ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2015 March 18; 6(2): 161-321

Published by Baishideng Publishing Group Inc

WJO World Journal of Orthopedics

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

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2015-2018

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WJO World Journal of Orthopedics

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Monthly Volume 6 Number 2 March 18, 2015

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Volume 6 Number 2 March 18, 2015

NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

FREQUENCY
Monthly

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PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
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E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
March 18, 2015

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-5836/g_info_20100722172650.htm

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Submit a Manuscript: http://www.wjgnet.com/esps/
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DOI: 10.5312/wjo.v6.i2.161

World J Orthop 2015 March 18; 6(2): 161-171
ISSN 2218-5836 (online)

REVIEW

Management and prevention of acute and chronic lateral ankle instability in athletic patient populations

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Conflict-of-interest: I declare that I have no conflicts of interest in the authorship or publication of this contribution.

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Received: December 29, 2013
Peer-review started: December 31, 2013
First decision: January 20, 2014
Revised: November 16, 2014
Accepted: December 29, 2014
Article in press: December 31, 2014
Published online: March 18, 2015

Abstract

Acute and chronic lateral ankle instability are common in high-demand patient populations. If not managed appropriately, patients may experience recurrent instability, chronic pain, osteochondral lesions of the talus, premature osteoarthritis, and other significant long-term disability. Certain populations, including young athletes, military personnel and those involved in frequent running, jumping, and cutting motions, are at increased risk. Proposed risk factors include prior ankle sprain, elevated body weight or body mass index, female gender, neuromuscular deficits, postural imbalance, foot/ankle malalignment, and exposure to at-risk athletic activity. Prompt, accurate diagnosis is crucial, and evidence-based, functional rehabilitation regimens have a proven track record in returning active patients to work and sport. When patients fail to improve with physical therapy and external bracing, multiple surgical techniques have been described with reliable results, including both anatomic and non-anatomic reconstructive methods. Anatomic repair of the lateral ligamentous complex remains the gold standard for recurrent ankle instability, and it effectively restores native ankle anatomy and joint kinematics while preserving physiologic ankle and subtalar motion. Further preventative measures may minimize the risk of ankle instability in athletic cohorts, including prophylactic bracing and combined neuromuscular and proprioceptive training programs. These interventions have demonstrated benefit in patients at heightened risk for lateral ankle sprain and allow active cohorts to return to full activity without adversely affecting athletic performance.

Key words: Ankle instability; Athlete; Treatment; Epidemiology; Prevention; Lateral; Sprain

Core tip: Competitive athletes and high-demand military servicemembers are at significant risk for lateral ankle instability during at-risk activity, particularly in the presence of certain modifiable and non-modifiable risk factors. In conjunction with semirigid ankle bracing, functional rehabilitation protocols emphasizing neuro-

muscular coordination, peroneal strengthening, and proprioceptive training are effective for the majority of patients with acute ankle sprain. However, with chronic lateral ankle instability unresponsive to conservative measures, anatomic ligamentous repair or reconstruction reliably restores active patients to full athletic function. Prophylactic bracing and targeted physical therapy may also be considered in selected, high-risk cohorts.

McCriskin BJ, Cameron KL, Orr JD, Waterman BR. Management and prevention of acute and chronic lateral ankle instability in athletic patient populations. *World J Orthop* 2015; 6(2): 161-171 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/161.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.161

INTRODUCTION

Acute and chronic ankle instability are common within athletic patient populations. Ankle sprain is a term often applied to a broad spectrum of traumatic soft tissue injuries about the ankle and hindfoot. However, the injury discussed in this review specifically addresses ligamentous instability about the talocrural joint[1]. Ankle instability has classically been organized into three categories: lateral, medial, and syndesmotic ligament injuries. These injuries are often seen in conjunction with other concomitant trauma, particularly involving the talar dome articular surface and peroneal tendons. Lateral ankle sprains, specifically those involving the anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL), and posterior talofibular ligament, account for over 85% of all ankle sprains[2]. Conversely, syndesmotic sprains (*i.e.*, "high ankle sprains") and medial ankle ligamentous injuries encompass up to 15% of all ankle sprains, although these injuries are far less thoroughly evaluated in the literature[3,4].

Acute ankle sprain has been reported to be the most common injury sustained by athletes, accounting for up to 40% of sports injuries[5-8]. Annually, an estimated two million acute ankle sprains occur each year in the United States, resulting in nearly 1.2 million healthcare-related visits and an annual aggregate health-care cost of up to $2 billion[9-11]. Ankle instability, when undertreated, may also result in chronic pain, muscular weakness, recurrent instability, and degenerative arthritis[2,12]. Significant time lost at work or further disability has been reported to occur in up to 60% of patients[9,13,14].

The purpose of this review is to summarize the relevant contemporary literature regarding acute and chronic lateral ankle instability and identify epidemiological risk factors for subsequent injury within an active patient population. Additionally, we will discuss the management and prevention of these common athletic injuries within the context of this higher-demand cohort.

EPIDEMIOLOGY

The incidence rates of ankle sprain may vary depending on patient demographics and method of surveillance, and several authors have reported between 2 to 7 individuals affected per 1000 in the general population each year[9,12,15]. Acute ankle sprain has also been identified as the most common injury sustained by United States military personnel[4,8], as well as young athletes[4,12,15,16]. In 2007, Fong *et al*[6] performed a systematic review of sports injuries sustained from 1977 to 2005, and ankle sprain was the major ankle injury in 33 of 43 sports.

With frequent, heavy load-bearing activity, rigorous physical demands, and unpredictable terrain, the incidence rates of ankle sprain among military service-members are an order of magnitude greater than that reported in the civilian population. Prior studies have underscored this epidemiological trend, with reported rates of ankle sprain ranging from 35 to 58 per 1000 person-years within the active duty United States military population[4]. Paratroopers may represent an even higher risk demographic. In this patient subset, ankle sprain accounts for 9%-33% of all parachute-related injuries and the incidence rate is estimated between 1 and 4.5 per 1000 jumps[17-19].

RISK FACTORS

Multiple studies have identified specific risk factors for ankle sprain in athletic cohorts, which are classically categorized as intrinsic or extrinsic factors[4,11,20,21]. Intrinsic risk factors may include age, gender, height, weight, body mass index (BMI), previous injury, aerobic fitness, limb dominance, flexibility, limb girth, muscle strength, proprioception, reaction time, postural stability, anatomical alignment, foot morphology, and inadequate rehabilitation. Extrinsic risk factors may include specific sport or at-risk activity, level of competition, shoe type, playing surface, and the use of external restraints such as ankle tape and/or braces[9,22]. Recently, injury epidemiologists have demonstrated a renewed focus on identifying modifiable and non-modifiable risk factors that tend to be associated with this common injury[4,20-23] (Table 1). Understanding variables within this framework may be useful in identifying high-risk populations. Furthermore, the targeting of modifiable risk factors may yield opportunities for further injury prevention[22].

Prior ankle instability

A history of previous ankle sprain appears to be an independent risk factor for recurrent acute ankle sprain. The index ankle sprain results in damage to the lateral ligaments responsible for stability of the tibiotalar joint and contributes to subsequent functional limitations. The initial inflammatory response from an

Table 1 Risk factors for ankle sprain among athletic populations

Non-modifiable risk factors	Modifiable risk factors
Sex	Weight
Age	Body mass index
Height	Bracing/taping
Race	Footwear
Foot/ankle anatomy	Neuromuscular control
Extremity alignment	Postural stability
Previous ankle sprain	Muscle strength
Generalized Joint Laxity	Exposure to sport
	Player position
	Playing surface
	Skill level

acute ankle sprain also leads to scar formation, which is more prone to failure than uninjured native tissue, with a 60% reduction in energy absorbing capacity[24]. Tyler *et al*[25] reported that among high school football players, overweight athletes with a history of previous ankle sprain were 19 times more likely to sustain a noncontact ankle sprain than was a normal-weight player without a history of previous ankle sprain. Even with less severe primary ankle sprains, re-injury may still occur in athletes and military recruits involved in basic training type activities[8,26-28]. This increased risk may also be attributable to insufficient rehabilitation and earlier perceived healing of less severe injuries, despite persistent proprioceptive deficits[28].

Neuromuscular control

Neuromuscular control and postural stability are likely important factors affecting an athlete's risk for ankle instability. The relationship between neuromuscular control and ankle sprain was first described by Freeman *et al*[29] in 1965. Subsequent investigations of athletes sustaining acute ankle sprains have extensively evaluated the proprioceptive deficit following the primary injury, and its resultant impairment of postural balance, ankle stability, and strength[30,31]. McGuine *et al*[32] reported that high school basketball players who sustained acute ankle instability events, demonstrated considerably greater postural sway on stabilometry, than their peers who did not sustain acute ankle sprains.

Other studies utilizing clinical assessments of postural stability have reported similar results, which underscores the likelihood of a neuromuscular predisposition for injury in certain athletes[33]. Muscle fatigue and loss of pre-injury strength may exacerbate neuromuscular impairment, resulting in the subsequent development of ankle instability[34]. Changes in ligament morphology and disruption of afferent nervous networks have been described in the setting of acute ankle sprain and may significantly affect postural stability; however, their contribution to the development of chronic instability is less well understood and requires further study[35-37].

Sex

While female gender has been previously associated with higher incidence rates of ankle sprain, studies evaluating gender disparity in acute ankle instability incidence have yielded mixed results. A study of military cadets at the United States Military Academy revealed an incidence rate for ankle sprain among female cadets of 96.4 per 1000 person-years in contrast to an incidence rate of 52.7 per 1000 person-years among male cadets (Incidence Rate Ratio 1.83)[4]. When examining the subset of intercollegiate athletes, no difference was detected by gender after controlling for athletic exposure and individual sport[4]. Beynnon *et al*[38] reported an incidence rate of ankle sprain of 1.6 per 1000 person-days for male college athletes, compared to 2.2 per 1000 person-days for female college athletes, although the reported disparity did not achieve statistical significance. Hosea *et al*[39] also reported a 25% greater risk for sustaining less severe (Grade Ⅰ) ankle sprains for female high school and college basketball players, than their male counterparts. They did not; however, find a statistically different incidence of more severe ankle sprains among the same population. A recent military study revealed that among active duty servicemembers, females sustained ankle sprains with an incidence rate 21% higher than male military personnel[4].

With increasing female participation in athletic activities, studies comparing the incidence of musculoskeletal injury between the sexes have become important in identifying potential disparities between male and female athletes. The cause of differences in injury frequency is likely multifactorial, with hypothesized explanations including differences in hormones, ligamentous laxity, neuromuscular control, lower extremity limb alignment and anatomy, and both the level type of athletic participation[9,22,40]. Based on the available literature, there may be a higher incidence rate of lateral ankle sprain in females. However, fundamental differences in exposure to, as well as the level of, at-risk activity may confound this apparent difference, highlighting the need for further rigorous study.

Anthropomorphic measures

With increasing weight and body mass index, an increasing mass moment of inertia acting at the talocrural joint potentially increases the risk for acute ankle sprain. Tyler *et al*[25] reported that among high school football players with a BMI greater than 25 sustained ankle sprains significantly more frequently than those with a normal BMI. Waterman *et al*[3] described a similar association among male United States Military Academy cadets, with an increased incidence of ankle instability in cadets with a higher mean weight and BMI than sex-matched, uninjured cohorts. Conversely, other investigations have not found

weight and BMI to be independent risk factors for ankle sprain[38,41]. Despite the varying results found in the literature, certain athletes and player positions may be at higher risk for ankle sprain.

At-risk activity or sport

Specific activity type resulting in ankle sprain also appears to vary by age, with young active patients involved in both competitive and recreational athletics occurring most often[4]. Activities that involve frequent running, jumping and cutting type movements place athletes at higher risk for ankle instability. Analysis of the National Electronic Injury Surveillance System for all ankle sprains presenting to emergency departments over a five-year period revealed that 49.3% of ankle sprains were caused by participation in sports, with basketball (41.1%), football (9.3%), and soccer (7.9%) accounting for over half of all ankle sprains sustained during athletic activity[9].

A more extensive investigation of the epidemiology of ankle sprains revealed that incidence rates vary depending on the unit of measurement utilized[6]. When evaluating for incidence per 1000 person-hours, rugby had the highest incidence (4.20), followed by soccer (2.52). Conversely, when reporting incidence more accurately in terms of athletic exposure, lacrosse had the highest incidence rate (2.56) of sprains per 1000 person-exposures, followed by basketball (1.90). Waterman *et al*[4] found a similar relationship with men's rugby (1.53), men's lacrosse (1.34) and basketball (women's, 1.14 and men's, 1.67),resulting in the highest incidences of ankle sprain per 1000 person-years among intercollegiate athletes.

Level of competition

Level of competition is another modifiable risk factor for ankle sprain that has been reported in the literature. Level of competition is a term commonly used to define both the intensity of competition as well as the skill level of participants (*i.e.,* recreational, intramural, intercollegiate, or professional). However, these two components both represent distinct risk factors that should be separately evaluated[9]. There is a higher risk of ankle sprain with increasing level of intensity of competition, with approximately 55%-66% of injuries sustained during games, as opposed training or practice type activities[42-45]. Increases in pace of play and propensity for risk-taking activity likely account for this difference[9]. However, the impact of athlete skill level on the incidence of ankle sprain is less clear. Previous investigations suggest that college athletes are at seven times the risk for ankle sprain than their intramural counterparts, when analyzing the incidence of injury per 1000 person-years[4]. When controlling for the amount of athlete-exposures; however, no statistically significant difference was found between these cohorts. Additionally, Beynnon *et al*[46] reported that the risk of first-time ankle injury is similar for high school and college-level athletes. Other authors have similarly reported increased risk among intercollegiate athletes[39], while others have demonstrated a decreased risk among higher-skill level soccer players than their lower-skill level counterparts[43,47]. Other variables likely contribute to such differences seen between the different skill level cohorts, such as more match exposure and higher collective numbers of athlete-exposures[42], higher match-to-training ratio[48], and a lower warm-up or stretching period[48-50].

