studies

Methodology criteria (maximum score)	Mean		Range
	Score	SD	
Part A			
Study size (10)	4.5	4.6	0-10
Follow-up (10)	3.3	2.4	0-5
No. of procedures (10)	6.6	5	0-10
Type of study (15)	3.4	5.4	0-10
Diagnostic certainty (5)	1.9	2.5	0-5
Description of surgical technique (5)	4.1	1.8	0-5
Rehabilitation and compliance (10)	4.8	5	0-10
Part B			
Outcome criteria (10)	4.7	3.7	0-10
Outcome assessment (15)	5.2	4.5	0-12
Selection process (15)	4.6	6	0-15
Methodology score (100)	40.1	18.9	2-79

methodology score negatively correlated with the reported success rate (r = -0.40, P < 0.001) suggesting that studies with lower methodology scores reported higher success rates (Figure 1). The methodology score positively correlated with the year of publication (r = 0.46, P < 0.001) suggesting that methodology has improved over the past 50 years (Figure 2).

DISCUSSION

Our review identified 62 studies investigating almost 3000 tendons followed up for almost 40 mo published over the last 50 years that looked at surgical outcome of Achilles tendinopathy. The studies included in our review reported a mean success rate of 84% (SD 14%). The studies had a mean Coleman Methodology Score of 40 (SD 19). Our results identified trends in Coleman Methodology Score with the year of publication and the success rate. It was interesting to note that as the Coleman Methodology Scores improve, the success rate of studies falls. This is likely to be due to the fact that more robust studies with a higher methodology score are more objective in assessing outcome and are associated with less bias. The Coleman Methodology Score is produced by assessing two parts and the more robust studies scored well in both of these. The first part scored higher for a robust high quality studies with a larger number of patients with diagnostic certainty, longer follow-ups, and describing only one surgical procedure. These studies described the surgical procedure and post-operative rehabilitation regime well. Studies that did not score well included retrospective studies with fewer patients, with poorer diagnostic certainty, shorter follow-up, and possibly describing more than one procedure. These factors although describe poor methodology, do lend them to a higher success rate. Retrospective short-term studies are associated with recall bias and are known to produce a higher success rate that randomised controlled trials with long-term follow-up. The second part scored higher for well-defined patient recruitment, valid outcome criteria and independent assessment. Studies that did not score well included poor reporting of patient recruitment, unreliable outcome measures and where there was greater

Table 4 Coleman Methodology Scores for all included studies

Ref.	Year of study	Mean follow-up (mo)	N Tendons	% Success	Coleman Methodology Scores
Snook[10]	1972		4		3
Burry and Pool[11]	1973		5		2
Clancy *et al*[12]	1976		5		5
Denstad and Roaas[13]	1979		58		46
Gould and Korson[14]	1980	12			8
Kvist and Kvist[15]	1980		201	97	35
Leach *et al*[16]	1981		20		10
Subotnick and Sisney[17]	1986		42		15
Saillant *et al*[18]	1987	42	65	86	36
Schepsis and Leach[19]	1987	36	45	87	44
Nelen *et al*[8]	1989		143	67	41
Leppilahti *et al*[20]	1991		150	86	12
Anderson *et al*[21]	1992	52	48	94	27
Clement *et al*[22]	1992	69	14		13
Leach *et al*[23]	1992		12	85	8
Leppilahti *et al*[24]	1994	48	275	73	50
Schepsis *et al*[25]	1994		79	79	66
Aström and Rausing[26]	1995		163		43
Alfredson *et al*[6]	1996	12	13		60
Johnston *et al*[27]	1997	24	41		22
Maffulli *et al*[28]	1997	22	52	71	70
Morberg *et al*[29]	1997	72	64	67	74
Rolf and Movin[5]	1997	25	60	75	69
Alfredson *et al*[30]	1998	12	11		59
Maffulli *et al*[31]	1999	35	14	36	56
Paavola *et al*[32]	2000	5	142		59
Wilcox *et al*[33]	2000	14	20		32
Ohberg *et al*[34]	2001	60	24	92	65
Shalabi *et al*[35]	2001	24	15	87	51
Maquirriain *et al*[36]	2002	16	7		37
Paavola *et al*[37]	2002	7	42		46
Shalabi *et al*[38]	2002	24	15	80	51
Yodlowski *et al*[39]	2002	39	41		39
Chiara Vulpiani *et al*[40]	2003	156	86	88	35
Den Hartog *et al*[41]	2003	35	29	88	34
Saxena[42]	2003	56	37	100	17
Martin *et al*[43]	2005	41	44		52
Costa *et al*[44]	2006	90	21		27
Johnson *et al*[45]	2006	34	22		32
Maffulli *et al*[46]	2006	37	93	81	74
Wagner *et al*[47]	2006	40	81		29
Alfredson *et al*[2]	2007	6	20		61
Cottom *et al*[48]	2008	27	62	95	37
Hahn *et al*[49]	2008	46	13		38
Maffulli et al[50]	2008	40	86	73	79
Vega *et al*[51]	2008	24	8	100	51
Bohu *et al*[52]	2009	42	137		29
Thermann *et al*[53]	2009	6	8		37
Will *et al*[54]	2009	22	19		34
Duthon *et al*[55]	2011	24	17	79	48
van Sterkenburg *et al*[56]	2011	12	3	100	44
Maffulli *et al*[57]	2011	36	30	85	54
Sarimo *et al*[58]	2011	30	24	100	42
Oshri *et al*[59]	2012		21	62	43
Kiewiet *et al*[60]	2013	35	12		30
Maffulli *et al*[61]	2013	204	39	77	42
Maquirriain[62]	2013	92	27	96	47
Benazzo *et al*[63]	2014	48	52		60
Tallerico *et al*[64]	2014	14	11		28
Maffulli *et al*[65]	2015	54	18	100	38
Nawoczenski *et al*[66]	2015	18	13	85	52

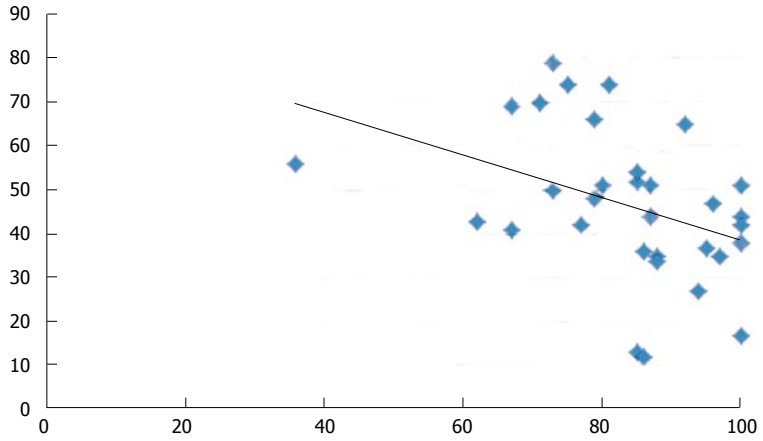

Figure 1 Relationship between Coleman Methodology Score (Y-axis) and reported percentage success rate (X-axis) showing a negative correlation.