ACUTE ANKLE SPRAIN TREATMENT

Early recognition and evidence-based management of these common injuries are of great importance, and the consequences of missed or undertreated ankle instability is well documented with chronic instability resulting in as many as 60% of patients[2,9,13,14,16,51]. An initial assessment should always include a thorough history and physical examination, with consideration for radiographic evaluation. The Ottawa Ankle Rules are one commonly utilized method for the identification or exclusion of ankle fracture or other osseous trauma, and weight-bearing images are recommended if possible. Additionally, stress radiographs, including the talar tilt and anterior drawer tests, are often useful in evaluating for ligamentous laxity in patients with chronic ankle instability, but are not recommended in the acute setting[52-55].

The most common treatment methods described for severe, grade Ⅲ acute ankle sprains are a brief period of rigid immobilization (*e.g.*, < 10 d), functional management with transition to a semi-rigid external restraint, and delayed surgical repair in select, high-demand patients. Rigid immobilization in a cast is typically reserved for lower demand patients and should be employed for a period of no more than 3 wk, followed by sustained course of physical therapy for muscle strengthening and proprioceptive retraining[54,56-59]. Functional management of the acute ankle sprain entails early mobilization, weight bearing with an external restraint such as a brace, non-steroidal anti-inflammatory medication, and other anti-edema measures (rest, ice, compression, elevation). Following the acute phase, a physical therapy regimen may be utilized to focus on muscle strengthening, ankle range of motion, and proprioceptive or postural training (Figure 1). Proprioceptive therapy, such as with a Biomechanical Ankle Platform System, is crucial in regaining and to re-establish positional control vis-à-vis inversion ankle stress[60]. Similarly, external restraints and orthotics not only confer mechanical stability, but also likely provide some degree of short-term proprioceptive feedback in order to accelerate the recovery process[56-62].

Karlsson *et al*[63] reported that early functional

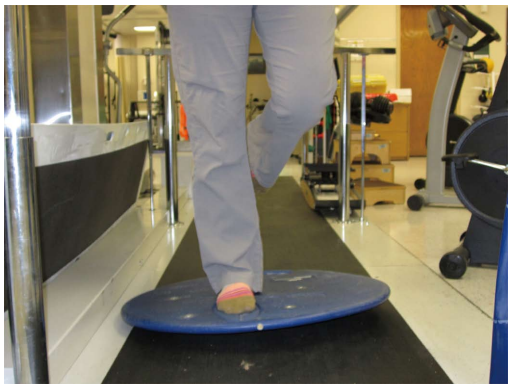

Figure 1 Clinical image demonstrating proprioceptive training during physical therapy.

treatment could significantly reduce the time required to return to work or preinjury sport. Furthermore, van Os *et al*[64] published a thorough review demonstrating that functional treatment with concomitant supervised physical therapy could yield superior recovery results when compared with functional treatment alone, specifically with regard to persistent swelling and time for return to work. Multiple authors have also reported significant reduction in recurrent ankle injury, attributable to proprioceptive training as part of a rehabilitation protocol[63-69].

Ardèvol *et al*[56] published results from a randomized controlled trial comparing cast immobilization with functional management in an athletic cohort. They found that patients managed with a functional protocol were able return to sporting activity sooner, and had fewer symptoms at three and six months following injury. Although they did not find a statistically significant difference in reinjury rates between the two groups, they did report less ligamentous laxity radiographically in the cohort managed with a functional protocol. In 2002, Kerkhoffs *et al*[57] performed a meta-analysis of randomized controlled trials comparing rigid immobilization and functional management of acute lateral ankle sprains. They reported a higher return to sport percentage in patients managed with functional protocols. They also reported faster return to work, better range of motion and a lower prevalence of persistent swelling and ligamentous laxity at intermediate follow-up, when compared to patients treated with rigid immobilization[54,57].

Surgical management of acute lateral ankle ligamentous injuries remains controversial; however, the majority of treating providers recommend a thorough three to six month course of nonoperative treatment before consideration of surgical management. In 2003, Pijnenburg *et al*[60] published their findings of a randomized prospective trial comparing functional treatment with primary surgical repair using the technique described by Prins[61], for patients with acute lateral ankle ligamentous injuries. The authors reported superiority with regard to pain, instability, and recurrent ankle sprains in patients treated with ligament repair. However, these authors advised caution in extrapolating their findings to the general population. They cited higher cost, higher risk of complications, and comparable results with delayed repair when comparing initial functional non-operative management of patients with acute ankle sprains[60].

Conversely, Tiling *et al*[70] performed a thorough review of 24 trials comparing surgical and functional management of ankle sprains and concluded that no significant difference was found between the two treatment strategies. More recently, in 2010, Pihlajamäki *et al*[71] reported the results of their prospective randomized trial, in an active Finnish patient population. These authors compared functional management to suture repair of ruptured ligaments within 1 wk of injury for acute grade Ⅲ lateral ankle ligaments. They concluded that surgical repair and functional treatment of these injuries resulted in equivalent results with respect to recovery to preinjury activity level. Although surgery did appear to decrease the incidence of lateral ligament reinjury in their study population, the found that osteoarthritis was observed significantly more frequently in the surgical group[71].

CHRONIC ANKLE INSTABILITY TREATMENT

Patients with chronic ankle instability can be further stratified into two categories, which are not necessarily mutually exclusive. Mechanical instability is identifiable on physical examination and stress radiographs, whereas functional instability reflects subjective, patient-reported complaints of the ankle instability with or without clinical laxity[54,72,73]. Surgery is generally reserved for patients with chronic ankle stability that have failed to improve with a thorough course of conservative management and physical therapy. Similar to that for acute ankle sprain, nonoperative measures for chronic instability emphasize peroneal strengthening, proprioceptive training, lateral heel wedges, and strapping or bracing[52]. Patients with functional instability without demonstrable mechanical instability are more likely to benefit from these non-operative measures[54,73].

Modern surgical techniques for chronic lateral ankle instability can be divided into two broad categories: anatomic ligament repair (Figure 2) and non-anatomic reconstruction (Figure 3). Anatomic repair can be performed with or without augmentation and/or tenodesis, while non-anatomic reconstruction is typically performed with tenodesis[54,74]. The goal of anatomic ligament repair is restore native ankle anatomy, stability, and joint kinematics, while preserving functional ankle and subtalar motion. This can be accomplished with the use of local tissue, free tendon graft, or both. While this type of repair is a technically simpler surgery than

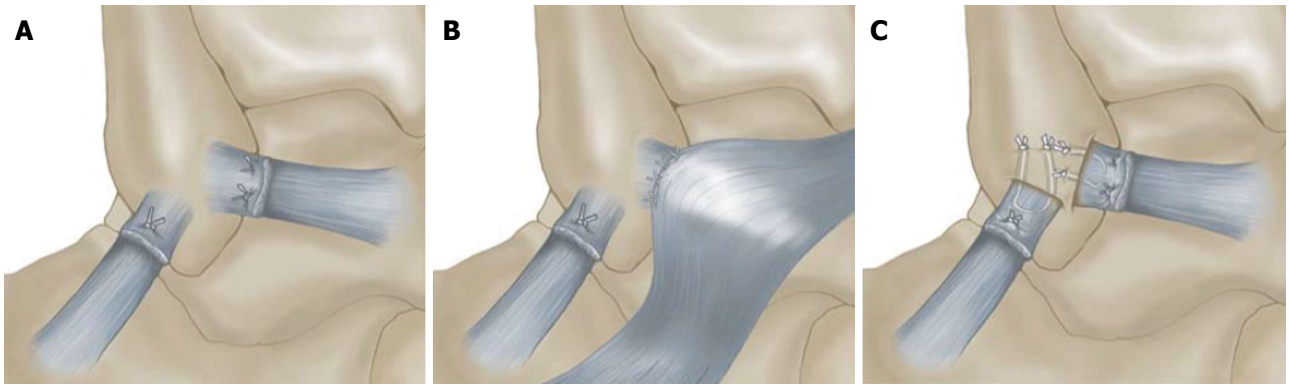

Figure 2 Anatomic repair of the lateral ligamentous complex[54]. Illustration demonstrating anatomic repair of chronic lateral ankle instability. A: Broström anatomic repair, demonstrating midsubstance imbrication and suture of the ruptured ligament ends; B: Gould modification augmented with the mobilized lateral portion of the extensor retinaculum; C: Karlsson modification, which involves anchoring the proximal ligament ends through drill holes.

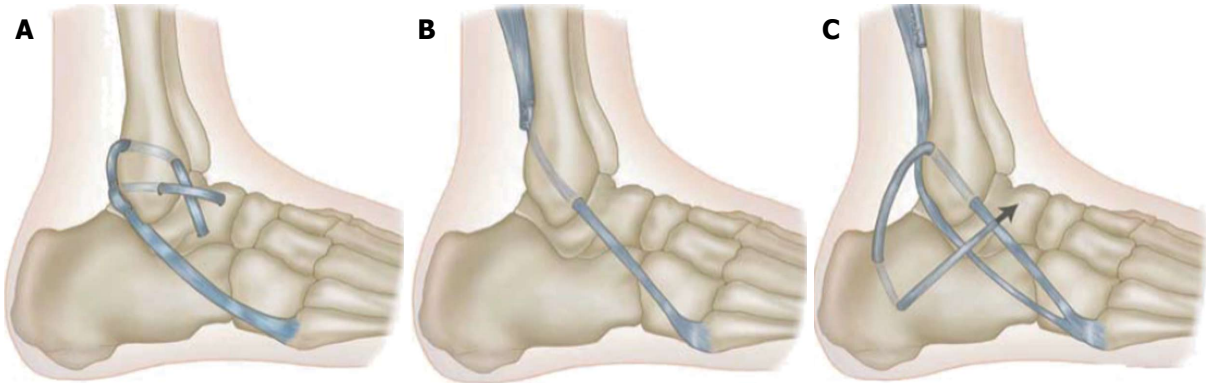

Figure 3 Selected techniques for non-anatomic lateral ligament reconstruction[54]. Tenodesis reconstruction for chronic lateral ankle instability. A: Watson-Jones procedure; B: Evans procedure; C: Chrisman-Snook procedure.

non-anatomic reconstruction procedures, its success is dependent on the condition of the injured tissues, and may sometimes require augmentation[74-78].

Non-anatomic reconstructions utilize tenodesis fixation to stabilize the ankle with the repair of the native ligaments. While multiple configurations have been described, most techniques involve rerouting of the peroneus brevis around the lateral ankle, and include the Watson-Jones, Evans, and Chrisman-Snook procedures (Figure 3)[74,79-82]. Long-term outcomes of non-anatomic reconstructions are hindered by alterations in ankle and hindfoot kinematics and often, resultant loss of subtalar motion[83-90]. Although initial reports were promising, comparison studies with longer follow-up generally favor anatomic repair over non-anatomic tenodesis reconstructions. Between 2000-2001, Krips *et al*[87,88] published a series of comparison studies, including more than 300 patients, with up to 30 years of follow-up data. These authors ultimately concluded that long-term, non-anatomic tenodesis lead to decreased function, increased pain, limited range of motion, instability, increased need for revision procedures, and greater degrees of osteoarthritis compared to anatomic reconstructions.

Since its first description in a series of 60 patients in 1966, the Broström technique has as evolved into the foundation for anatomic lateral ankle ligament repairs, with imbrication of ruptured ATFL and/or CFL[54,91]. In 1980, Gould *et al*[92] described the augmentation of the Broström repair with the inferior extensor retinaculum secured to the fibula following ligament repair. In 1988, Karlsson *et al*[93] reported that the ATFL and CFL were often found to be elongated and scarred, rather than disrupted. Based on this observation, these authors recommended imbrication of the attenuated ligaments followed by reinsertion into the fibula in their anatomic position with drill holes. Variations of anatomic repairs of the lateral ankle ligaments have a long track record in the literature, yielding good to excellent results in 85% of patients[54,74,86-88,94]. The use of a periosteal flap from the fibula, as well as autologous free tendon graft and allograft augments, has also been well described with favorable results[75,76,78]. Furthermore, sustained excellent patient outcomes have been reported by Bell *et al*[95] at greater than 20-year follow-up, and this procedure has demonstrable success in high-demand athletes[96].

Anatomic tenodesis procedures have recently been the subject of multiple investigations and have demonstrated promising results[54,74,87,88,97]. The goal of

this type of a repair is to augment an anatomical lateral ankle ligament repair, without sacrificing anatomy or kinematics in the reconstruction. In 1995, Colville *et al*[77], described introduced a reconstruction using a split peroneus brevis tendon to augment the repair of the ATFL and CFL in a small series, with encouraging clinical outcomes. Although long term data is not yet available, multiple authors have demonstrated maintenance of mechanical stability after these procedures while preserving the normal range of motion of the ankle and subtalar joints[74,77,87,88]. Graft position and ankle position during graft tensioning are likely critical for the success of this type of reconstruction and may become more relevant in light of the declining, long-term results of standard non-anatomic tenodesis[98,99].

In 1996, Hennrikus *et al*[86] prospectively compared the modified Broström with the Chrisman-Snook procedure in 40 patients. Both demonstrated improvement in more than 80% of patients, although those who underwent a modified Broström procedure had a lower rate of complications and a higher Sefton[100] outcomes scores. The authors concluded that the modified Broström procedure was superior to the Chrisman-Snook procedure for chronic lateral ankle instability. Subsequently, meta-analyses by de Vries *et al*[89,90] have evaluated the available randomized trials comparing the surgical procedures commonly performed. The authors were not unable to reach a conclusion regarding the best surgical option for management of chronic ankle instability, given the lack of statistical significance and poor methodological quality of the randomized controlled trials performed to date. Rigorous research is still needed to determine the most effective surgical strategy for treating this important problem.

The role of ankle arthroscopy in lateral ligament reconstruction is not yet well defined. In 1955, Bosien *et al*[101] cited a 6.5% incidence of osteochondral fractures of the talus with ankle sprains, and more recent studies have investigated the presence of articular abnormalities with both acute ankle sprain and chronic instability[102]. In 1999, Komenda *et al*[103] examined arthroscopically 54 consecutive patients with lateral ankle instability before ligament stabilization and noted frequent intra-articular pathology, including a 25% incidence of articular chondral injury. These authors concluded that articular cartilage injuries are common in patients with lateral ankle instability and can be successfully addressed with ankle arthroscopy in addition to open ligament stabilization. The indications for arthroscopy before lateral ligamentous repair remain ill defined, but these reports and others suggest that it is important to rule out associated injuries in patients with painful unstable ankles.

Advancements in MRI technology and its ready availability in many healthcare settings may be helpful in identifying associated osteochondral lesions of the talus and peroneal tendon pathology. Its use may be valuable in determining the utility of concomitant arthroscopy, particularly in the presence of mechanical symptoms, chronic ankle pain, or other focal findings on physical examination.

Bony malalignment can play an important role in the etiology and treatment of ankle instability. Specifically, hindfoot varus, first ray plantarflexion, or midfoot cavus can predispose patients to chronic lateral ankle instability and contribute to early operative failure if not addressed with a corrective procedure at the time of surgery. Concomitant calcaneal osteotomy for cavovarus deformity has been advocated for patients with varus hindfoot deformity in conjunction with lateral ligamentous surgery[74,104,105]. Csizy *et al*[104] published a series of six patients with ankle instability and a varus calcaneus treated successfully with a Dwyer-type osteotomy and ligament reconstruction. Fortin *et al*[105] reported 13 patients with combined cavovarus foot deformity and ankle instability, half of whom required ankle fusion due to advanced degenerative changes. The remaining patients were effectively treated with calcaneal osteotomy and dorsiflexion osteotomy of the first metatarsal, depending on the rigidity of the deformity.

A high index of suspicion for ankle and hindfoot malalignment, associated peroneal tendon pathology and generalized ligamentous laxity are each of great importance when evaluating the patient with and planning surgery for ankle instability[74]. Concomitant osteoarticular injuries are an increasingly identified component of ankle pain associated with ankle instability[52,101,103]. It is crucial that these common defects, as well as other periarticular pathology be recognized when ankle instability is diagnosed and treated.

PREVENTATIVE MEASURES

There are multiple practical measures that may be utilized to mitigate modifiable risk factors and reduce the risk of ankle sprain in athletic patient populations. Weight loss with BMI optimization, as well as activity appropriate footwear and external restraints are among recommendations that may be considered. Several interventions have demonstrated success in achieving these goals without significant effects on quality of life or impeding athletic performance. By increasing passive restraints to ankle inversion and enhancing postural stability, prophylactic bracing in high-risk athletes has demonstrated success reducing the risk of primary and recurrent ankle sprain by up to 50%[41,106,107]. In one prospective randomized trial, Sitler *et al*[41] demonstrated a threefold increased risk for ankle sprain among unbraced basketball players when compared to braced athletes over a two-year time period at the United States Military Academy. Among paratroopers, a recent systematic review revealed that the external parachute ankle brace

reduced all ankle injuries, including ankle sprain, by approximately half while saving between 0.6 and 3.4 million dollars in direct and indirect costs[19].

Neuromuscular training programs have also demonstrated success in reducing the risk of ankle sprain. In a meta-analysis, McKeon *et al*[37] reported that targeted balance control training resulted in a 20% to 60% relative risk reduction for lateral ankle sprain, particularly in athletes with having sustained prior ankle sprains. More effective screening of high-risk athletes and better objective measures for diagnosis, prophylactic interventions have to potential to benefit a larger number of athletes, reducing the overall incidence of ankle sprain and its potential burden on healthcare systems.

CONCLUSION

Acute and chronic ankle stability are a common source of disability in athletes and other high-demand patient populations, and may result in significant long-term sequelae, particularly with osteochondral lesions of the talus or peroneal tendon pathology. With enhanced screening based on known epidemiological risk factors, functional rehabilitation programs and prophylactic bracing may mitigate further lateral ankle instability with further physical activity. Anatomic surgical repair or reconstruction may be considered after failure of nonoperative measures, with high rates of return to full function in active patient cohorts.

ACKNOWLEDGMENTS

We would like to thank MAJ Justin D Orr, MD for his clinical images. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of Defense or the United States government. The authors are employees of the United States nment.

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P- Reviewer: Paschalis V, Vosoughi AR **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i2.172

World J Orthop 2015 March 18; 6(2): 172-189
ISSN 2218-5836 (online)

REVIEW

Biological response to prosthetic debris

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Author contributions: Both authors were involved in the design, acquisition of data, and analysis of this study; both contributed to the writing of this manuscript.

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Received: April 12, 2014
Peer-review started: April 12, 2014
First decision: April 28, 2014
Revised: September 24, 2014
Accepted: October 14, 2014
Article in press: October 16, 2014
Published online: March 18, 2015

Abstract

Joint arthroplasty had revolutionized the outcome of orthopaedic surgery. Extensive and collaborative work of many innovator surgeons had led to the development of durable bearing surfaces, yet no single material is considered absolutely perfect. Generation of wear debris from any part of the prosthesis is unavoidable. Implant loosening secondary to osteolysis is the most common mode of failure of arthroplasty. Osteolysis is the resultant of complex contribution of the generated wear debris and the mechanical instability of the prosthetic components. Roughly speaking, all orthopedic biomaterials may induce a universal biologic host response to generated wear débris with little specific characteristics for each material; but some debris has been shown to be more cytotoxic than others. Prosthetic wear debris induces an extensive biological cascade of adverse cellular responses, where macrophages are the main cellular type involved in this hostile inflammatory process. Macrophages cause osteolysis indirectly by releasing numerous chemotactic inflammatory mediators, and directly by resorbing bone with their membrane microstructures. The bio-reactivity of wear particles depends on two major elements: particle characteristics (size, concentration and composition) and host characteristics. While any particle type may enhance hostile cellular reaction, cytological examination demonstrated that more than 70% of the debris burden is constituted of polyethylene particles. Comprehensive understanding of the intricate process of osteolysis is of utmost importance for future development of therapeutic modalities that may delay or prevent the disease progression.

Key words: Debris; Adverse reaction; Osteolysis; Macrophages; Cytokines; Chemotaxis; Polyethylene; Phagocytosis

Core tip: After a comprehensive review of joint arthroplasty history, this article outlines the fundamental pathophysiology of the debris-induced biological reaction common to all particles types. Furthermore, specific characteristics of polyethylene, metal, ceramic, and polymethylmethacrylate particles are stated separately with their associated clinical relevance. Lastly, future therapeutic strategies to down-regulate periprosthetic osteolysis are enumerated, including anti-inflammatory agents used to modulate the cytokines release, anti-osteolytic agents used to disintegrate osteoclasts morphology, and antioxidants used to demolish the free oxygen radicals produced by the activated macrophages. The reader will find an extensive literature review encompassing all aspects of the debris-induced hostile cellular reaction.

Bitar D, Parvizi J. Biological response to prosthetic debris. *World J Orthop* 2015; 6(2): 172-189 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/172.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.172

JOINT ARTHROPLASTY HISTORICAL REVIEW

As stated by the famous French philosopher of science, Auguste COMTE (1798-1857), we cannot completely know a science without knowing its history.

The first implanted total joint arthroplasty goes back to 1890 where the German surgeon "Themistocles Gluck"[1] performed in Berlin a total ivory prosthesis on the tuberculous knee of a 17-year-old woman. Professor Gluck, whom revolutionary effort was dismissed during his lifetime, was also the first surgeon to use bone cement, about 65 years before Sir John Charnley[2].

Afterward, many biological (fascia lata grafts; pork bladder submucosa; skin) and inorganic materials were used as interpositional layer in an attempt to resurface the arthritic joints: In 1885, Léopold Ollier used adipose tissue and in 1912, Jones used gold foil to perform their "interpositional arthroplasty".

In 1922, the English surgeon Hey-Groves replaced the femoral head by an ivory sphere of same caliber with satisfactory result up to 4 years only. In 1923, the American surgeon "Marius Smith-Petersen" introduced the concept of "mold arthroplasty"[1] where he chose glass as material of his first mold after he removed a glass foreign body from a patient's back and found it surrounded by a synovial membrane. Many other inorganic materials were tried (Pyrex, Bakelite, viscaloid...) without success either because of their fragility or the toxicity of their debris.

In 1936, Venable *et al*[3] discovered the single electrically inert metal alloy, "Vitallium", composed of cobalt (60%), chromium (20%) and molybdenum (5%). Subsequently in 1940, Austin MOORE and Harold BOHLMAN placed the "first metal hip joint" made of Vitallium, in United States, Columbia, South Carolina: one piece femoral head and stem inserted in the intra-medullary canal.

In 1946, the 2 French brothers JUDET conceived the "Plexiglas" [polymethyl methacrylate (PMMA)] femoral sphere attached to a short stem, replacing the hip arthrodesis by hip prosthesis[2]. A short-lived good result was achieved since the PMMA material was extremely fragile and yielded tremendous wear debris.

In 1951 at Norwich (United Kingdom), McKee was the first surgeon to replace both sides of the hip articular surfaces using a metal-on-metal (MOM) prosthesis. Sir John Charnley is considered the "father of modern arthroplasty" where in 1960 at Manchester (United Kingdom), he pioneered the concept of "low friction arthroplasty", called like so because he promoted the use of a small femoral head in order to minimize the wear[1]. In 1962, he finalized his totally cemented prosthesis: a cemented polyethylene (PE) acetabular component and "monoblock" (one-piece) cemented femoral stem with 22 mm femoral head.

The initial work of all these surgeons focused on the design and fixation method of the implants. Once this goal has been achieved with Charnley, more attention was drawn toward the longevity of the prosthesis where "aseptic loosing" started to be noted since the early 1960's[4]. Implant aseptic loosening is the result of the complex intrication of fibrous membrane formation, peri-prosthetic bone resorption and inflammatory cytokines production[5].

Based on the extensive research work performed throughout the historical existence of arthroplasty, especially that of the hip joint, we were able to conclude that an extended longevity of an artificial joint depends mainly on 3 fundamental factors: (1) the durability of implant fixation; (2) the wear rate of the bearing surfaces; and (3) the accuracy of the surgical technique of prosthesis implantation.

This review article will discuss the wear factor stating the different types of generated prosthetic debris (PE, PMMA, metal, and ceramic) along with their specific characteristics (if present) and subsequent host biological reactions. The current knowledge of the adverse biologic reaction induced by different types of wear debris derives from the histo-pathologic analysis of the retrieved peri-prosthetic tissue during revision surgery, from genetic studies or from animal models studies.

At present, more than sixty years after the pioneering of the modern notions of arthroplasty, that underwent an active perpetual progress during this whole period, tens of thousands of hip and knee replacements are performed each year in United States and Europe[1,6]. "According to the Agency for Healthcare Research and Quality, more than 285000 total hip arthroplasties (THA) and more than 600000 knee arthroplasties are performed each year in the United States" (www.AAOS.org). According to the national joint registry (www.njrcentre.org.uk), approximately 160000 total hip and knee replacement procedures are performed each year in England and Wales, with the same number of replaced hip and knee joints. Based on the absolute number of THA performed per 100.000 inhabitants, Germany is the first on the list (296 THA/100.000 residents), followed by Switzerland (287/100.000) and Belgium (240/100.000)[6]. In United States and United Kingdom, 184 and 194 THAs respectively are performed per 100.000 inhabitants[6]. The number of annually performed arthroplasty is worldwide steadily increasing with time.

Building on the brilliant success attained, especially with (THA), the indication of joint replacement surgery was enlarged to include young active patients[1,7] suffering from disabling joint diseases, raising the problem of bearing surfaces wear that induces a chronic

inflammatory reaction leading to osteolysis[4,8] which accounts for the greatest majority of revision surgery that can be sometimes extensive and complicated. In addition, with the advances accomplished in the majority of medical fields, the life expectancy of the general population is lengthened, with more physically active elderly individuals being candidates for total joint replacements[8] with higher stresses exerted on the bearing surfaces for longer periods of time.

For THA, different types of bearing surfaces are available nowadays and can be broadly classified into 2 groups: hard-on-hard surfaces including ceramic-on-ceramic (COC) and MOM, and hard-on-soft surfaces including metal-on-polyethylene (MOP) and ceramic-on-polyethylene (COP). The most widely used bearings are metal-on-polyethylene that showed, since its introduction with Charnley prosthesis, good, cost-effective and predictable outcomes for decades[1] with concordant results whatever school or country is considered: 85% survival rate at 25 years and 78% at 35 years of follow-up[6]. Each couple of bearing surfaces has its advantages and drawbacks. It is incontestable that the development of these materials knew a marvelous evolution during the second half of the 20th century, but yet none can be considered to be absolutely perfect.

PERI-PROSTHETIC OSTEOLYSIS: BASIC SCIENCE

Total joint arthroplasty is considered one of the most prosperous branches of Orthopaedic surgery, where the damaged and painful articular surfaces are substituted by artificial anatomically-shaped components, ameliorating the patient quality of life by providing painless and unrestricted range of motion of the affected joint. Total hip and total knee replacement surgeries are part of the "top 5" surgical interventions in Orthopaedic surgery, alongside with carpal tunnel decompression, arthroscopic meniscal surgery and hardware removal[6]. However, as published by numerous long-term studies, all total joint replacements end up by loosening[4,9-14] with different time-frame longevity for every joint of the body.

The fact that endurance of arthroplasty is not everlasting is due to osteolysis of the bone surrounding the implants; it get established gradually as wear débris (mainly PE particles) are continuously produced by the mobile articulating bearings[5,15], increasing with time[4,9,14,16], with "aseptic loosening" being the end-point of the bone loss. While it is uncontestable that aseptic loosening is the resultant of wear debris production, the exact responsible mechanism and the risk factors are still ill-defined[14]. Likewise, since the adverse biologic reaction to prosthetic debris is not yet elucidated from A to Z, no universal definition for aseptic loosening can be given[14]. Peri-prosthetic osteolysis is rarely limited over many years; most likely, it progresses with time and, if unrecognized, can lead to extensive bone loss, requiring very complex reconstructive revision surgeries with compromised long-term outcomes[9].