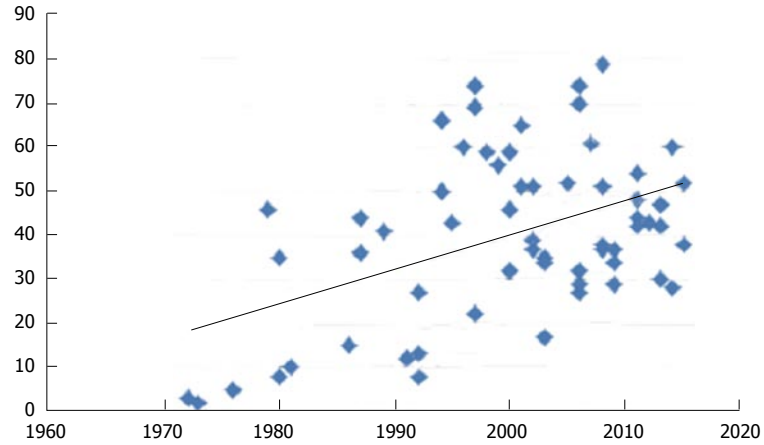

Figure 2 Relationship between Coleman Methodology Score (Y-axis) and year of publication (X-axis) showing a positive correlation.

investigator assistance in completing assessment. Again, these factors would contribute to a higher success rate. Over the past 50 years we have shown that the Coleman Methodology Scores has been increasing. There was a shift from retrospective to prospective studies. Over the last 50 years the number of journals and publications has increased, but this is associated with an increase in the quality of studies. Historically, most studies were retrospective studies reporting short-term follow-up for a small number of patients. More recent studies have included randomised controlled trials that recruit a large number of patients and report longer follow-ups. More recent studies are also more likely to confirm the diagnosis radiologically before instigating treatment, and describe the surgical procedure and post-operative rehabilitation regime well. We suggest future studies to continue to use a robust methodology. This should include multi-centre randomised controlled trials using a large number of patients with long-term follow-up where possible. It is important to have well-defined inclusion and exclusion criteria. These studies should have a uniform pre-operative, operative and post-operative rehabilitation course, with a greater degree of diagnostic certainty. They should be free from selection bias and results bias by describing the selection process and having a good follow-uprate. It is important to use a valid, reliable and responsive outcome measure that is free from bias. Blinding and independence of the investigator is useful. These studies are however associated with greater costs. We hope that poorer success rates that are associated with better methodology do not result in publication bias.

COMMENTS

Background

Insertional and non-insertional Achilles tendinopathy is a difficult problem to manage and surgery is performed when non-operative treatmentoptions fail.

Research frontiers

Studies for insertional and non-insertional Achilles tendinopathy surgery describe a variable outcome in the literature. Future studies need to use a more robust methodology.

Innovations and breakthroughs

The authors performed a systematic review in accordance with the PRISMA guidelines to assess the methodology of studies investigating the outcome of surgery in chronic Achilles tendinopathy over the last 50 years to identify any trends that would account for the variable results. The Coleman Methodology Scores were correlated with the reported percentage success rates and with the publication year to determine any trends using Pearson's correlation. The authors found a negative correlation between reported success rate and overall methodology scores (r = -0.40, P < 0.001), and a positive correlation between year of publication and overall methodology scores (r = 0.46, P < 0.001). The authors conclude that although the success rate of surgery for chronic Acilles tendinopathy described in the literature has fallen over the last 50 years, this is probably due to a more rigorous methodology of the studies.

Applications

Although the success rate of surgery for chronic Acilles tendinopathy described

in the literature has fallen over the last 50 years, this is probably due to a more rigorous methodology of the studies. Future studies with more robust methodologies will hopefully address some of the unanswered questions in the surgical management of this difficult condition.

Terminology

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) is an evidence-based minimum set of items for reporting in systematic reviews and meta-analysis.

Peer-review

This work proposes an extensive review on Achilles tendinopathy over the last 50 years. There are merits in this study because it may give some cues for future researches and clinical application in Achilles tendinopathy. As such, the theme is of interest.

REFERENCES

1 **Kvist M**. Achilles tendon injuries in athletes. *Sports Med* 1994; **18**: 173-201 [PMID: 7809555 DOI: 10.2165/00007256-199418030-00004]

2 **Alfredson H**, Ohberg L, Zeisig E, Lorentzon R. Treatment of midportion Achilles tendinosis: similar clinical results with US and CD-guided surgery outside the tendon and sclerosing polidocanol injections. *Knee Surg Sports Traumatol Arthrosc* 2007; **15**: 1504-1509 [PMID: 17879083 DOI: 10.1007/s00167-007-0415-8]

3 **Tallon C**, Coleman BD, Khan KM, Maffulli N. Outcome of surgery for chronic Achilles tendinopathy. A critical review. *Am J Sports Med* 2001; **29**: 315-320 [PMID: 11394602]

4 **Alfredson H**, Lorentzon R. Chronic Achilles tendinosis: recommendations for treatment and prevention. *Sports Med* 2000; **29**: 135-146 [PMID: 10701715 DOI: 10.2165/00007256-200029020-00005]

5 **Rolf C**, Movin T. Etiology, histopathology, and outcome of surgery in achillodynia. *Foot Ankle Int* 1997; **18**: 565-569 [PMID: 9310767 DOI: 10.1177/107110079701800906]

6 **Alfredson H**, Pietilä T, Lorentzon R. Chronic Achilles tendinitis and calf muscle strength. *Am J Sports Med* 1996; **24**: 829-833 [PMID: 8947407 DOI: 10.1177/036354659602400620]

7 **Puddu G**, Ippolito E, Postacchini F. A classification of Achilles tendon disease. *Am J Sports Med* 1996; **4**: 145-150 [PMID: 984291 DOI: 10.1177/036354657600400404]

8 **Nelen G**, Martens M, Burssens A. Surgical treatment of chronic Achilles tendinitis. *Am J Sports Med* 1996; **17**: 754-759 [PMID: 2624286 DOI: 10.1177/036354658901700605]

9 **Coleman BD**, Khan KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. *Scand J Med Sci Sports* 2000; **10**: 2-11 [PMID: 10693606 DOI: 10.1034/j.1600-0838.2000.010001002.x]

10 **Snook GA**. Achilles tendon tenosynovitis in long-distance runners. *Med Sci Sports* 1972; **4**: 155-158 [PMID: 5076453 DOI: 10.1249/00005768-197200430-00009]

11 **Burry HC**, Pool CJ. Central degeneration of the Achilles tendon. *Rheumatol Rehabil* 1973; **12**: 177-181 [DOI: 10.1093/rheumatology/12.4.177]

12 **Clancy WG**, Neidhart D, Brand RL. Achilles tendonitis in runners: a report of five cases. *Am J Sports Med* 1976; **4**: 46-57 [PMID: 961968 DOI: 10.1177/036354657600400202]

13 **Denstad TF**, Roaas A. Surgical treatment of partial Achilles tendon rupture. *Am J Sports Med* 1979; **7**: 15-17 [PMID: 420383 DOI: 10.1177/036354657900700104]

14 **Gould N**, Korson R. Stenosing tenosynovitis of the pseudosheath of the tendo Achilles. *Foot Ankle* 1980; **1**: 179-187 [PMID: 7319434 DOI: 10.1177/107110078000100308]

15 **Kvist H**, Kvist M. The operative treatment of chronic calcaneal paratenonitis. *J Bone Joint Surg Br* 1980; **62**: 353-357 [PMID: 7410468]

16 **Leach RE**, James S, Wasilewski S. Achilles tendinitis. *Am J Sports Med* 1981; **9**: 93-98 [PMID: 7223927 DOI: 10.1177/036354658100900204]

17 **Subotnick SI**, Sisney P. Treatment of Achilles tendinopathy in the athlete. *J Am Podiatr Med Assoc* 1986; **76**: 552-557 [PMID: 3772761 DOI: 10.7547/87507315-76-10-552]

18 **Saillant G**, Thoreux J, Benazet JP. The surgical treatment of Achilles tendinitis in athletes. *French J Orthop Surg* 1987; **1**: 368-372

19 **Schepsis AA**, Leach RE. Surgical management of Achilles tendinitis. *Am J Sports Med* 1987; **15**: 308-315 [PMID: 3661810 DOI: 10.1177/036354658701500403]

20 **Leppilahti J**, Orava S, Karpakka J, Takala T. Overuse injuries of the Achilles tendon. *Ann Chir Gynaecol* 1991; **80**: 202-207 [PMID: 1897887]

21 **Anderson DL**, Taunton JE, Davidson RG. Surgical management of chronic Achilles tendinitis. *Clin J Sport Med* 1992; **2**: 38-42 [DOI: 10.1097/00042752-199201000-00007]

22 **Clement D**, Taunton J, Davison R. Evaluation of performance of following Achilles tendon surgery in competitive runners. *New Studies in Athletes* 1992; **7**: 33-37

23 **Leach RE**, Schepsis AA, Takai H. Long-term results of surgical management of Achilles tendinitis in runners. *Clin Orthop Relat Res* 1992; **(282)**: 208-212 [PMID: 1516314 DOI: 10.1097/00003086-199209000-00026]

24 **Leppilahti J**, Karpakka J, Gorra A. Surgical treatment of overuse injuries to the Achilles tendon. *Clin J Sport Med* 1994; **4**: 100-107 [DOI: 10.1097/00042752-199404000-00006]

25 **Schepsis AA**, Wagner C, Leach RE. Surgical management of Achilles tendon overuse injuries. A long-term follow-up study. *Am J Sports Med* 1994; **22**: 611-619 [PMID: 7810784 DOI: 10.1177/036354659402200508]

26 **Aström M**, Rausing A. Chronic Achilles tendinopathy. A survey of surgical and histopathologic findings. *Clin Orthop Relat Res* 1995; **(316)**: 151-164 [PMID: 7634699]

27 **Johnston E**, Scranton P, Pfeffer GB. Chronic disorders of the Achilles tendon: results of conservative and surgical treatments. *Foot Ankle Int* 1997; **18**: 570-574 [PMID: 9310768 DOI: 10.1177/107110079701800907]

28 **Maffulli N**, Testa V, Capasso G, Bifulco G, Binfield PM. Results of percutaneous longitudinal tenotomy for Achilles tendinopathy in middle- and long-distance runners. *Am J Sports Med* 1997; **25**: 835-840 [PMID: 9397274 DOI: 10.1177/036354659702500618]

29 **Morberg P**, Jerre R, Swärd L, Karlsson J. Long-term results after surgical management of partial Achilles tendon ruptures. *Scand J Med Sci Sports* 1997; **7**: 299-303 [PMID: 9338949 DOI: 10.1111/j.1600-0838.1997.tb00157.x]

30 **Alfredson H**, Pietilä T, Ohberg L, Lorentzon R. Achilles tendinosis and calf muscle strength. The effect of short-term immobilization after surgical treatment. *Am J Sports Med* 1998; **26**: 166-171 [PMID: 9548107]

31 **Maffulli N**, Binfield PM, Moore D, King JB. Surgical decompression of chronic central core lesions of the Achilles tendon. *Am J Sports Med* 1999; **27**: 747-752 [PMID: 10569361]

32 **Paavola M**, Orava S, Leppilahti J, Kannus P, Järvinen M. Chronic Achilles tendon overuse injury: complications after surgical treatment. An analysis of 432 consecutive patients. *Am J Sports Med* 2000; **28**: 77-82 [PMID: 10653548]

33 **Wilcox DK**, Bohay DR, Anderson JG. Treatment of chronic achilles tendon disorders with flexor hallucis longus tendon transfer/augmentation. *Foot Ankle Int* 2000; **21**: 1004-1010 [PMID: 11139028]

34 **Ohberg L**, Lorentzon R, Alfredson H. Good clinical results but persisting side-to-side differences in calf muscle strength after surgical treatment of chronic Achilles tendinosis: a 5-year follow-up. *Scand J Med Sci Sports* 2001; **11**: 207-212 [PMID: 11476425 DOI: 10.1034/j.1600-0838.2001.110403.x]

35 **Shalabi A**, Kristoffersen-Wiberg M, Aspelin P, Movin T. MR evaluation of chronic Achilles tendinosis. A longitudinal study of 15 patients preoperatively and two years postoperatively. *Acta Radiol*

2001; **42**: 269-276 [PMID: 11350284]
36 **Maquirriain J**, Ayerza M, Costa-Paz M, Muscolo DL. Endoscopic surgery in chronic achilles tendinopathies: A preliminary report. *Arthroscopy* 2002; **18**: 298-303 [PMID: 11877618 DOI: 10.1053/jars.2002.30065b]
37 **Paavola M**, Kannus P, Orava S, Pasanen M, Järvinen M. Surgical treatment for chronic Achilles tendinopathy: a prospective seven month follow up study. *Br J Sports Med* 2002; **36**: 178-182 [PMID: 12055111 DOI: 10.1136/bjsm.36.3.178]
38 **Shalabi A**, Kristoffersen-Wiberg M, Papadogiannakis N, Aspelin P, Movin T. Dynamic contrast-enhanced mr imaging and histopathology in chronic achilles tendinosis. A longitudinal MR study of 15 patients. *Acta Radiol* 2002; **43**: 198-206 [PMID: 12010305 DOI: 10.1034/j.1600-0455.2002.430221.x]
39 **Yodlowski ML**, Scheller AD, Minos L. Surgical treatment of Achilles tendinitis by decompression of the retrocalcaneal bursa and the superior calcaneal tuberosity. *Am J Sports Med* 2002; **30**: 318-321 [PMID: 12016069]
40 **Chiara Vulpiani M**, Guzzini M, Ferretti A. Operative treatment of chronic Achilles tendinopathy. *Int Orthop* 2003; **27**: 307-310 [PMID: 12802517 DOI: 10.1007/s00264-003-0472-7]
41 **Den Hartog BD**. Flexor hallucis longus transfer for chronic Achilles tendonosis. *Foot Ankle Int* 2003; **24**: 233-237 [PMID: 12793486]
42 **Saxena A**. Results of chronic Achilles tendinopathy surgery on elite and nonelite track athletes. *Foot Ankle Int* 2003; **24**: 712-720 [PMID: 14524523]
43 **Martin RL**, Manning CM, Carcia CR, Conti SF. An outcome study of chronic Achilles tendinosis after excision of the Achilles tendon and flexor hallucis longus tendon transfer. *Foot Ankle Int* 2005; **26**: 691-697 [PMID: 16174498]
44 **Costa ML**, Donell ST, Tucker K. The long-term outcome of tendon lengthening for chronic Achilles tendon pain. *Foot Ankle Int* 2006; **27**: 672-676 [PMID: 17038276]
45 **Johnson KW**, Zalavras C, Thordarson DB. Surgical management of insertional calcific achilles tendinosis with a central tendon splitting approach. *Foot Ankle Int* 2006; **27**: 245-250 [PMID: 16624213]
46 **Maffulli N**, Testa V, Capasso G, Oliva F, Sullo A, Benazzo F, Regine R, King JB. Surgery for chronic Achilles tendinopathy yields worse results in nonathletic patients. *Clin J Sport Med* 2006; **16**: 123-128 [PMID: 16603881 DOI: 10.1097/00042752-200603000-00007]
47 **Wagner E**, Gould JS, Kneidel M, Fleisig GS, Fowler R. Technique and results of Achilles tendon detachment and reconstruction for insertional Achilles tendinosis. *Foot Ankle Int* 2006; **27**: 677-684 [PMID: 17038277]
48 **Cottom JM**, Hyer CF, Berlet GC, Lee TH. Flexor hallucis tendon transfer with an interference screw for chronic Achilles tendinosis: a report of 62 cases. *Foot Ankle Spec* 2008; **1**: 280-287 [PMID: 19825729 DOI: 10.1177/1938640008322690]
49 **Hahn F**, Meyer P, Maiwald C, Zanetti M, Vienne P. Treatment of chronic achilles tendinopathy and ruptures with flexor hallucis tendon transfer: clinical outcome and MRI findings. *Foot Ankle Int* 2008; **29**: 794-802 [PMID: 18752777 DOI: 10.3113/FAI.2008.0794]
50 **Maffulli N**, Testa V, Capasso G, Oliva F, Panni AS, Longo UG, King JB. Surgery for chronic Achilles tendinopathy produces worse results in women. *Disabil Rehabil* 2008; **30**: 1714-1720 [PMID: 18608368 DOI: 10.1080/09638280701786765]
51 **Vega J**, Cabestany JM, Golanó P, Pérez-Carro L. Endoscopic treatment for chronic Achilles tendinopathy. *Foot Ankle Surg* 2008; **14**: 204-210 [PMID: 19083643 DOI: 10.1016/j.fas.2008.02.005]
52 **Bohu Y**, Lefèvre N, Bauer T, Laffenetre O, Herman S, Thaunat M, Cucurulo T, Franceschi JP, Cermolacce C, Rolland E. Surgical treatment of Achilles tendinopathies in athletes. Multicenter retrospective series of open surgery and endoscopic techniques. *Orthop Traumatol Surg Res* 2009; **95**: S72-S77 [PMID: 19892618 DOI: 10.1016/j.otsr.2009.09.006]
53 **Thermann H**, Benetos IS, Panelli C, Gavriilidis I, Feil S. Endoscopic treatment of chronic mid-portion Achilles tendinopathy: novel technique with short-term results. *Knee Surg Sports Traumatol Arthrosc* 2009; **17**: 1264-1269 [PMID: 19288082 DOI: 10.1007/s00167-009-0751-y]
54 **Will RE**, Galey SM. Outcome of single incision flexor hallucis longus transfer for chronic achilles tendinopathy. *Foot Ankle Int* 2009; **30**: 315-317 [PMID: 19356355 DOI: 10.3113/FAI.2009.0315]
55 **Duthon VB**, Lübbeke A, Duc SR, Stern R, Assal M. Noninsertional Achilles tendinopathy treated with gastrocnemius lengthening. *Foot Ankle Int* 2011; **32**: 375-379 [PMID: 21733439 DOI: 10.3113/FAI.2011.0375]
56 **van Sterkenburg MN**, Kerkhoffs GM, van Dijk CN. Good outcome after stripping the plantaris tendon in patients with chronic mid-portion Achilles tendinopathy. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1362-1366 [PMID: 21541711 DOI: 10.1007/s00167-011-1514-0]
57 **Maffulli N**, Del Buono A, Testa V, Capasso G, Oliva F, Denaro V. Safety and outcome of surgical debridement of insertional Achilles tendinopathy using a transverse (Cincinnati) incision. *J Bone Joint Surg Br* 2011; **93**: 1503-1507 [PMID: 22058302 DOI: 10.1302/0301-620X.93B10.27379]
58 **Sarimo J**, Orava S. Fascial incision and adhesiolysis combined with radiofrequency microtenotomy in treatment of chronic midportion Achilles tendinopathy. *Scand J Surg* 2011; **100**: 125-128 [PMID: 21737390]
59 **Oshri Y**, Palmanovich E, Brin YS, Karpf R, Massarwe S, Kish B, Nyska M. Chronic insertional Achilles tendinopathy: surgical outcomes. *Muscles Ligaments Tendons J* 2012; **2**: 91-95 [PMID: 23738280]
60 **Kiewiet NJ**, Holthusen SM, Bohay DR, Anderson JG. Gastrocnemius recession for chronic noninsertional Achilles tendinopathy. *Foot Ankle Int* 2013; **34**: 481-485 [PMID: 23399888 DOI: 10.1177/1071100713477620]
61 **Maffulli N**, Oliva F, Testa V, Capasso G, Del Buono A. Multiple percutaneous longitudinal tenotomies for chronic Achilles tendinopathy in runners: a long-term study. *Am J Sports Med* 2013; **41**: 2151-2157 [PMID: 23841991 DOI: 10.1177/0363546513494356]
62 **Maquirriain J**. Surgical treatment of chronic achilles tendinopathy: long-term results of the endoscopic technique. *J Foot Ankle Surg* 2013; **52**: 451-455 [PMID: 23643200 DOI: 10.1053/j.jfas.2013.03.031]
63 **Benazzo F**, Zanon G, Klersy C, Marullo M. Open surgical treatment for chronic midportion Achilles tendinopathy: faster recovery with the soleus fibres transfer technique. *Knee Surg Sports Traumatol Arthrosc* 2014 Sep 6; Epub ahead of print [PMID: 25193565 DOI: 10.1007/s00167-014-3232-x]
64 **Tallerico VK**, Greenhagen RM, Lowery C. Isolated Gastrocnemius Recession for Treatment of Insertional Achilles Tendinopathy: A Pilot Study. *Foot Ankle Spec* 2014 Nov 10; Epub ahead of print [PMID: 25389232 DOI: 10.1177/1938640014557077]
65 **Maffulli N**, Del Buono A. Release of the medial head of the gastrocnemius for Achilles tendinopathy in sedentary patients: a retrospective study. *Int Orthop* 2015; **39**: 61-65 [PMID: 25315026 DOI: 10.1007/s00264-014-2553-1]
66 **Nawoczenski DA**, Barske H, Tome J, Dawson LK, Zlotnicki JP, DiGiovanni BF. Isolated gastrocnemius recession for achilles tendinopathy: strength and functional outcomes. *J Bone Joint Surg Am* 2015; **97**: 99-105 [PMID: 25609435 DOI: 10.2106/JBJS.M.01424]