Willert *et al*[17] were the first to notice in 1977, the hostile biologic effect associated with the wear débris, which is characterized by peri-prosthetic bone loss. But Salvati *et al*[18] were the first to describe in detail, in 1993, the "debris disease" triggered by PE or metallic debris. Aseptic loosening is the most common cause of arthroplasty failure representing around 75% of cases, with infection (7%), recurrent dislocations (6%), and fractures (5%) accounting for the remaining reasons for failure[10]. Peri-prosthetic osteolysis may be manifested radiographically by radiolucent lines which consist mainly of macrophages incorporating prosthetic debris[9]. As stated by Ollivere *et al*[14], once osteolysis is manifested radiographically, it will be coupled with a more hostile biologic reaction, as it is reflected by the increased cytokines levels. Progression of the radiographic evidence of peri-prosthetic bone loss is a very slow process that is extremely uncommon before 5 years after implantation[9]. This disease can have completely asymptomatic or symptomatic presentations[9]. For this reason, it is extremely important to periodically assess the patients radiographically, especially 5 to 8 years after implantation, looking for subclinical peri-prosthetic osteolysis. Most series have reported increased incidence of osteolysis around 10 years following arthroplasty, but few cases occur before 10 years interval. Symptomatic osteolysis can be manifested by painful loosening and/or fracture.

Foreign bodies particles can be generated from any part of the prosthesis: from the articulating surfaces or from the bone/implant or bone/cement interface[4,19]. These particles accumulate in the joint synovial fluid and may, after stimulation of the host cellular response, get incorporated in the inner aspect of the neo-capsule which is usually formed after joint prosthesis insertion[19]. Consequently, granulomas (nodules consisting of inflammatory cells phagocytizing the foreign bodies) with central necrosis, fibrosis or scar tissue can form within the capsule[19,20].

Osteolysis, originally called "cement disease" since it was first described after revision of cemented prosthesis, is the consequence of the adverse cellular host reaction to wear débris that can emanate from any interface of the prosthetic implants[4,14]. Roughly speaking, all orthopedic biomaterials may induce a universal biologic host response to generated wear débris with little specific characteristics for each material; but some debris has been shown to be more cytotoxic than others[5,14,19]. Likewise, peri-prosthetic bone loss can occur with any fixation method: cemented or cementless prosthesis[4]. The universality of wear debris behavior have been challenged recently where a study conducted on animals has shown that various types of wear particles influence differently the

differentiation and maturation of the osteo-genetic cells and that stimulated bone marrow stromal cells may play a primordial role in the pathogenesis of debris-induced aseptic loosening[21].

Histo-pathologically, the peri-prosthetic tissue is a fibrous granulomatous tissue constantly composed of a complex amalgam of cellular infiltration and particulate debris. The cellular component of this tissue includes numerous cell types: histiocytes, fibroblasts, osteoblasts, osteoclasts, osteo-progenitor cells [adult mesenchymal stem cells (MSCs)], synovial cells, endothelial cells and less commonly lymphocytes[4,5,8,22]. Neutrophils are only found in septic loosening cases[5]. Plasma cells and lymphocytes are found even without evidence of infection; they constitute a sign of humoral immunity defense mechanism[19].

Monocyte/macrophage lineage is the major cell type involved in the inflammatory wear-induced peri-prosthetic osteolysis by their phagocytic role and pro-inflammatory mediator's release[5,14,19,22-24]. Macrophages are one of the first cells to act where 48 h after exposure to debris, their cytoplasm enlarge assuming a balloon-like appearance (diameter size increasing from 10-20 μm to 40-50 μm)[22], and they release different inflammatory biomarkers, like tumor necrosis factor alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein-1 alpha[14,25]. MCP-1 is one of the most important inflammatory cytokines, playing a chemotactic role where it recruits peripheral monocytes and osteoclasts (that derive from the common cell lineage of macrophages)[14,24]. Many signaling pathways may stimulate macrophages leading to the release of different types of inflammatory cytokines[14]. The classical macrophage activation pathway (M1) is mainly enhanced by T-helper 1 cells (Th 1) and their specific cytokines group, especially interferon-Y, which is normally secreted by microbial activation. This pathway results chiefly in interleukin-1 (IL-1) and TNF-α production by the macrophages. The alternative macrophage activation pathway (M2), which consists of broad spectrum of responses, is mainly regulated by Th 2 cytokines, mainly IL-4 and IL-13. This pathway activation leads to the secretion of different cytokines by the macrophages, like prostaglandin E2 (PGE2), as well as to the stimulation of variant detrimental cellular reactions, such as the nuclear factor kappa-B (NF-κB) apoptotic pathway and the mitogen-activated protein kinases, an intracellular stress and inflammatory signal transduction trail[14].

The alternative macrophage activation pathways, which are the culprit pathogenesis mechanisms of multiple systemic inflammatory diseases (multiple sclerosis, tuberculosis, Gaucher's disease, athero-sclerosis), seem to play a major role also in the wear-induced osteolysis. The knowledge of these alternative pathways is still in its infancy; this may be a rational explanation behind our failure to reproduce *in vitro* the extremely complicated *in vivo* osteolysis process.

Histiocytes are part of the reticulo-endothelial system (AKA lympho-reticular system or mononuclear phagocyte system). Different types of histiocytes exist including macrophages (which main function is phagocytosis), dendritic cells (which main function is antigen presentation) and Langerhans cells. Most of the research investigating the biological response to wear debris has focused on macrophages before clarifying the role of other cell types[8]. Foreign body giant cells (which are fused macrophages generated in response to the presence of a large foreign body) are notably present in the osteolytic tissue surrounding cemented implants; these cells are considered a reaction to the acrylate (cement) fragments[4,19]. All these cell types actively interact with each other, where for example, fibroblasts trigger the formation of foreign body giant cells, and osteoblasts contribute to the differentiation and maturation of osteoclasts[5]. Wang *et al*[26] showed that fibroblasts release osteolytic enzymes in response to debris exposure, especially stromelysin and Collagenase in the presence of Ti particles. However the exact role of lymphocytes is still debatable where the hypothetical synergism between lymphocytes and macrophages in cytokines release could not be demonstrated in one study; T-cells at the interface membrane may alter the cellular response to wear debris[22].

Leukocytes are hematogenous cells produced in the bone marrow, are then transported to the blood vessels and finally to the concerned host tissue containing foreign products, after crossing the endothelial-lining of the vessels wall. Hereafter, endothelial cells represent an active and essential contributor to the transport process allowing the leukocytes to reach the interface membrane[5]. In addition to their role in hemostasis, endothelial cells play an important role in inflammation by synthetizing and releasing von Willebrand factor (vWf) from their intracellular granules, "Weibel-Palade bodies", once they are activated or damaged[5]. The collagen-binding domains of vWf bind tightly to the collagen tissue surrounding the vessels, forming the "peri-vascular cotton wool-like cuff" in the synovium-like interface membrane[5].

Elucidating the specific involvement of each cell type was not of great evidence or ease. It was Kadoya *et al*[27] who first reported that, next to the interface membrane of aseptically loose implants, bone formation was by far more prominent than bone loss; They highlighted the presence of osteoblasts in the reactive tissue and demonstrated that macrophages, not only stimulate bone lysis by releasing cytokines which activate osteoclasts, but also have microstructures that allow them to resorb the bone actively and directly. But actually, it is well known that osteoblasts, beside their role in osteo-genesis, produce Receptor activator of nuclear factor kappa-B ligand ("RANKL") and macrophage colony stimulating factor ("M-CSF") that are cell membrane receptors involved in bone resorption and

release cytokines stimulating osteoclasts formation[5]. In fact few studies explored the role of osteoblasts in peri-prosthetic osteolysis, while numerous studies explored osteoclasts that have been always considered central to the active bone resorption process[14]. Lohmann *et al*[28] demonstrated that osteoblasts may phagocytize prosthetic debris enhancing cytokines expression and release. Osteoblasts originate from the differentiation and maturation of the osteo-progenitor stem cells contained in the periosteum, under the effect of many growth factors like platelet-derived growth factors (PDGFs), bone morphogenetic proteins (BMPs), transforming growth factor beta (TGF-β) and fibroblast growth factors (FGFs)[14]. Osteoblasts can be stimulated differently according to the type and dose of the culprit wear debris[21,28]: low dose of ultra-high molecular weight polyethylene (UHMWPE) or PMMA particles (0.63 mg/mL) displayed strong alkaline phosphatase activity while Co-Cr and Ti particles exhibited minimal effects on the osteoblasts. UHMWPE exposure down-regulate osteoblasts production of collagen type Ⅰ and Ⅲ[14].

The generated débris can have one of 2 different forms: soluble ions or insoluble particles which aggregate with the serum protein forming protein-particles complexes, of different sizes[8,10]. The adverse effect of wear debris is primarily manifested locally by an aggressive inflammation whose maestro is the macrophages[10]. The effect of systemic dissemination of wear debris, especially metal and PE debris is controversial without established risk of toxicity and carcinogenicity to date.

The different orthopedic biomaterial particles, when binding to the serum protein, can change their conformation causing them to be recognized as foreign proteins by T-lymphocytes[22]. To undergo phagocytosis or pinocytosis, a particle should have a size inferior to 10 μm (ranging from 150 nm to 10 μm)[4,8,10]. Once ingested by macrophages or other cells, the wear debris trigger the host biologic response characterized by the release of inflammatory mediators, T-cell activation through antigen presentation, oxidative stress and DNA damage[10]. Cellular activation (mainly macrophages) differs with the engendered form: ions trigger the biologic cascade after they are phagocytosed and non-phagocytosable complexes activate the cell *via* its membrane receptors[8,23].

The debris particles can manifest their adverse effect either directly by eliciting the biologic cascade leading to osteolysis or indirectly by third-body mechanism accelerating the polyethylene's wear once they reach the articulation[4,29]. Third body débris (such as metallic particles, PMMA cement or even cortical bone) can be entrapped between the articulating surfaces of the prosthesis causing "abrasive wear" of both the soft UHMWPE and the hard surface of the femoral head (metal or ceramic)[29]. The relationship between the hardness of the third-body débris and the hardness of the bearing surfaces is the major determinant of the predisposition to abrasive wear[29].

Detailed cytological examination of the lytic tissue demonstrated that 70% to 90% of the debris load is constituted of polyethylene[4,30]. These particles have predominantly a spheroid shape and a size inferior to 1 μm (> 90%) with a mean size of 0.5 μm[4,30]. According to the type of prosthesis implanted, other sorts of particles may be detected in the peri-prosthetic membrane: polymethylmethacrylate, Co, Ti and ceramic. Silicates and stainless steel debris may also be seen but in a small amount since they are most likely contaminants from surgical tools or manufacturing process[4]. It is well admitted that the peri-prosthetic osteolysis does not ensue from the hostile effect of a single type of debris, but rather it is the cumulation of multiple physical, chemical and biologic factors.

The bio-reactivity of wear particles depends on 2 major elements: (1) Particle characteristics (size, concentration and composition); and (2) Host characteristics (genetic variation dictating the immune system reactivity)[4,8,30]. Higher doses and smaller sizes induce more pertinent host response; this response also differs with the particle type where for example, Ti débris are more potent than PE particles of similar sizes[4]. Little agreement exists on what type of biomaterial debris is more bio-reactive, but there is a growing consensus that metallic debris is more pro-inflammatory *in vivo* than polymer debris, despite contradictory statement reported by some authors[10].

Low doses of particles (Co-Cr, Ti and UHMWPE) strikingly promote the proliferation of the bone marrow stromal cells while high doses, mainly of Co-Cr, lead to cell death probably by reaching a toxic level[18,21,31]. The amount of generated wear debris is very critical to the stimulation of biologic response. In general, hard-on-soft bearings produce larger debris than hard-on-hard bearings do, where the average size of metal and ceramic debris is approximately 0.05 μm[10]. The aspect ratio of the debris is also important: elongated particles (fibers) are more potent than round particles in triggering the inflammatory reaction[10]. In general, the intensity of local inflammation depends on several critical debris characteristics: chemical reactivity, aspect ratio and particle load (size and volume)[10]. The critical size inciting the biologic response is one of controversial issues; in general, it is admitted, based on *in vitro* testing, that a particle should have a phagocytosable size to induce an inflammatory reaction (< 10 μm), with (0.24-7.2 μm) size range being the most pro-inflammatory.

Time of exposure is also an important factor contributing to osteolysis[5,31]. In addition, debris bio-reactivity can be determined by the surface charge, energy and roughness as well as the aspect ratio (particle shape), and the composition and nature of the absorbed proteins[4,30]. Despite that particle features are considered to be the main factors controlling the induced biologic reaction, other factors also influence the onset and magnitude of this reaction.

Many radio-stereometric clinical and experimental studies have shown that mechanical instability of the implants is fundamental to induce the inflammatory reaction, where various amounts of different particles were shown to play a secondary role in osteolysis[8,32,33]; in contrary, particles seem to mainly inhibit bone formation around unstable implants more than induce osteolysis. Peri-prosthetic osteolysis could be the resultant of synergy between particulate debris and mechanical instability at the bone implant interface. Motion can lead to fibrous tissue formation that secrete different inflammatory mediators stimulating osteoclasts or can stimulate the extracellular matrix resulting in PGE2 and other cytokines release[32]. Therefore, primary implant fixation or instability portend subsequent clinical failure, result of loosening. Also interface mechanical stability, reflected by bone ingrowth, offers a sealing effect preventing the passage of PE debris from and to the effective joint space.

Interestingly, also the local fluid pressure in the fibrous membrane surrounding loose implants could be responsible of osteocytes apoptosis more than osteoclast activation; a fact that can be supported by the physiopathology of arthrosis-induced subchondral cysts and vascular aneurysms-induced bone erosion[33].