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E- Editor: Wu HL

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DOI: 10.5312/wjo.v6.i6.498

World J Orthop 2015 July 18; 6(6): 498-504
ISSN 2218-5836 (online)

CASE REPORT

Femoroacetabular impingement with chronic acetabular rim fracture - 3D computed tomography, 3D magnetic resonance imaging and arthroscopic correlation

Avneesh Chhabra, Shaun Nordeck, Vibhor Wadhwa, Sai Madhavapeddi, William J Robertson

Avneesh Chhabra, Shaun Nordeck, Vibhor Wadhwa, Sai Madhavapeddi, Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9178, United States

William J Robertson, Department of Orthopaedics, University of Texas Southwestern Medical Center, Dallas, TX 75390-9178, United States

Author contributions: Chhabra A and Robertson WJ designed research; Nordeck S, Wadhwa V and Madhavapeddi S performed research; Chhabra A, Nordeck S and Wadhwa V wrote the paper.

Conflict-of-interest statement: Chhabra A has received research grants from Siemens Medical solutions, Integra Life Sciences, GEAUR and Gatewood grant. He also serves as a research consultant with Siemens CAD systems; Robertson WJ serves as a consultant for Conmed Linvatec; the other authors have no potential conflict-of-interest relevant to the manuscript.

Correspondence to: Avneesh Chhabra, MD, Associate Professor, Section Chief, Department of Radiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9178,
United States. avneesh.chhabra@utsouthwestern.edu
Telephone: +1-214-6482122

Received: January 31, 2015
Peer-review started: January 31, 2015
First decision: March 6, 2015
Revised: March 13, 2015
Accepted: June 4, 2015
Article in press: June 8, 2015

Published online: July 18, 2015

Abstract

Femoroacetabular impingement is uncommonly associated with a large rim fragment of bone along the superolateral acetabulum. We report an unusual case of femoroacetabular impingement (FAI) with chronic acetabular rim fracture. Radiographic, 3D computed tomography, 3D magnetic resonance imaging and arthroscopy correlation is presented with discussion of relative advantages and disadvantages of various modalities in the context of FAI.

Key words: 3D computed tomography; 3D magnetic resonance imaging; Femoroacetabular impingement; Rim fracture

Core tip: Rim fracture is an uncommon finding in the context of femoroacetabular impingement and its management can be aided by bony remodeling and labral-cartilage assessment on pre-operative 3D computed tomography and 3D magnetic resonance imaging.

Chhabra A, Nordeck S, Wadhwa V, Madhavapeddi S, Robertson WJ. Femoroacetabular impingement with chronic acetabular rim fracture - 3D computed tomography, 3D magnetic resonance imaging and arthroscopic correlation. *World J Orthop* 2015; 6(6): 498-504 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/498.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.498

INTRODUCTION

Femoroacetabular impingement is uncommonly associated with a large rim fragment of bone along the superolateral acetabulum. The fragment can put surgeons in a dilemma, whether to excise the fragment or to operatively re-attach it to the acetabulum. Computed tomography (CT) and magnetic resonance imaging (MRI) can be very helpful in pre-operative planning. We report radiographic, 3D CT, 3D MRI and arthroscopy correlation in such a case of chronic acetabular rim fracture and discuss the relative advantages and disadvantages of various imaging modalities.