While a consensus about pro-inflammatory parameters, like particle load, has been established, the host reaction variability is still an area of darkness. As stated by Harris[9], many patients with extensive amounts of PE debris may not develop peri-prosthetic osteolysis. Distinct cellular response to prosthetic debris of loosened elbow arthroplasties has been demonstrated between patients with and without rheumatoid arthritis[13]. This different biologic reaction was not related to the amount or type of the prosthetic debris but was alleviated by anti-TNF therapy.

Hence, individual difference in macrophage sensitivity and/or osteoclast/osteoblast reaction, reflecting intrinsic variability in the immuno-regulation, is probably the most important underlying etiology of the debris-induced hostile biologic reaction. Future investigations are warranted to determine whether individual genetic variances is the "maestro" of the inflammatory cascade.

The particle-induced chronic granulomatous inflammation can be of 2 types: non-immune and immune[8]. Non-immune inflammation is a nonspecific reaction stimulating mainly the innate immune system[5,8] where fibroblasts and macrophages are the prominent cell types with scarce lymphocytes; it is specially caused by ceramic and polymeric debris. Immune reactions are induced by excessive metallic ions and particulates that stimulate both the innate and adaptive immune system[5,8]. The immune granulomas are dominated by lymphocytes (B and T) that are widespread, interacting with specific epitopes where they may form the so-called "peri-vascular cuffing"[5,8]. The innate immune system can be activated by the toll-like receptors on the cell-membrane ("Toll" is a German word meaning "great, formidable"), that are one subtype of the specific receptors identifying the "molecular motif"; or it can be activated by the inflammasomes which are oligomeric protein complexes. The inflammasome complexes contain several types of proteins: caspase-1, NALP, PYCARD and sometimes caspase-5; its exact composition changes according to the activator that lead to its assembly. The inflammasome, especially activated by the metal particles[23], maturate the pro-inflammatory factors IL-1 and IL-18 by cleaving their inactive domains once the inflammatory caspase-1 cascade is stimulated[8]. The metallic ions-induced immune reaction has a spectrum of physiopathology ranging from benign fibrosis to severe type Ⅳ T lymphocytes-mediated hypersensitivity reaction leading in some cases to painful pseudo-tumors[8,23,30].

The inflammatory cascade generated once the prosthetic debris activate the cell, is an extremely complex process that is still not fully elucidated. Many older and recent studies have demonstrated the release of different families of inflammatory factors by several cell types of the peri-prosthetic tissue in reaction to all prosthetic debris. Goldring *et al*[34] were the first to state that the bone-implant interface in loose THA is composed of synovial-like membrane made of inflammatory cells producing PGE2 and collagenase.

The key cytokines, released by the inflammatory cells and responsible of bone resorption mainly include: IL-1, IL-6, IL-8, IL-10, IL-11 and TNF-α[4,8,26]. Also many other different factors are involved in this intricate reaction like prostaglandins (mainly PGE2)[4,8], growth factors (PDGF-α and TGF-β)[26], reactive oxygen intermediates (peroxide and nitric oxide)[8,24] and lysosomal enzymes (MMPs collagenase and stromelysin)[4] that are involved in the catabolism and reorganization of the organic extra-cellular bone matrix. Pap *et al*[35] reported that the fibroblasts and osteoclasts of the synovial-like peri-prosthetic tissue exhibit increased expression of several metalloproteinases (MMPs), like MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13 contributing to matrix degradation.

The inflammatory response may be material-dependent where a certain type of cytokine is more released in response to a specific particle, ex: IL-1 predominates the stainless steel-induced reaction and PGE2 and IL-6 predominate the titanium-induced reaction[26].

TNF-α is an essential and extremely potent inflammatory mediator of the particle-induced bone resorption[36]. Merkel *et al*[36] showed, in an animal model study, that TNF-α is a crucial osteoclastogenic agent where "mice failing to express both the p55 and p75 TNF receptors were protected from the profound bone resorption induced by the polymethylmethacrylate particles". This information has a valuable clinical implication, where TNF receptors blockage can prevent wear particle-induced osteolysis.

In the presence of TNF-α and M-CSF, macrophages isolated from the peri-prosthetic tissue may differentiate

to osteoclasts *in vitro*, expressing vitronectin receptor and tartrate-resistant acid phosphatase (TRAP)[26]. TRAP, also known as acid phosphatase 5, is a glycosylated monomeric metallo-enzyme normally highly expressed by activated macrophages, osteoblasts and neurons.

Macrophage interaction with wear debris is constantly the chief phenomenon initiating the complex adverse local tissue reaction (ALTR) that lead to osteolysis and subsequent aseptic loosening. Among the numerous potent inflammatory mediators released, nitric oxide (NO) is copiously produced by the macrophages in a type- and dose-dependent manner of the challenging particles[26,37]. NO production is mainly stimulated by Ti-alloy particles followed by PMMA particles. The role of NO in the wear-induced adverse biologic reaction is not fully elucidated, since few studies investigated this chemical mediator. But it seems that it may play a role in the stimulation of PGE2 release and the inhibition of DNA synthesis[37].

Endotoxin adherence to the wear particles may play a primordial role in increasing the release of inflammatory cytokines in the peri-prosthetic tissue. This fact was demonstrated *in vitro* by several studies, but also was refuted by others[38-42]. Endotoxins, a term used nowadays as synonym for lipopolysaccharides, are large molecules found on the outer membrane of Gram negative bacteria. They are released only after complete destruction of the bacterial cell wall, hence eliciting a potent immune response. Their role in wear-induced osteolysis is still controversial and needs to be more clarified in the future.

Recently, RANKL and osteoprotegerin (OPG) have been shown to play a major role in the initiation and progression of osteolytic lesions[4,8]. RANKL is an osteoblast receptor which activates osteoclasts by binding their surface receptor (Receptor Activator of NF-κB, also known as TRANCE Receptor) "RANK". It is, like osteoprotegerin, a member of the TNF cytokine superfamily. The RANK pathway is the chief regulator of bone turnover (osteolysis) whereas osteoprotegerin is the antagonist of this pathway. Based on many animal model studies, RANK/RANKL/OPG pathway is now considered crucial for the occurrence of osteolysis[14]. The released inflammatory factors can act in a paracrine and autocrine manner[8], up-regulating osteoclast differentiation and maturation and sometimes reciprocally regulating their synthesis (like IL-1 and PGE2)[4].

Normal bone turnover rely on a balanced bone formation and bone resorption which are adjusted in harmony with the homeostatic and electrolytic condition of the organism. Many clinical studies and animal models demonstrated that the particle-induced inflammatory cascade not only up-regulate osteoclast function but also down-regulate the osteoblast and osteo-progenitor cells function[8,16,26,43], resulting in an unopposed bone resorption. In particular, several studies focused of the adverse effect of Ti particles stating that these particles suppress the gene expression and the proteo-synthesis of collagen type I and bone sialoprotein, alter the adhesive behavior of osteoblasts and trigger their apoptosis[26]. Similar sizes of Ti particles and ZrO_2 have different effect on the osteoblastic gene expression: chronic Ti debris exposure, which can be secondary to mechanical instability of the implant, compromise "human MSC differentiation into functional osteoblasts"[26].

Mesenchymal stem cell apoptosis is induced by an increased level of the tumor suppressor proteins, p53 and p73. P53 (also known as p53 up-regulated modulator of apoptosis) may trigger cell death through several long and complex pathways, one of them starts by inhibition of the anti-apoptotic Bcl-2 family proteins, then activation of mitochondrial dysfunction, leading to the release of apoptogenic proteins from the mitochondrial membrane, like second mitochondria-derived activator of caspases, apoptosis-inducing factor and cytochrome C[26]. P53 can lead to cell apoptosis through activation of death domain by soluble TNF cytokine receptors, like TNF-α and TNF-related apoptosis inducing ligand.

In other words, the osteogenetic function of osteoblasts is inhibited at the price of osteoclasto-genesis which is regulated by mediators released by the peri-prosthetic osteoblasts themselves[43]. Hence, peri-prosthetic osteolysis is the resultant of 2 vectors: increased bone resorption by the inflammatory cytokines and the shifted osteoblast function, as well as decreased bone formation by the inhibited osteoblasts/osteoprogenitor stem cells.

The extent of the inflammatory reaction could be not locally confined to the prosthetic joint where debris is generated. Biomaterials debris (mainly PE and metallic) can be detected remotely from the affect joint, in the blood, urine, bone marrow, even in the liver, spleen, kidney, iliac and para-aortic lymph nodes, hair and nails[20,26]. The systemic immune reaction depends primarily on the macrophages chemotactic-function[8,24,44]. After stimulation of local peri-prosthetic cells, peripheral macrophages are recruited exacerbating the osteoclasto-genesis and subsequently peri-prosthetic bone resorption. Foreign bodies' particles can be transported to distant cells of the reticulo-endothelial system *via* the peri-vascular lymphatic vessels; a fact that is supported by the presence of particle-collecting macrophages in the direct vicinity of blood vessels[19,20]. The extent of the distant transportation of wear debris depends on the amount produced as well as the capacity of the peri-articular capsule to transport them[19]. It is assumed that systemic dissemination (mainly of metal particles) occurs when the ability of local cells to store foreign bodies is bypassed.

PROSTHETIC DEBRIS SPECIFICITY

The materials currently available for all prosthetic interface couples were present since more than 40 years but recently, with the advances of metallurgy

processing and tribology knowledge, the manufacturing of these materials has been refined in order to decrease the volumetric wear associated with the traditional surfaces[30]. The new alternative couples nowadays available consist of the metal-on-highly cross-linked polyethylene and hard-on-hard bearing couples. All these new bearings require a meticulous surgical technique, specifically an excellent acetabular positioning in order to avoid the early complications that have been reported: squeaking, chipping or breakage, edge loading and impingement wear (stripe wear) associated with ceramic-on-ceramic couples[8], fracture or rim cracking of the highly cross-linked polyethylene liner and runaway wear and immune system-related complications (hypersensitivity and pseudo-tumors) associated with metal-on-metal couples.

Polyethylene debris

Polyethylene was part of the historical MOP Charnley prosthesis. Even currently, the greatest majority of implemented THA consist of hard-on-soft couples (metal-on-polyethylene or ceramic-on-polyethylene), yet using the newest UHMWPE[7].

Polyethylene debris is considered the main culprit in inciting a hostile biologic response leading to osteolysis and aseptic loosening[4,7,15,20,29,30,45,46]. PE debris can transform appositional bone growth around well-fixed implants to chronic inflammatory tissue with abundant foreign body giant cells[16]. This fact resulted in growing interest in hard-on-hard bearings which have lower friction and wear rates, hence, theoretically, decreased incidence of aseptic loosening.

The wear rate for a "Charnley type" prosthesis couple is in average 0.1 mm/year, thus 1 mm/10 years[6], where the generated debris have a size range of 0.5 to 5 μm, rarely increasing to 100 μm[15,19]. More than 90% of PE debris is smaller than 1μm with a mean size of 0.53 ± 0.3 μm[4,8,10,14,47]. This predominantly tiny size led originally to underestimation of the particles number contained in the peri-prosthetic membrane, until new identification methods came up (electron microscopy, proteolytic enzymes use and density-gradient centrifugation)[14]. Kubo *et al*[48] showed that PE particles of 11 μm size are more biologically potent than larger PE particles; moreover, they showed that the particle's material composition is more strongly related to the histiocytes reaction than the particle size and load.

In a review of PE and metal debris features, Doorn *et al*[47] reported that "approximately 500 billion particles can be produced per year, for a total amount of trillions of particles during the lifetime of a prosthesis".

PE debris is colorless and can have different shapes (flakes, needles, spears): the larger ones have the shape of splinters or plates and the smaller, that of granules or elongated platelets[19,47]. Since the majority (> 90%) of the PE particles is smaller than 1 μm, the spheroid shape is predominant[4,8]. The size could be related to the specific wear mode: smaller particles are generated when the PE surface is rubbing against bone cement or metals[47]. Polyethylene particles are immunologically inert and are not toxic[47].

Willert *et al*[19] noted that, unlike metallic debris, PE debris do not cause necrosis or fibrin exudation of the capsular tissue; but they do produce, as metal products, a marked fibrosis where a meshwork of differentiated collagen fibers form around the foreign body giant cells and phagocytes. According to these authors, this extensive fibrosis is not directly correlated to the embedded PE particles. Plastic particles may travel away from the involved joint occupying the perivascular space[19].

Wear property of conventional PE can be markedly improved by cross-linking of ultrahigh molecular weight PE, either with radiation or with chemical means[49]. Five Mrad gamma radiation treatment lead to 85% improvement of wear resistance of the polyethylene. The improved wear characteristics of UHMWPE were proved in clinical studies as well as in laboratory testing using hip joint simulators. In a laboratory study where crossing-path motion was applied to hip simulator, McKellop *et al*[49] tested the wear resistance of crosslinked PE against extremely damaged femoral ball, trying to simulate extreme *in vivo* femoral head scratch by third-body abrasion. Laboratory crossing-path motion simulates more accurately hip joint *in vivo* than linear motion that could show an erroneous increased wear rate of cross-linked PE[50]. They demonstrated that cross-linked PE, with or without accelerated aging, still exhibit better wear rate than conventional PE even against harshly damaged femoral head[49].

Despite that highly cross-linked polyethylene debris is smaller than conventional PE debris with a critical size range of 0.2 to 0.8 μm[7], they are more bio-reactive; however their decreased volumetric wear prevails over their increased biologic reaction triggering[30]. It is of utmost importance to notice that it is not the wear volume that determines the biologic response but mainly the dose and the smaller size of generated debris[7].

Metallic debris

MOM couple was the first bearing used ever in the literature, first by Wiles, as early as 1938[20] then by McKee in 1940's. Initially, higher revision rate was reported with McKee-Farrar prosthesis than the Charnley low friction arthroplasty. Despite the stated imperfection of the initial design (equatorial contact produce higher frictional torque and wear than polar contact), recent studies have shown good to excellent survival of McKee-Farrar prosthesis[6,15].

MOM bearings had enormously regained interest recently based on their main advantage over MOP bearings, which is a smaller volumetric wear by

more than an order of magnitude (10-40 times less wear for MOM than MOP). Even UHMWPE failed to eliminate the problem of osteolysis and aseptic loosening[20,23,29,30,47,51-53]. In one study, Willert *et al*[20] reported 39-fold higher wear rate for UHMWPE than MOM bearings. As it was once supposed that eliminating cement from THA could address the problem of aseptic loosening, exclusion of polyethylene liners by using MOM bearing was proposed as conceivable solution for osteolysis[47]. Second-generation MOM couples were introduced in the 1990's to eliminate polyethylene-induced osteolysis[12,13]. Commercially available Co-Cr alloys have either low-carbide content (< 0.07%) or high-carbide content (> 0.2%)[12]. Carbide content affects the volumetric wear rate of CoCr alloys but not the particle size or morphologic features of the debris; high-carbide alloys have a wear rate of 2 to 5 μm/year whereas low-carbide alloys show a wear rate of 7.6 μm[12]. Low-carbide content MOM alloys are associated with more prominent immunologic adverse response where in one clinical study[12], extensive necrosis was present in 90% of the interface membrane surrounding failed MOM along with higher intensity of diffuse peri-vascular lymphocytic infiltration.

Although PE particles are considered the main etiology of peri-prosthetic osteolysis, metallic debris have been accused to cause ALTR leading to osteolysis, especially the Ti-alloy implants (Ti-6Al-4 V) more than Co-Cr alloy or stainless steel implants[12,13,26,47,54]. ALTR may cause intra-articular joint effusion characterized by sterile, watery, yellowish or grayish, hazy (tissue debris in suspension), basic (elevated pH) fluid with low cell count (lymphocytes)[54]. In fact, the metal-induced ALTR encompasses a spectrum of histo-pathologic changes including pure metallosis, aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) (detailed later in this paragraph) and granulomatous inflammation; ALVAL represents the precursor of lymphoid neogenesis[55].

The incidence of aseptic loosening leading to early failure of (MOM) TJA was recently estimated to be 4% to 5%, 6 to 7 years after implantation[10]. Metal products can be released from any part of the implant and by different mechanisms: wear, corrosion, stress, fretting and fatigue[56].

On the other hand, the generated metallic particles are smaller in size, of nanometer-order ranging from 30 nm to 200 μm (with majority of < 50 nm)[10,23,30,51]. Willert *et al*[19,20] reported a range size of 0.5 to 5 μm for the metallic wear debris; likewise other authors reported only micron-order size (0.1-1 μm) for the metallic debris with no clear difference between different metal alloys[47]. So despite the decreased volumetric wear associated with MOM couples, the resultant surface/area mass is extensive since the tiny particle sizes of metallic débris are produced at higher rate than MOP bearings[23,30,53]. Nevertheless, macrophage activation and cytokine release can be induced only by high volumetric concentrations of Co-Cr wear particles[51]. If not phagocytosed by macrophages, metallic products can be disseminated to the reticulo-endothelial system *via* the lymphatic vessels[53].

Wear of the metallic articulating surfaces can be manifested macroscopically by delicate scratches (that are sometimes more located in the weight-bearing areas) or polishing of various locations and sizes[20]. However scratches of the prosthesis articulating surfaces are not the primary source of metallic debris, where the anchoring surfaces of the implant represent the more powerful source of debris exhibiting polishing that is secondary to debonding of the implant and its subsequent movement against the bone cements[20]. Only in the circumstance of impingement between the cup rim and the stem neck, metallic wear debris emanates mainly from the articulating surfaces of the prosthesis[20].

Moreover, MOM bearings can undergo corrosion (electro-chemical dissociation) releasing free metallic products that can interact with the surrounding cells of the host tissue and the local body fluids forming complex organic and inorganic metallic products[20,23,30,51]. The process underlying the generation of metal products is ill-defined[30]. The wear debris derived from MOM implants can have one of 2 forms[23]: metal particulates or free metal ions like Cr^{3+}, Cr^{6+} and Co^{2+}. The predominant type of metallic wear particles is nanometer-sized chromium oxide (Cr_2O_3); but chromium particles are not the main offender in triggering the biological cascade[20,25]. In decreasing order after chromium particles, cobalt, nickel and molybdenum debris can be produced[19,20]. But also other soluble metal ions can be formed based on the type of the implanted alloy, like: aluminum, vanadium and titanium[10].

One clinical study found that aseptic loosening of uncemented MOM hip prosthesis result in a significant increase in cobalt serum level but not chromium[56]. The authors reported a 2.8 relative risk of implant loosening for a serum cobalt concentration greater than 9 nmol/L.

Metallic particles have an amorphous, irregular shape (flakes or needles) with sharp edges and a black color staining black the inner layer of the joint capsule[19,20,47]. Submicron sized metal debris procure a blue color to the cellular cytoplasm[47].

The *in vivo* number of metal particles released per year is estimated to range from 6×10^{12} to 250×10^{12} particles[23]. Basic processes of the adverse biologic responses apply also to metal products. Metal debris up-regulate the transcription factor NF-κB and activate the monocyte/macrophage lineage releasing inflammatory cytokines like IL-1β, IL-6, IL-8 and TNF-α. However, metal debris has the specificity of activating the inflammasome danger-signaling in macrophages; this inflammasome activation lead to the maturation of IL-1β and IL-8[10,23]. Once the inflammatory mediators are released, osteoblast inhibition and osteoclast activation ensue, as previously mentioned in detail.

Systemic dissemination of the metallic debris *via* the lymphatic circulation: The cumulative effects of the biological behavior of the metallic debris and their nanometer size range may result in a systemic increase of ions levels, mainly cobalt and chromium serum, urine and synovial fluid concentrations[15,23,30,51,53,57]. Likewise patients with bilateral large-head MOM have higher serum metal ions concentrations compared to the patients with unilateral MOM[23]. To diagnose systemic release of metal ions, normal human serum concentrations of the mostly inserted metals should be recognized: [Cr] = 0.15 ng/mL, [Co] = 0.1-0.2 ng/mL, [Al] = 1-10 ng/mL, [Ti] less than 4.1 ng/mL and [V] less than 0.01 ng/mL.

In one study, there was up to 6- to 7-fold increase in the serologic concentration of cobalt and chromium with small increase in molybdenum level[58]. Another study comparing 4 groups of patients (healthy controls, patients with O.A. without TJA, patients with well-functioning MOP and patients with well-functioning MOM THA), has shown a 13-fold increase in Co and 58-fold increase in Cr concentrations[31]. Several studies reported similar Co and Cr levels in the serum of patients with stable MOM prosthesis and those who do not have any implanted prosthesis[56]. To be noted that there is imperfect correlation between the serologic ion levels, wear rate and incidence of ALTR[54].

The systemic release of metallic ions is a major concern even though acute and forthright toxicity is exceedingly rare, where the incidence of patients necessitating revision for probable hypersensitivity to otherwise well-performing MOM bearings is very low[30]. Even well-performing MOM arthroplasties have shown 3 to 5 times increase in Co and Cr levels[13]. Renal failure can potentiate the detrimental effect of the metallic debris, highlighting the problem of chronic toxicity which is still uncertain nowadays[30,53]. However, it is admitted that the local concentration of metallic debris in the synovial fluid seldom exceed the threshold identified as toxic *in vitro* or dangerous in occupational medicine[53]. Willert *et al*[20] reported a low metal content in the peri-prosthetic tissue of MOM bearings (metal debris representing 0.1% of this tissue), but Huo *et al*[46] reported higher metal and Ba content for loosened implants. The *in vivo* relationship between intracellular debris content and disease development is not fully clear, but toxicity and carcinogenicity of metallic debris have been demonstrated in animal experimental models and in *in vitro* tissue cultures, as well as in clinical studies[57]. Numerous neoplastic tumors have been reported in tissue contiguous to metal prosthesis: lymphomas, malignant fibrous histiocytomas, sarcomas, and haemangio-endothelioma[57]. Likewise, increased incidence of lymphoma and leukemia has been reported after THA in 2 epidemiologic studies[57] but was refuted by other reports[10]. Increased levels of chromium can lead to carcinogenesis, hypersensitivity and nephropathy[57]. Excessive amounts of cobalt can cause hypothyroidism, polycythemia, neoplasia and cardiomyopathies[10]; although Co-induced cardiomyopathy is a theoretical concern, several reports stated that cobalt-containing beer could be the possible culprit of lethal cardiac myopathies[59,60]. Vanadium as well, has been associated with renal and cardiac disorder, hypertension and bipolar psychosis[10]. Nickel and aluminum carcinogenicity to the lung and bladder tissue was reported in industrially exposed workers; nickel is also associated with hypersensitivity and eczematous dermatitis[10,57]. Similarly, increased aluminum level was shown to be a possible etiology of senile dementia, encephalopathy and diminished bone mineral density.

Despite all these literature reports, no clear correlation has been established between metal release from implants and neoplastic, toxic or metabolic diseases. Whenever wear debris are copiously generated, they will exceed the capacity of the local tissue to eliminate them, leading to accumulation and consequently systemic dissemination of these metallic particles which can be, theoretically, harmful to any reached organ. Besides, it has been shown that cobalt chrome alloy-containing prosthesis (whether MOM or MOP) can cause chromosomal aberrations, like translocations (1.5-fold) and aneuploidy (2 to 4-fold) which clinical significance is still unclear[23,30,51,59].

Metal products have a specific biological behavior consisting of triggering a significant and complex immune response involving B and T lymphocytes; this can result in abnormal masses (fibrosis or hystiocytosis), bursa hypertrophy or tissue necrosis[23,30]. A shift in the $CD4^+$/$CD8^+$ circulating lymphocyte ratio was demonstrated in patients with well-functioning implants[5]. It is still unclear if this immune response is the resultant of patient hypersensitivity or increased metal products concentration in the peripheral blood. Recently, Lohmann *et al*[61] stated that the type of tissue reaction in failed MOM arthroplasties may be predicted by the peri-prosthetic tissue metal content and not by the serum metal content. They demonstrated that tissues with higher metal content (222.2 ± 52.9 μg/g) exhibited a predominantly lymphocytic response and those with lower metal content (3.0 ± 0.9 μg/g) showed a non-specific macrophage-mediated granulomatous response.

A long-standing problematic issue was and is still to be "metal allergy" that is irrefutably a real clinical fact but with uncertain prevalence and clinical repercussion[30,31,51]. Evans *et al*[62] were the first to report, in 1974, that metal sensitivity is a cause for bone necrosis and prosthesis loosening where metallic particles released from MOM bearings may obliterate the blood vessels irrigating the peri-prosthetic bone leading to its necrosis. Hypersensitivity can be manifested clinically by urticaria, dermatitis, and vasculitis.

The main metal sensitizers embrace, in order of potency: nickel (Ni), cobalt (Co) and chromium (Cr); Titanium (Ti), vanadium (V) and tantalum (Ta) are exceedingly rare cause of immune hypersensitivity[31]. Nickel is the most potent and most common metal

sensitizer where 14% of the general population has dermal sensitivity to Ni[10]. Dermal metal sensitivity has an estimated prevalence of 10% among the general population, 25% among patients with well-functioning TJA and 60% among patients with poorly-performing TJA[10,31]. In case of early MOM failure, the prevalence of metal sensitivity is estimated to be six-times that of the general population[10].

Metal-induced allergic response is similar to T Lymphocytes-mediated delayed-type hypersensitivity response (type Ⅳ); in this response, T lymphocytes are activated by a primary then secondary stimulus, which are respectively metal ions (or metal particulates-proteins complexes) and danger-associated molecular patterns (DAMPs). DAMPs can be endogenous alarmins released from damaged cells (such as monosodium urate crystals) or exogenous microbial pathogen-associated molecular patterns that can incite innate immunity through Toll-like receptors (TLR) activation. This will lead to a complex interaction between the antigen-presenting dendritic cells that release TNF-α and IL-1 and T lymphocytes that release interferon-γ. A recent *in vitro* study has showed that "Toll-like receptor 4" on the macrophage surface are crucial in mediating the pro-inflammatory immune response to cobalt-alloy particles[23]. TLRs are cell surface receptors expressed in neutrophils, B-cells, dendritic cells and macrophages; More than 10 human TLRs are identified where TLR4 is one of the best described TLR. Particle-challenged human monocytes, beside contributing to other important aspects of the inflammatory response, up-regulated IL-1β, TNF-α and IL-8[23]; and this rise in cytokine release was proportional to particle:cell ratio and was induced either by particle phagocytosis or by extra-cellular stimulation of TLR4. Blocking TLR4 by antibodies before exposure to Co debris caused 46% inhibition of IL-8 mRNA expression and 72% decrease in IL-8 protein synthesis in 24 h[23].

Despite that metal-induced allergic reaction is considered idiosyncratic, some clinical studies could demonstrate dose-dependent reaction intensity with proportional relationship between lymphocyte reactivity levels and serum-metal levels[23,31]. But no clear causativeness could be established between metal-induced lymphocyte reactivity and poor metallic implant performance[31].

Latterly, MOM bearings showed a unique histologic reaction of prominent perivascular and/or diffuse intramural lymphocytic infiltration which is evocative of a cell-mediated delayed-type hypersensitivity response. Willert *et al*[63] termed this response to failed second-generation MOM bearings, ALVAL or "lymphocyte-dominated immunological answer" (LYDIA) which is actually an area of active investigation. ALVAL or LYDIA is an histologic reaction consisting of "diffuse and peri-vascular infiltrate of T- and B-lymphocytes and plasma cells, high endothelial venules, localized bleeding, massive fibrin exudation, accumulation of macrophages with drop-like inclusions and infiltrates of eosinophils and necrosis"[63]. The histo-chemical examination of the macrophages inclusions did not show the phagocytosis of implant-debris but more likely phagocytosis of organic material. The majority of the examined tissue "contained small amounts of histologically visible metal wear particles", suggesting no correlation between the observed immunologic reaction and the particle dose confined in the tissue[63].

Clinically, ALVAL can be manifested by persistent or recurrent pain, soon after primary THA, along with prominent hip effusion, necessitating revision surgery even for well-fixed implants[63].