CASE REPORT

A 46-year-old man presented to the sports clinic with recalcitrant bilateral hip pain, right worse than left. He was in a motorcycle accident 3 mo before when he landed on his left hip. He noted some pain in the right hip at that time. However, it significantly worsened after playing golf recently, a week before the current presentation. With swinging and rotating movements, he had worsening pain, rated as 9 to 10/10. He had a positive "C sign" and he localized his pain anteriorly in the groin. He also noted that he is limping because of pain and experiences a click and pain getting in and out of a car. He had other prior injuries, namely a motor vehicle accident 14 years ago, which led to right knee injury and meniscus repair; and another injury 7 mo ago when he was running and slipped in a small hole. There, he heard and felt a pop in his left knee and experienced swelling with difficulty in activities over the next several days, which gradually decreased over time. The past medical history was unremarkable, except for type Ⅱ diabetes mellitus and hypertension. On examination, he walked with a coxalgic gait favoring the right side. The range of motion of the right hip *vs* left hip was as follows, flexion 95/100, abduction 40/50, internal rotation at 90° of flexion 5/5, external rotation at 90° of flexion 40/40. He had some tenderness anteriorly. No sacroiliac or abductor tenderness was present. He had a positive impingement sign and positive flexion abduction and external rotation (FABER) sign. His motor strength was - 5/5 hip flexion, abduction and adduction; 5/5 tibialis anterior, gastrocnemius and extensor halluces longus (EHL). Straight leg raise was negative. In the left hip, he was slightly tender over the trochanter and had positive impingement on that side as well. FABER was negative and his strength was 5/5 in tibialis anterior, gastrocnemius, EHL and throughout the hip. He had intact sensation and palpable pulses. The clinical diagnosis was femoroacetabular impingement.

The radiographs of pelvis in anteroposterior standing, and dedicated views of both hips confirmed bilateral femoroacetabular impingement anatomy. The right hip showed a large bony osteophyte, possibly an os acetabulum, resulting a center edge angle of 46°.

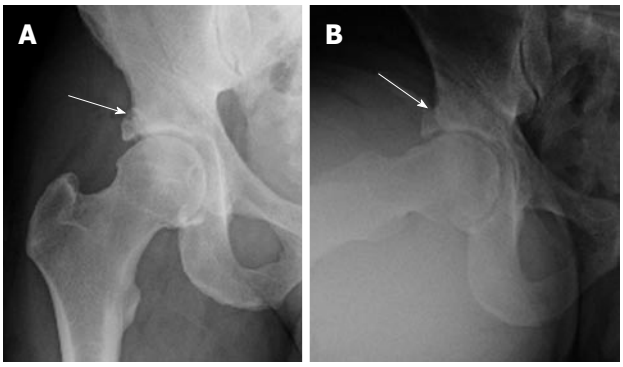

Figure 1 AP (A) and Dunn lateral (B) views of the right hip show right femoral head and neck bump and superolateral acetabular over coverage with suggestion of a rim fracture (arrows). Notice mild subchondral acetabular sclerosis.

There was a suggestion of prior rim fracture with a lucent line between the fragment and the underlying bone (Figure 1). The alpha angle was 68° with significantly decreased head and neck offset. Some sclerosis was observed in the acetabulum; however, no substantial joint space narrowing was present. In the left hip, there was some calcification in the area of the labrum as well.

3D CT of the pelvis was obtained on a 64 slice scanner (Aquillion Intuition, Toshiba, Tustin, CA, United States) using 0.625 mm beam collimation for pre-surgical planning purposes. It confirmed bilateral mixed type femoroacetabular impingement (FAI) anatomy and right acetabular rim fracture (Figure 2). The patient also had a CT abdomen and pelvis with contrast 2 years before for other reasons, which showed similar findings in bilateral hips. 3D surface rendered bone reconstructions and thick slab maximum intensity projection obtained on an independent work (Aquarius, Tera Recon, Foster City, CA, United States) nicely showed the volumetric display of the anatomic right hip derangement, rim fracture and a potentially loose anterior superior fragment (Figure 2). The alpha angle was 65°, coronal center edge angle and sagittal center edge angles were 44° and 61°, respectively. The femoral neck shaft angle was 126° and the acetabular version measurements, adjusting for pelvic tilt near zero were 9.4°, 21.3° and 18.1° at 1:00, 2:00 and 3:00 clock positions, respectively. The femoral anteversion was 12.9°.

MRI of right hip was obtained for labral and cartilage evaluation. The MRI protocol included both high resolution 2D (3 mm) and isotropic (0.7 mm) 3D proton density weighted and fat suppressed proton density imaging sequences on a 3 Tesla scanner (Achieva, Philips, Best, Netherlands) using a torso coil. The imaging demonstrated again showed the CAM and PINCER anatomy, chronic rim fracture with pseudoarthrosis and cystic changes. There were multifocal labral tears extending from the anterior-superior labrum to the posterior-superior labrum and associated large multiloculated para labral cyst measuring 2.8 cm (AP)

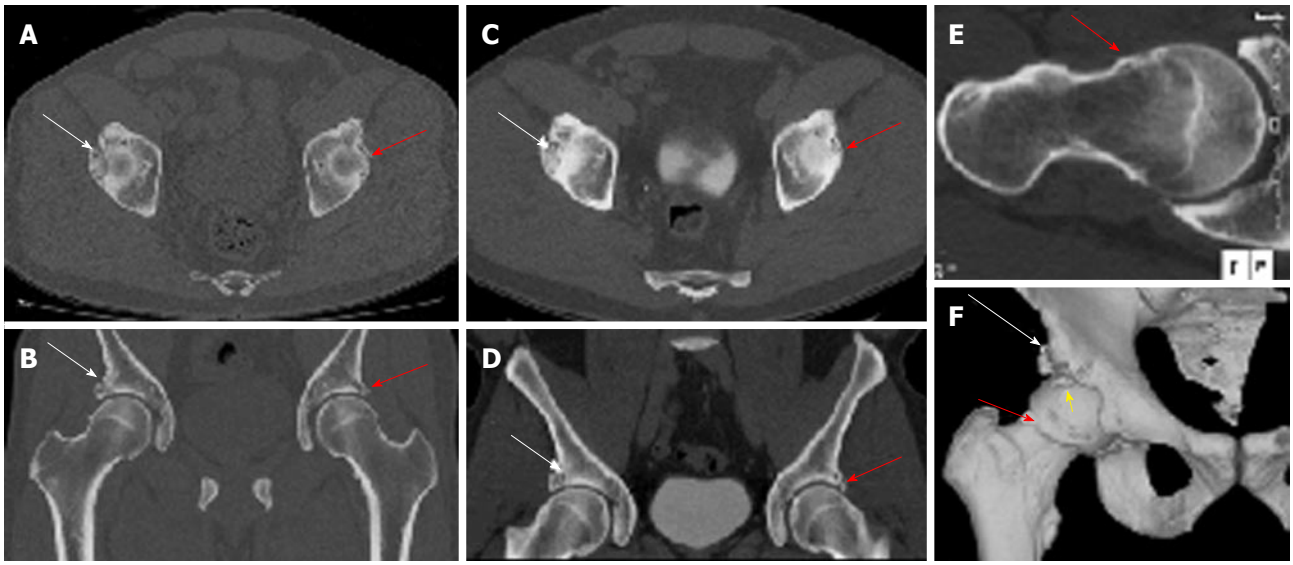

Figure 2 3D computed tomography imaging of the pelvis. Computed tomography pelvis obtained at current presentation (A, B) and 2 years before (C, D) confirm the unchanged bilateral mixed femoroacetabular impingement anatomy with a chronic right acetabular rim fracture (white arrows) and small left Os acetabulum/labral calcification (yellow arrow). Oblique axial thick slab maximum intensity projection reconstruction (E) along the right femoral neck axis shows the CAM deformity (red arrow) and fibrocystic change at the head and neck junction. Surface rendered 3D bone reconstruction (F) confirms the rim fracture (white arrows) and the CAM deformity (red arrow). Also note loose fragment anteriorly and superiorly, which was subsequently removed on surgery (yellow arrow).