Based on recent clinical studies, a correlation was established between positive patch test or histologic evidence of ALVAL, and early osteolysis in patients with MOM bearings. Definitely, a poorly-functioning MOM prosthesis produce higher wear rate and subsequently established osteolysis that leads to implant loosening.

Patients with "ALVAL" may experience pain or may develop pseudo-tumors[20,23,64] that are one of the serious consequences of metal debris. Pseudo-tumors, which mechanism of formation is unclear, are complex lesions of lymphocytes, fibroblasts, multi-nucleated cells (with metallic debris inclusions)[20] and granulocytes[23] with significantly high IL-8 (approximately 200-fold higher than IL-1β and TNF-α levels released by the challenged macrophages)[23]. IL-8 is characterized by strong chemotactic effect that may instigate and maintain cellular infiltration leading to pseudo-tumor formation. Pandit *et al*[64] were the first, in 2008, to describe abnormal soft-tissue mass around the hip using the term of "pseudotumors" because these masses are neither infective neither neoplastic. In their large series of hip resurfacings (1300 cases), they observed 12 cases of pseudotumors reporting an incidence of 1% at 5 years; they also stated that some cases were asymptomatic and were discovered incidentally, indicating that the incidence of this abnormal mass, which can be overlooked clinically, could be higher than initially estimated. The most common presentation of pseudotumors was hip discomfort, but also nerve palsy, spontaneous dislocation, rash and obvious palpable mass could occur[64]. To be noted that Boardman *et al*[65] reported, in 2006, a single case of benign psoas mass, secondary to MOM hip resurfacing, that resolved after conversion to conventional THR. Interestingly, a case report was recently published stating pseudo-tumor formation and metallosis in a modular hip hemiarthroplasty where the corrosion products arose from the non-articulating modular prosthetic junction[66].

Since host factors determining the reactivity to wear products are still ill-defined (where some patients develop marked reactivity after a short period of MOM implantation and others can tolerate great debris loads for long period)[31], and since the toxicological implication of high metal ions are not fully elucidated[10,30], patients monitoring, in the circumstance of any clinical or radiographic doubt, with regular metal

ions measurements seems to be judicious[54].

In summary, MOM bearings use in arthroplasty had re-emerged recently after UHMWPE failed to prevent osteolysis. The wear rate of MOM determines the potential of these bearings to trigger the adverse biologic reactions; still to be determined in the future, what wear rate of modern MOM couples is considered safe, precluding the innumerable toxicity associated with metal products. This wear rate, that is by far less than that of plastic, can be further reduced with the use of better design (especially carbon-containing alloy and metal fabrication by forging rather than casting) and larger femoral head with improved radial clearance or perhaps with combination of different hard surfaces[12,15,51,52]. And even when metallic wear is histo-pathologically demonstrated, metal debris do not dominate the adverse histologic reaction[20]. Conformity between the prosthesis components is required, but at least a 0.15- to 0.20-mm clearance should exist between the ball and socket to allow fluid ingress[20]. Despite all the achieved advances in the manufacturing process, creating metallic material with excellent tribologic qualities (wear, friction and lubrication), metal hypersensitivity, toxicity and pseudo-tumors risks remain a dreaded issue which is still not fully controllable.

Ceramic debris

The French surgeon, Pierre BOUTIN, was the first to implement a COC total hip replacement[6]. Since then, COC couples had become an attractive, reliable and more durable alternative to traditional bearings of THA, especially with the design and material improvements accomplished with time (microstructure, density, mechanical strength and surface finish of ceramic materials). Despite their earlier use in Europe, alumina femoral heads were not available in the United States until the early 1980's and Zirconia heads until 1989[15].

Ceramics are stable solid compounds of metals and nonmetals (like oxygen or other anions), with the 2 main ceramic materials, nowadays in clinical use, being alumina (Al_2O_3) and Zirconia (ZrO_2)[15,67]. Ceramics gained interest because of their favorable characteristics of biochemical inertness, hardness (they resist scratching and maintain their polished finishing), wettability, high-strength, corrosion and wear resistance and thermodynamic stability[15,67,68]. Ceramics are considerably harder than both CoCr and Ti alloy tapers[15]. Resistance to abrasive wear is proportional to the hardness of the bearing surface; subsequently ceramic surfaces are more resistant to abrasive wear than metallic surfaces[29]. Laboratory testing had demonstrated that different kinds of wear debris can cause a visible abrasion of all metal surfaces (including nitrogen ion implanted Ti-6Al-4V) but not of ceramic surfaces which, in addition, produce less UHMWPE wear than metallic surfaces[29].

Ceramic compounds are extremely inert biologically and chemically because the reaction of their formation (where base metals, like aluminum, react with oxygen) is highly exothermic, setting these compounds in a very low energy state, hence precluding any further dissociation[67]. Unlike PE that are nonpolar and nonionic molecules, ceramic materials have an ionic structure making their surface hydrophilic; this allows the "polar" water-based fluids to spread over their surface reducing the intimate contact between PE and ceramic[15].

On the other hand, ceramic's brittleness constitutes a drawback which carries a dreaded risk of fracture which cause is, nowadays, attributed to a manufacturing defect[6,67]. The strongest zirconium oxide was introduced to reduce the risk of catastrophic failure (fracture) and to expand the available size range of ceramic components[15]. With the greater fracture toughness (approximately twice that of Al_2O_3) and higher strength of ZrO_2, smaller heads and longer necks could be used but still without attaining the size range available with CoCr heads[15].

Ceramics have exceptional compression strength but poor bending strength making them unable to deform without breakage[68]. The fracture rate reported in the literature varied tremendously from 0% to 13%. Among others, Hannouche *et al*[68] reported an extremely low fracture rate of 0.2% (13 components fracture out of 5500 implanted over a period of 25 years). They recommended a meticulous surgical technique in the use of ceramic femoral head to preclude fracture and stated that this exceedingly rare complication can be overcome by the more common risk of wear and osteolysis associated with MOP or even MOM bearings. Interestingly, Heck *et al*[69] reported that the fracture rate of alumina ceramic is less than PE liner fracture (that represents the weakest link in THA) or metallic stem fracture. Recently, even lower fracture rate has been reported (0.004%)[70]. It is worth to note again that ceramic fracture can be effectively reduced by following a scrupulous surgical technique avoiding excessive abduction of the acetabular component and ensuring a concentric fit of the femoral head on the Morse taper. Before axial impaction, the femoral head should be rotated to guarantee its concentric seating on the trunion to avoid any gouging of the taper by the border of ceramic head[15]. Failure of the Morse taper can be catastrophic leading to fretting corrosion and severe metallosis with metallic embedding in the ceramic bearing surfaces[71].

The wear volume associated with ceramic bearings is considerably less than that of metallic bearings[6,30,31]. PE component in COP bearings exhibits a linear wear that is 5 to 10 fold lower than PE wear in MOP bearings[15]. Because they do not experience surface roughening with time as metal bearings do, ceramics reduce the long-term UHMWPE wear, more than metals[72]. Likewise, COC wear rate is 10-times less than the lowest PE wear rate, being around 0.003 mm/year[15]. This decreased debris generation accounts for the reduced likelihood of adverse biologic reaction and osteolysis with ceramic bearings.

As previously mentioned, bulk form of ceramics is

inert, sparing the environmental oxidative deterioration[30]. On the other hand, once ceramic particles are produced, only in the setting of flawed or poorly functioning components, they induce a cellular response similar in intensity and quality to that triggered by the polymeric and metallic debris[15,30]. A recent study showed that, in contrast to failed MOP bearings, ceramic wear debris and osteolysis are the consequence rather than the cause of COC bearings failure[11]. It is true that the initial design and tribologic material of ceramics were responsible of wear generation and subsequent early failure. But at the present time, early failure of COC is deemed to be secondary to mechanical problems (initial malpositioning or instability) or infection. Hereafter, ceramic bearings are more sensitive to technical errors of implantations than other bearings.

Like metallic products, the ceramic wear debris is small in size, henceforth are produced in greater number, saturating the surface area of the host cells[15]. Some authors reported that ceramic particles size range from 0.13 to 7.2 μm with an average of 0.71 μm[15]; But allegedly, ceramic particles size range is bimodal: nanometer-scale of magnitude for most of these particles and submicron- to micron-order for the remaining part with a mean size of 0.7 μm (as for the polyethylene debris)[30]. Once again, the main biologic factors that determine the cellular response remain to be the particle characteristics (shape, volume and size). But unlike metal products, different ceramic wear products (alumina or Zirconia) do not stimulate the adaptive immune system because they do not experience any corrosion.

Despite the fact that ceramics are considered biologically indolent, ceramics products bio-inertness has been questioned by some studies. Li *et al*[73] showed that alumina and hydroxyapatite have no cytotoxic effects to the *in vitro* cultured human fibroblasts challenged by different particle doses (1-500 μ/mL), while zirconia and tricalcium phosphate inhibited cell viability, where a concentration of about 50 μg/mL decreased cell viability by 50%. Likewise, Lerouge *et al*[74] demonstrated, through an *in vivo* characterization of wear debris generated from COC THA, that ZrO_2 and not Al_2O_3 particles, induce a histiocytic foreign-body reaction and are the major particles responsible of aseptic loosening associated with COC bearings. Alumina oxide particles were found in only 12% of the histologic sections analysis, whereas zirconium oxide debris were by far more numerous and were found in 76%; the third particle type retrieved being Ti alloy debris. In contrast to these studies, a more recent study showed that Al_2O_3 and ZrO_2 do not alter the metabolism of arachidonic acid of synoviocytes cell membrane neither increase IL-1 and IL-6 release[75]. Synovial tissue contains two different cell types: Type A, macrophage-like synoviocytes and, type B, fibroblast-like synoviocytes. The latter are responsible for synovial hyperplasia and are involved in activating the cellular inflammatory reaction by releasing several kinds of inflammatory mediators. Both IL-1 and IL-6 are elevated in the synovial fluid of rheumatoid arthritis (RA) patients. Arachidonic acid metabolites [like (LTB4) leukotriene B4] play a major role in the pathogenesis of multiple inflammatory diseases like asthma, inflammatory bowel disease and RA. A recent *in-vitro* study suggested that biocompatibility of zirconia is greater than that of titanium[76]. Cultured macrophages challenged with both titanium or Zirconia particles expressed increased mRNA for TLRs 2, 3, 4 and 9, and their intracellular adaptors and pro-inflammatory cytokines. However, quantitative differences were evident where zirconia-induced pro-inflammatory gene expression was lower than that provoked by titanium particles.

In summary, COC bearings have the great advantage, over other bearings, of decreased wear rate due to their hardness which resist scratching, making them more suitable for younger patients. Disadvantages of ceramics include their cost[70] and the limited range of neck size available because of the fracture risk. Fracture risk can be tremendously reduced by following a thorough surgical technique and by ensuring an excellent ceramic manufacturing with a quality is nondestructively pre-clinically tested. The increased cost of ceramics seems to be justified, especially in young patients, by the decreased wear rate of COP *vs* MOP, even with traditional PE[70]. Ceramic-on-polyethylene bearings exhibit a wear rate of 0.034 mm/year compared to 0.1 mm/year for metal-on-polyethylene bearings. Ceramic-on-crosslinked PE couples display a wear rate of 0.019 mm/year compared to 0.03 mm/year for metal-on-crosslinked PE.

Polymethylmethacrylate debris

Cemented fixation of both components of THA was the initial fixation method proposed by Charnley[1,14]. In 1989 at Boston, William Harris was the 1st to develop and implement a hybrid hip prosthesis with cementless press-fitted hemispherical metallic cup and cemented titanium femoral stem[6].

It is recommended nowadays not to use a cemented titanium stem because it can generate tremendous amount of Ti debris once loosened, and to use proximally or fully hydroxyapatite-coated cementless titanium stem[6]. Salvati *et al*[18] stated that the synovial fluid contain a significantly higher levels of metal debris with loosened cemented titanium stem (21-fold) than loosened cemented cobalt-chromium stem (7-fold).

The biologic response triggered by PE wear particles is almost similar to that induced by other types of particles. A majority of studies challenged inflammatory cells by different kinds of debris, including PMMA debris, and showed quit identical cellular reaction[21,44]. In fact, PMMA debris are not the sole foreign material found in the peri-prosthetic tissue; based on the type

of implanted prosthesis, other particles can be found (metal, plastic...). Hence, if one of these foreign particles triggers the inflammatory cascade, other particles types perpetuate this adverse reaction[19]. Willert *et al*[20] showed that cement-induced reaction more frequently outweighs metal-induced reaction; but different scenarios may also exist but less frequently.

Macrophages are always the primordial cell type involved in the adverse biologic response, secreting several inflammatory mediators mainly IL-1 and TNF-α. Likewise, PMMA debris recruit peripheral monocyte/macrophages enhancing cell cluttering in the nidus of wear debris, the peri-prosthetic interface membrane[44].

If the cement mantle is macroscopically destroyed or disorganized, PMMA particles may be found within the capsular tissue[19]. Acrylic particles have a size range of 1-2 μm to several hundreds of microns and different shape organization: the smallest ones are dust-like granules and the largest are like pearls clusters or grapes bunch[19,20]. According to their size, PMMA particles can be or not phagocytosed and stored within inclusions in the foamy cytoplasm of macrophages[19]. As previously mentioned, foreign body giant cells predominate in cement-induced aseptic loosening, surrounding the non-phagocytosable large cement fragments. Hence, fibrosis or hyalinization and necrosis of granulomas (formed by Histiocytes incorporating foreign materials) are less common with acrylic particles, as well as plasma cells and lymphocytes infiltration[19].

If the polymethylmethacrylate bone cement contains radio-opaque contrast media, ZrO_2 or $BaSO_4$, traces of these molecules can be detectable in macrophages (or less commonly in foreign body giant cell) inclusions reflecting the disintegration of the bone cement storage in the tissue. The $BaSO_4$ or ZrO_2 particles have an average size of 0.5 to 8 μm[20]. So disintegration of the bone cement can produce PMMA particles and/or ZrO_2 or $BaSO_4$ particles that, besides their direct effect, can cause a third-body wear once they reach the articulation compartment[20].