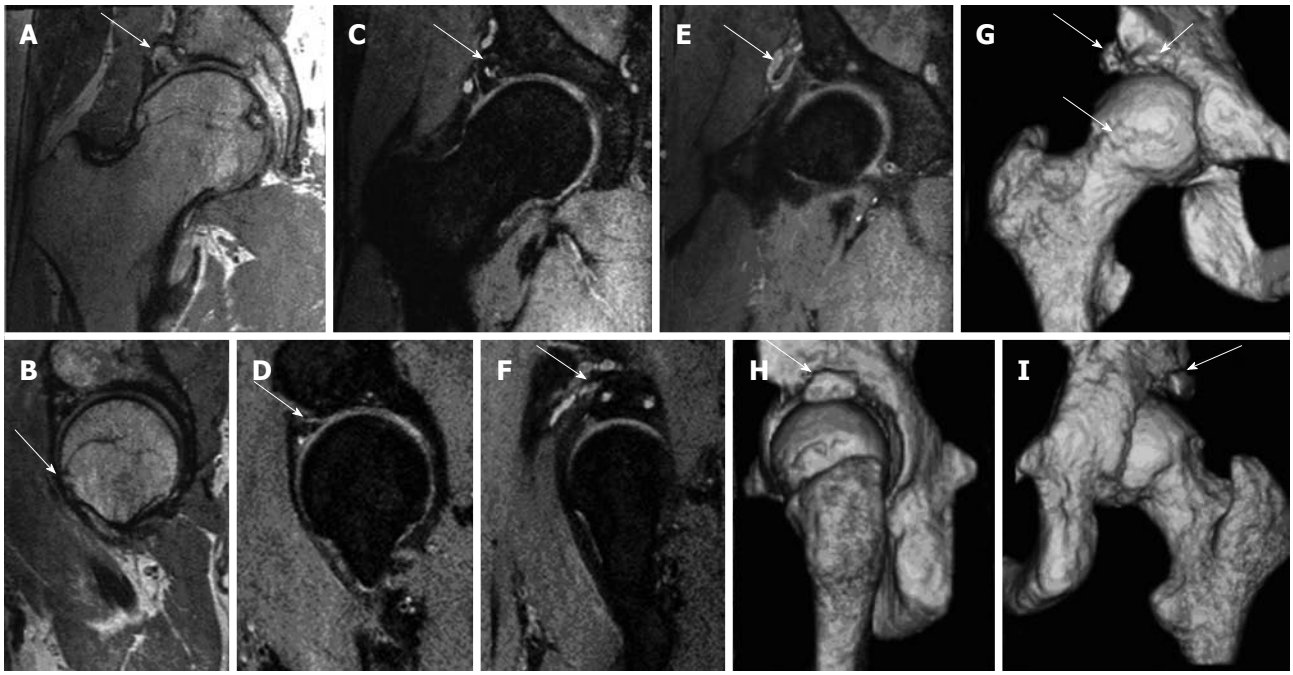

Figure 3 3D magnetic resonance imaging of the right hip. Multiplanar isotropic reconstructions from 3D fast spin echo proton density weighted (PDW) (A, B) and fat suppressed PDW (C-F) show the acetabular rim fracture (arrows in A, C, F) with pseudoarthrosis and cystic changes; paralabral cyst wrapping around the rectus femoris tendon (arrows in E, F) and CAM deformity (arrow in B). 3D surface rendered bone reconstructions show the bony changes akin to the computed tomography (CT) images with a CAM deformity and bone fragments (arrows in G) and the rim fracture (arrows in H, I), as with 3D CT.

× 1.4 cm (Tr) × 2.9 cm (CC), which had undercut and wrapped around the indirect head of the rectus femoris tendon. The femoral cartilage was normal. The acetabular cartilage showed small area of high grade fissuring involving the anterior-superior and superior-lateral acetabulum with underlying subchondral cystic changes (Figure 3). There was low-grade partial tear of the proximal iliofemoral ligament. 3D surface rendered bone reconstructions were obtained from the isotropic 3D imaging on the same work station using semi-automated contour drawing tool that also demonstrated the bony anatomy of FAI and rim fracture. The patient

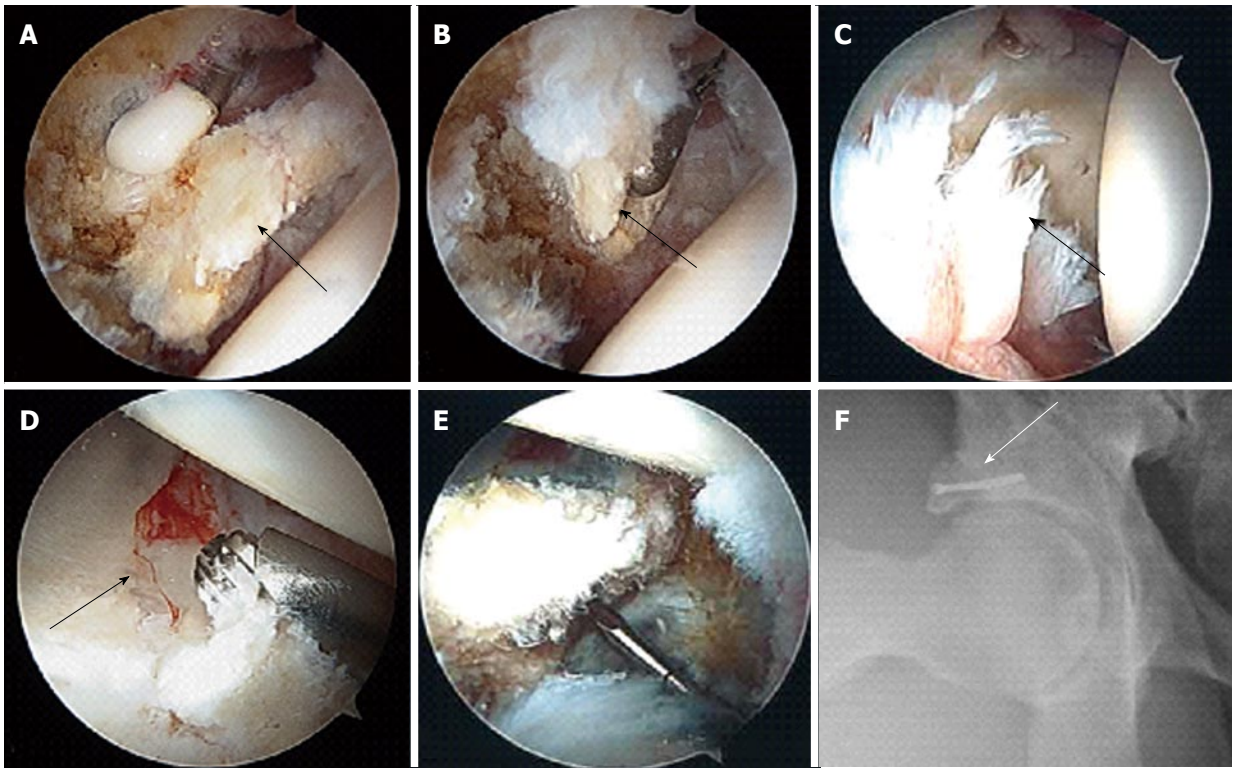

Figure 4 Arthroscopic and follow up images. Intra-operative photos show the anterior superior acetabular loose fragment (arrow in A) being freed with a radiofrequency device and then removed with an arthroscopic grasper *via* the mid-anterior portal (arrow in B). Notice the shredded labrum that remained anteriorly (arrow in C). A 4.5 mm burr pictured above the lateral rim fracture fragment. The crack in articular cartilage can be seen running from anterior to posterior (arrow in D). This rim fragment was fixed arthroscopically using a 2.4 mm headless screw (E). Follow up Dunn view shows the nicely fixed acetabular rim fracture with the screw (arrow in F).

received physical rehabilitation and an ultrasound guided local anesthetic and steroid injection of right hip over the next 4 mo without much relief.

Further 4 mo later, the patient underwent right hip arthroscopy with labral debridement as well as open reduction and internal fixation of acetabular rim fracture with a screw, rim trim and femoroplasty cam decompression. The acetabular labrum was found to be attached to the loose mobile fragment, which disrupted the continuity of the labrum at the 1 to 2 o'clock position as defined with respect to the acetabular notch (Figure 4). This fragment was removed. The remaining anterior labrum was shredded from the 3 o'clock to 6 o' clock position. There was an additional lateral acetubular rim fracture that extended from the 1 o'clock position anteriorly to the 11 o'clock position posteriorly. The rim fragment was mobile, but contained both intact articular cartilage and a labral rim. Femoral head cartilage was intact. The acetabular cartilage was found to be intact anteriorly and posteriorly; however, at the site of the acetabular rim fracture, there was a crack through the acetabular cartilage. The loose body at the calcified acetabulum was somewhat tethered to the soft tissues of the capsule. This was released with radiofrequency and then removed as 1 piece, approximately 1 cm × 1 cm in size. Using an arthroscopic shaver and radiofrequency device, the labrum was debrided back to a stable rim over this area from 3 to 6 o'clock. The labrum also stabilized at its truncation point at 1 o'clock. Acetabular rim trim was then performed using a 4.5 mm shaver along the 1 to 3 o'clock positions. The removal of the acetabular rim fragment would have resulted in a significant loss in lateral acetabular cartilage and labrum. Therefore, it was fixed with a 2.4 mm headless cannulated screw. The screw was inserted arthroscopically and resulted in excellent compression across the fracture site. Finally, femoroplasty and Cam decompression was performed by debriding the femoral head and neck junction over the anterior-superior and anterolateral aspect of the femoral head-neck junction. The patient did well on follow-up obtained over next 6 mo.

DISCUSSION

Femoroacetabular impingement is a patho-mechanical process due to presence of either a mis-shapen femoral head (CAM lesion) or mal-rotated/deep acetabulum (PINCER lesion) resulting in early and accelerated fibrocartilage and/or hyaline cartilage degeneration[1-5]. For the correction of the altered anatomy, the surgeon pre-operatively needs to know the extent of bony as well as soft tissue lesions or any odd lesions, such as a rim fracture in this case. Our patient showed bilateral FAI anatomy on CT abdomen and pelvis obtained 2 years ago for other reasons but he did not have hip symptoms

at that time. It is well reported in the literature that many asymptomatic subjects might show radiographic evidence of altered anatomy suggesting FAI on various imaging modalities and therefore, clinical correlation of symptomatology, positive impingement test, "C sign" and focused hip examination is essential for the FAI diagnosis[6,7].

The association of FAI anatomy with labral tears and hyaline cartilage degeneration is well known. Most common areas of labral tears are in anterosuperior or superolateral quadrants[8]. Higher offset alpha angles are associated with larger labral tears, more cartilage delamination, male sex and decreased range of motion as in this case, where alpha angle was 65°-68°[9]. 3D CT is the current reference standard for demonstration of bony alterations of FAI and is widely used for pre-operative planning[10-12]. It provides exquisite surface rendered reconstructions and affords easy and accurate calculation of various angular and linear measurements intended for prospective surgical bony re-alignment[13,14]. It was difficult to tell on radiographs due to their planar nature, whether the superolateral acetabular rim represented a large os acetabulum with labral ossification or a rim fracture. 3D CT reconstruction confirmed the presence of a rim fracture with pseudoarthrosis and also detected an anterior potentially loose fragment. It has been previously reported that os acetabulum related lucency is parallel to the joint surface unlike the rim fracture, which is more perpendicular in orientation[15]. However, the above differentiation might not be clear cut, and further MR imaging demonstration or surgical inspection of hyaline cartilage extension to the broken fragment might be needed for accurate identification. It has been shown that 3D CT can also moderately predict the internal soft tissue derangement findings of FAI based on altered bony anatomy[16], however, MR imaging is the current reference standard for labrum and hyaline cartilage evaluation for detection of locations of tears, their characterization and determining the extent of secondary osteoarthrosis[4,17].

A high-resolution, non-arthrographic technique at 3 Tesla (T) imaging potentially provides more accurate and reproducible preoperative information regarding the presence and anatomic location of labral and cartilage abnormalities similar to arthrographic technique at 1.5T[18,19]. Soft tissue internal derangement findings nicely correlated with surgical findings. Except for cartilage crack at fracture site, cartilage fissuring was not reported on arthroscopy despite small area being present on MRI with subchondral cystic change. This might be explained by overt sensitivity of MRI. In addition, 3D isotropic spin echo type imaging (0.6-0.75 mm isotropic resolution, TR: 1400-1700 ms, TE: 35-45 ms) on 3T scanner not only allows similar resolution multiplanar reconstructions, but also bone segmentation and surface rendering using the available CT software. MR imaging thereby offers benefits of soft tissue evaluation, bone remodeling, radiation free imaging, and finally convenience for the patient with single stop shop for FAI assessment[20,21]. However, this approach is not free of limitations. These include required availability of 3T scanner, technique optimization, long imaging time of 3D sequence (about 7 min) with potential for patient motion artifacts, and not very crisp bony reconstructions due to the lack of dedicated MR imaging based software at current times. The reconstruction also takes about 20 min for the technologist/reader. Additionally, one is limited in accomplishing pelvic tilt correction similar to whole pelvis CT imaging, which is required for better reproducibility and accuracy of measurements[22,23]. Finally, CT imaging at knee and hip can be used to evaluate the femoral version. Femoral version can either protect (anteversion making CAM deformity less likely to impinge) or make it more susceptible (relative retroversion making it more likely to impinge). Similar technique can be done with MRI but this approach requires more time for acquisition and potential coil movement with some vendors.

Stress injuries of acetabulum, labral ossification, femoral neck stress fractures and rim fracture can occur in the setting of FAI due to altered anatomy[15,24,25]. Rim fracture puts the surgeon in a dilemma whether to remove the bone fragment to mitigate the impingement anatomy, or to re-attach it so as not to the leave the femoral head substantially uncovered and consequently, an unstable hip[26]. Measurement of lateral center edge angle or visual impression on surface rendered 3D CT or 3D MR images can give an indication to the surgeon pre-operatively, as to the amount of resultant undercoverage, if the fractured lateral rim were to be removed. Surgical excision and re-fixation using a cannulated screw by drilling across the fibro-cartilaginous junction helps to promote healing of these fragments or any associated labral tears[26,27], as was also accomplished in our case. Absence of large areas of cartilage abnormality or significant arthritis on MR imaging is good predictor of successful outcome in FAI cases[28,29]. The patient did well on 6 wk and 4 mo follow-up visits. We do not have a long term follow-up on our patient but he did well in the short term.

To conclude, rim fracture is an uncommon finding in the context of FAI and its management can be aided by bony remodeling and labral-cartilage assessment on pre-operative 3D CT and 3D MR imaging.

COMMENTS

Case characteristics

A 46-year-old man presented with bilateral hip pain, right worse than left.

Clinical diagnosis

Femoroacetabular impingement (FAI).

Differential diagnosis

Tumor, infection or inflammatory condition, fracture, and avascular necrosis.

Imaging diagnosis

3D computed tomography (CT) and 3D magnetic resonance imaging (MRI) confirmed FAI with chronic acetabular rim fracture.

Treatment

Right hip arthroscopy with labral debridement as well as open reduction and internal fixation of acetabular rim fracture with a screw, rim trim and femoroplasty cam decompression.

Related reports

It is well reported in the literature that many asymptomatic subjects might show radiographic evidence of altered anatomy suggesting FAI on various imaging modalities and therefore, clinical correlation of symptomatology, positive impingement test, "C sign" and focused hip examination is essential for the FAI diagnosis.

Term explanation

Femoroacetabular impingement is a patho-mechanical process due to presence of either a mis-shapen femoral head (CAM lesion) or mal-rotated/deep acetabulum (PINCER lesion) resulting in early and accelerated fibrocartilage and/or hyaline cartilage degeneration.

Experiences and lessons

Rim fracture is an uncommon finding in the context of FAI and its management can be aided by bony remodeling and labral-cartilage assessment on pre-operative 3D CT and 3D MR imaging.

Peer-review

The authors present an unusual case of FAI with chronic acetabular rim fracture. Radiographic, 3D CT, 3D MRI and arthroscopy correlation is presented with discussion of their relative advantages and disadvantages in the context of FAI.

REFERENCES

1 **Hofmann S**, Tschauner Ch, Graf R. Mechanical causes of osteoarthritis in young adults. *Hip Int* 2003; **13**: 3-9 [PMID: 24030576 DOI: 10.5301/HIP.2008.4415]

2 **Ganz R**, Parvizi J, Beck M, Leunig M, Nötzli H, Siebenrock KA. Femoroacetabular impingement: a cause for osteoarthritis of the hip. *Clin Orthop Relat Res* 2003; **(417)**: 112-120 [PMID: 14646708]

3 **Tannast M**, Siebenrock KA, Anderson SE. Femoroacetabular impingement: radiographic diagnosis--what the radiologist should know. *AJR Am J Roentgenol* 2007; **188**: 1540-1552 [PMID: 17515374 DOI: 10.2214/AJR.06.0921]

4 **Pfirrmann CW**, Mengiardi B, Dora C, Kalberer F, Zanetti M, Hodler J. Cam and pincer femoroacetabular impingement: characteristic MR arthrographic findings in 50 patients. *Radiology* 2006; **240**: 778-785 [PMID: 16857978 DOI: 10.1148/radiol.2403050767]

5 **Cobb J**, Logishetty K, Davda K, Iranpour F. Cams and pincer impingement are distinct, not mixed: the acetabular pathomorphology of femoroacetabular impingement. *Clin Orthop Relat Res* 2010; **468**: 2143-2151 [PMID: 20431974 DOI: 10.1007/s11999-010-1347-z]

6 **Jung KA**, Restrepo C, Hellman M, AbdelSalam H, Morrison W, Parvizi J. The prevalence of cam-type femoroacetabular deformity in asymptomatic adults. *J Bone Joint Surg Br* 2011; **93**: 1303-1307 [PMID: 21969426 DOI: 10.1302/0301-620X.93B10.26433]

7 **Hack K**, Di Primio G, Rakhra K, Beaulé PE. Prevalence of cam-type femoroacetabular impingement morphology in asymptomatic volunteers. *J Bone Joint Surg Am* 2010; **92**: 2436-2444 [PMID: 20962194 DOI: 10.2106/JBJS.J.01280]

8 **Beall DP**, Sweet CF, Martin HD, Lastine CL, Grayson DE, Ly JQ, Fish JR. Imaging findings of femoroacetabular impingement syndrome. *Skeletal Radiol* 2005; **34**: 691-701 [PMID: 16172860 DOI: 10.1007/s00256-005-0932-9]

9 **Johnston TL**, Schenker ML, Briggs KK, Philippon MJ. Relationship between offset angle alpha and hip chondral injury in femoroacetabular impingement. *Arthroscopy* 2008; **24**: 669-675 [PMID: 18514110 DOI: 10.1016/j.arthro.2008.01.010]

10 **Beaulé PE**, Zaragoza E, Motamedi K, Copelan N, Dorey FJ. Three-dimensional computed tomography of the hip in the assessment of femoroacetabular impingement. *J Orthop Res* 2005; **23**: 1286-1292 [PMID: 15921872 DOI: 10.1016/j.orthres.2005.03.011]

11 **Tannast M**, Kubiak-Langer M, Langlotz F, Puls M, Murphy SB, Siebenrock KA. Noninvasive three-dimensional assessment of femoroacetabular impingement. *J Orthop Res* 2007; **25**: 122-131 [PMID: 17054112 DOI: 10.1002/jor.20309]

12 **Kang RW**, Yanke AB, Espinoza Orias AA, Inoue N, Nho SJ. Emerging ideas: Novel 3-D quantification and classification of cam lesions in patients with femoroacetabular impingement. *Clin Orthop Relat Res* 2013; **471**: 358-362 [PMID: 23129477 DOI: 10.1007/s11999-012-2693-9]

13 **Milone MT**, Bedi A, Poultsides L, Magennis E, Byrd JW, Larson CM, Kelly BT. Novel CT-based three-dimensional software improves the characterization of cam morphology. *Clin Orthop Relat Res* 2013; **471**: 2484-2491 [PMID: 23361933 DOI: 10.1007/s11999-013-2809-x]

14 **Murphy RJ**, Subhawong TK, Chhabra A, Carrino JA, Armand M, Hungerford M. A quantitative method to assess focal acetabular overcoverage resulting from pincer deformity using CT data. *Clin Orthop Relat Res* 2011; **469**: 2846-2854 [PMID: 21748515 DOI: 10.1007/s11999-011-1958-z]

15 **Martinez AE**, Li SM, Ganz R, Beck M. Os acetabuli in femoro-acetabular impingement: stress fracture or unfused secondary ossification centre of the acetabular rim? *Hip Int* 2006; **16**: 281-286 [PMID: 19219806]

16 **Heyworth BE**, Dolan MM, Nguyen JT, Chen NC, Kelly BT. Preoperative three-dimensional CT predicts intraoperative findings in hip arthroscopy. *Clin Orthop Relat Res* 2012; **470**: 1950-1957 [PMID: 22528376 DOI: 10.1007/s11999-012-2331-6]

17 **James SL**, Ali K, Malara F, Young D, O'Donnell J, Connell DA. MRI findings of femoroacetabular impingement. *AJR Am J Roentgenol* 2006; **187**: 1412-1419 [PMID: 17114529 DOI: 10.2214/AJR.05.1415]

18 **Robinson P**. Conventional 3-T MRI and 1.5-T MR arthrography of femoroacetabular impingement. *AJR Am J Roentgenol* 2012; **199**: 509-515 [PMID: 22915390 DOI: 10.2214/AJR.12.8672]

19 **Park SY**, Park JS, Jin W, Rhyu KH, Ryu KN. Diagnosis of acetabular labral tears: comparison of three-dimensional intermediate-weighted fast spin-echo MR arthrography with two-dimensional MR arthrography at 3.0 T. *Acta Radiol* 2013; **54**: 75-82 [PMID: 23093725 DOI: 10.1258/ar.2012.120338]

20 **Kang X**, Zhang H, Garbuz D, Wilson DR, Hodgson AJ. Preliminary evaluation of an MRI-based technique for displaying and quantifying bony deformities in cam-type femoroacetabular impingement. *Int J Comput Assist Radiol Surg* 2013; **8**: 967-975 [PMID: 23549935 DOI: 10.1007/s11548-013-0837-3]

21 **Kavanagh EC**, Read P, Carty F, Zoga AC, Parvizi J, Morrison WB. Three-dimensional magnetic resonance imaging analysis of hip morphology in the assessment of femoral acetabular impingement. *Clin Radiol* 2011; **66**: 742-747 [PMID: 21524414 DOI: 10.1016/j.crad.2011.02.014]

22 **Dandachli W**, Ul Islam S, Tippett R, Hall-Craggs MA, Witt JD. Analysis of acetabular version in the native hip: comparison between 2D axial CT and 3D CT measurements. *Skeletal Radiol* 2011; **40**: 877-883 [PMID: 21181403 DOI: 10.1007/s00256-010-1065-3]

23 **Lohan DG**, Seeger LL, Motamedi K, Hame S, Sayre J. Cam-type femoral-acetabular impingement: is the alpha angle the best MR arthrography has to offer? *Skeletal Radiol* 2009; **38**: 855-862 [PMID: 19565238 DOI: 10.1007/s00256-009-0745-3]

24 **Klaue K**, Durnin CW, Ganz R. The acetabular rim syndrome. A clinical presentation of dysplasia of the hip. *J Bone Joint Surg Br* 1991; **73**: 423-429 [PMID: 1670443]

25 **Epstein NJ**, Safran MR. Stress fracture of the acetabular rim: arthroscopic reduction and internal fixation. A case report. *J Bone Joint Surg Am* 2009; **91**: 1480-1486 [PMID: 19487528 DOI: 10.2106/JBJS.H.01499]

26 **Larson CM**, Stone RM. The rarely encountered rim fracture that contributes to both femoroacetabular impingement and hip stability:

a report of 2 cases of arthroscopic partial excision and internal fixation. *Arthroscopy* 2011; **27**: 1018-1022 [PMID: 21693352 DOI: 10.1016/j.arthro.2011.04.006]

27 **Espinosa N**, Rothenfluh DA, Beck M, Ganz R, Leunig M. Treatment of femoro-acetabular impingement: preliminary results of labral refixation. *J Bone Joint Surg Am* 2006; **88**: 925-935 [PMID: 16651565 DOI: 10.2106/JBJS.E.00290]

28 **Larson CM**, Giveans MR, Stone RM. Arthroscopic debridement versus refixation of the acetabular labrum associated with femoroacetabular impingement: mean 3.5-year follow-up. *Am J Sports Med* 2012; **40**: 1015-1021 [PMID: 22307078 DOI: 10.1177/0363546511434578]

29 **Meftah M**, Rodriguez JA, Panagopoulos G, Alexiades MM. Long-term results of arthroscopic labral debridement: predictors of outcomes. *Orthopedics* 2011; **34**: e588-e592 [PMID: 21956049 DOI: 10.3928/01477447-20110826-04]

P- Reviewer: Cartmell S, Fenichel I, Malik H **S- Editor**: Tian YL
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