Aseptic loosening of cemented prosthesis can display one of 2 forms: extensive granulomatosis or non-granulomatous aseptic loosening[77]. PMMA debris can elicit an immunologic-type adverse biologic reaction, a T-lymphocyte mediated hypersensitivity immune response[77]. The bone-cement interface membrane is infiltrated by monocytes-macrophages and multinucleated giant cells encumbered with cement particles. Whereas Santavirta *et al*[77] demonstrated a difference in the immune-pathologic response between granulomatous and non-granulomatous aseptic loosening, Gil-Albarova *et al*[78] showed no difference with increase of both total and activated CD2-positive T lymphocytes in both types of loosening. Likewise, Santavirta *et al*[77] considered these 2 forms of aseptic loosening as 2 different conditions on the basis of the relative lack of fibroblasts in the peri-prosthetic membrane, with activated fibroblasts being the main cell constituent of non-granulomatous aseptic loosening. Gil-Albarova *et al*[78] stated that both histo-pathological patterns have a single systemic immune response and have no difference regarding lymphocytes subtypes (increase in B and T lymphocytes, mainly CD2, CD22 and CD25 positive cells), patch test reactivity and lymphoblast transformation test induced by PMMA material[77].

FUTURE DIRECTIONS AND TREATMENT STRATEGIES

One of the essential repercussions of advanced understanding of the problematical osteolysis process is the development of novel therapeutic modalities that may slow down or prevent disease progression. The pharmacotherapy may target any stage of the intricate inflammatory reaction to wear debris: anti-inflammatory agents may be used to modulate the cytokines release, anti-osteolytic agents to disintegrate osteoclasts morphology, and antioxidants to demolish the free oxygen radicals produced by the activated macrophages. On the other hand, osteolysis may be prevented using osteogenic growth factors that play a critical role in bone formation, remodeling and reparation.

Based on the fact that cytokines constitute the major mediators of the debris-induced adverse response, anti-inflammatory agents have been proposed to down-regulate this reaction. Blaine *et al*[79] reported the modulatory effect of some pharmacologic agents, that alter the intracellular levels of cAMP, on cytokines production (IL-6 and TNF-α) by titanium-stimulated human peripheral blood monocytes[79]. Interestingly, active cAMP analogs (Dibutyryl cAMP) and prostaglandins (E1 and E2) enhanced IL-6 synthesis but inhibited TNF-α production. They showed also that some anti-inflammatory products (indomethacin) may potentiate cytokine production (3 fold increase in TNF-α production). This finding implicate that one should understand the echelon of action of anti-inflammatory medication proposed to delay the disease process, and that the role of culprit cytokines should be stratified by potency weight, since the used agent may inhibit one inflammatory mediator at the price of enhancing other. Likewise, Schwarz *et al*[80] stated that periprosthetic osteolysis and inflammation can be controlled by anti-TNF-α therapy. In an exceptionally novel technique, Keeney *et al*[24] stated that the debris-induced inflammatory response can be modulated by mutant MCP-1 protein delivery from biodegradable layer-by-layer coatings on orthopedic implants. As previously mentioned, MCP-1 is one of the most potent cytokines involved in macrophages recruitment, whose receptors may be blocked using a decoy drug, such as 7nd, a mutant MCP-1 protein. Interestingly, Vallés *et al*[81] stated that simvastatin pre-treatment of human osteoblastic cells down-regulated Ti particle-induced *IL-6* gene expression at mRNA and protein levels. Statins, well-known hypo-lipidemiant

drugs, have anti-inflammatory, immune-modulatory and osteo-anabolic effects where they suppress osteoclastic bone resorption and support osteoblast-precursors recruitment enhancing proliferation, differentiation and mineralization of osteoblasts. Metal debris particularly up-regulate IL-6 release by osteoblasts and peri-prosthetic membranous tissues.

Bisphosphonates have been shown to be potent anti-osteolytic agents that interfere with internal enzymatic cell system disrupting the osteoclast cytoskeleton, effectively used in the treatment of metabolic bone disease with prominent bone resorption, including osteoporosis, Paget's disease and metastatic hypercalcemia[82,83]. Several animal model studies demonstrated the inhibitory effect of bisphosphonates on particle-induced bone resorption. Horowitz *et al*[84] showed that disodium pamidronate is effective in reversing the bone resorption secondary to macrophage exposure to bone cement particles. Similarly, Shanbhag *et al*[85] reported that alendronate, which is integrated in the mineralizing matrix inhibiting osteoclastic activity, reduced debris-induced osteolysis (PE/Ti/Co-Cr) in a canine THA model. A recent meta-analysis, including six randomized controlled trials, suggested that bisphosphonates are advantageous in preserving more peri-prosthetic bone mineral density than that in controls[86]. More recently, a clinical study showed that parenteral (intra-muscular) administration of neridronate, every fortnight for the first three months then every month for the remaining period of 1-year follow-up, reduced pain, improved function and halted the roentgenographic evolution of peri-prosthetic osteolysis, as well as amplified peri-prosthetic bone mineral density as confirmed by DEXA measurements[87]. Since reactive oxygen species (mainly produced by the phagocyte immune cell type) and reactive nitrogen species (a family of antimicrobial molecules derived from NO and superoxide) may mediate aseptic inflammation affecting directly periprosthetic osteolysis, antioxidants use is an attractive manner to modulate the disease process. Antioxidants, such as ascorbic acid[88], bioflavonoid pycnogenol[89], N-acetylcysteine[90], pyrrolidinedithiocarbamic acid[90], are potent free radical scavengers down regulating the phagocytic immune response. Bioflavonoids, class of plant secondary metabolites previously known as vitamin P, have been reported to reduce the gene expression and synthesis of IL-1β and IL-2 by inactivating NF-κB and activator protein-1, two major transcription factors considerably involved in cytokines gene expression[89].

Prevention of osteolysis constitutes the alternative mode of intervention, alongside the down-regulation of the inflammatory process. For this purpose, osteogenic growth factors may be used to locally regulate bone configuration and remodeling. BMPs, insulin-like growth factors (IGFs), and various TGF-β = a known regulator of collagen type Ⅰ represent fundamental local regulators of osteogenesis; most significantly these growth factors interact with nuclear transcription factors (like Core Binding Factor a1) in response to sex steroids, glucocorticoids, parathyroid hormone, or PGE2, which are all well-known controllers of bone turn-over[91]. Hill *et al*[92] demonstrated that osteoblast survival is promoted by IGF-Ⅰ, IGF-Ⅱ, insulin and basic FGF but not the PDGF; however, they stated that PDGFs, even though they have no direct effect on osteoblast survival, they potentiate the survival-promoting effects of IGF-Ⅰ, IGF-Ⅱ, and insulin. The authors concluded that TNF-alpha, a monocyte-derived factor, prominently boosts cellular apoptosis and may negate the osteoblastogenic effects of other unidentified growth factors or components of the extracellular matrix. Dobai *et al*[93] established that, *in-vitro* treatment of osteoblasts with 1α, 25-$(OH)_2$ vitamin D3 (hormonally active form of vitamin D also known as calcitriol) may reverse the particle-induced (Ti/Cr/UHMWPE) diminished osteoblast function of collagen gene expression and synthesis.

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P- Reviewer: Drosos GI, Laudner K, Solomon LB **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i2.190

World J Orthop 2015 March 18; 6(2): 190-201
ISSN 2218-5836 (online)

REVIEW

Economic impact of minimally invasive lumbar surgery

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Received: May 29, 2014
Peer-review started: May 29, 2014
First decision: June 18, 2014
Revised: October 4, 2014
Accepted: October 14, 2014
Article in press: October 16, 2014
Published online: March 18, 2015

Abstract

Cost effectiveness has been demonstrated for traditional lumbar discectomy, lumbar laminectomy as well as for instrumented and noninstrumented arthrodesis. While emerging evidence suggests that minimally invasive spine surgery reduces morbidity, duration of hospitalization, and accelerates return to activites of daily living, data regarding cost effectiveness of these novel techniques is limited. The current study analyzes all available data on minimally invasive techniques for lumbar discectomy, decompression, short-segment fusion and deformity surgery. In general, minimally invasive spine procedures appear to hold promise in quicker patient recovery times and earlier return to work. Thus, minimally invasive lumbar spine surgery appears to have the potential to be a cost-effective intervention. Moreover, novel less invasive procedures are less destabilizing and may therefore be utilized in certain indications that traditionally required arthrodesis procedures. However, there is a lack of studies analyzing the economic impact of minimally invasive spine surgery. Future studies are necessary to confirm the durability and further define indications for minimally invasive lumbar spine procedures.

Key words: Value-based medicine; Cost efficiency; Minimally invasive spine surgery; Arthrodesis; Outcomes

Core tip: Minimally invasive lumbar microdiscectomy, decompression and short segment fixation result in clinical outcomes similar to traditional open surgery while decreasing the amount of blood loss, local tissue trauma, and length of hospitalization. Overall, there are few studies focusing on the economic impact of minimally invasive lumbar spine surgery. There is some evidence that minimally invasive short segment arthrodesis procedures are associated with higher cost effectiveness in acute perioperative period compared to traditional open surgery. Early results of minimally invasive surgical techniques for deformity correction appear promising, however, future studies need to address durability and cost effectiveness of these procedures.

Hofstetter CP, Hofer AS, Wang MY. Economic impact of minimally invasive lumbar surgery. *World J Orthop* 2015; 6(2): 190-201 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/190.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.190

INTRODUCTION

National spending on health care varies considerably among Organisation for Economic Co-operation and Development (OECD) countries. In 2012, health care costs in the United States accounted for 16.9% of its GDP, while all OECD countries spent a mean 9.3% of their GDP on healt care[1]. Technological progress has been proposed as the main driving force behind the growth of health care expenditures[2,3]. One of the medical fields that has intensively utilized the most advanced technologies is complex spinal surgery. A multitude of novel types of instrumentation, implants, navigation and biologics have recently become available for the use in complex spine surgery[4]. However, critics point out that technologically advanced treatments may offer little or no clinical benefit compared to traditional treatment strategies[5]. Thus, the use of expensive technology, combined with an increase in the number of complex spine procedures, has attracted public attention to the expenditures associated with spinal surgery.

One of the countervailing issues is that epidemiologically, spinal degenerative disease and particular low back pain are most prevalent amongst musculoskeletal disorders. Nearly 100% of all adults end up with spinal problems at least once during their lifetime, with a point prevalence of 4%-33%[6]. According to the Ontario Health Survey, 40% of all chronic disorders are caused by musculoskeletal conditions. Additionally, 54% of all cases of long-term disability are caused by to musculoskeletal diseases[7]. Based on surveys carried out in Canada, the United States, and Western Europe, physical disabilities caused by musculoskeletal conditions assume a 4%-5% prevalence in the adult population[8]. Symptomatic degenerative spinal disorders are treated with a myriad of treatment strategies ranging from medical management, physical therapy, chiropractic adjustments, injections, to complex spine surgery. In 2005, $85.9 billion was spent on the treatment of low back pain, representing a 65% increase from 1997[9,10]. The majority of those expenditures are related to non-surgical management of spinal pain. Nevertheless, data regarding clinical efficacy of spinal procedures are lacking in general. Indeed, less than 1% of studies on lumbar spine arthrodesis procedures published from 2004 to 2009 include cost effectiveness analysis[10]. There is an even more significant lack of data on the benefits of newer minimally invasive spinal (MIS) surgeries. It has been proposed that MIS procedures may have a lower complication rate and thus use fewer hospital resources compared to traditional open spine surgeries[11-13]. The current review attempts to shed light onto the current scientific evidence for cost effectiveness of MIS procedures compared to traditional open spine surgery.

VALUE-BASED HEALTH CARE

Recently, strategies in medical economics have changed: attempts have been made to move away from the traditional system of service-oriented payment, toward a value-based health care system[14]. With other words: the value of a health care intervention equals its quality divided by its cost measured over a certain period of time. Quality of care is evaluated by a variety of measures, including process measures, safety measures and outcome measures, with the latter being either disease specific or general health values[10,15]. Using the recent value-based model, each healthcare intervention can be assessed by the following simple formula:

$$Value = Quality/Cost$$

For value-based calculations, the direct and indirect costs of a particular medical intervention must be determined. Direct costs include the charges accumulated by the medical procedures, hospitalization, medications, imaging services and future direct costs that arise from the same medical condition. Indirect costs include decreased productivity caused by disability associated with the medical condition. The quality of a medical procedure is equivalent to the procedure's effectiveness to improve the life of affected individuals[10]. For international comparability and reproducibility, it is crucial that outcome measures can be calculated easily in order to have consistent and valid data, which can be compared between different interventions, therapies and patient populations. Furthermore, outcome measures should focus on the patients' wellbeing. The impact of lumbar disorders on quality of life (QoL) may be assessed with disease specific measures such as the oswestry disability index (ODI) or general measures such as Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), or the EuroQol (EQ)-5D. Patient's functional impairment with activities of daily living caused by pain is assessed by the ODI, which is low-back-specific[16-18]. In contrast, the SF-36 is a general health measure, consisting of 8 scales, including a physical pain and bodily function scale, and two main groups based on physical and mental assessments[16-19]. Similar to the SF-36, the EQ-5D constitutes a general health measure. Utilizing the EQ-50, five health-dimensions of quality-of-life can be evaluated: mobility, self-care, daily activities, pain and discomfort and anxiety or depression. Typically, its fields of application are clinical investigation, cost-effectiveness analysis, and comparison of treatment effects across different disease states. Each of these 5 dimensions is evaluated utilizing a scale of 3 scores. In total, 243 different health states can be assessed using the EQ-5D. The quality-adjusted life year (QALY) is another outcome measure, which is used to assess the value of certain health outcomes, with value being defined as quality per cost over time. QALY measures both quality and duration of treatment.

As Prieto *et al*[20] propose, QALY equals health as a measure of quantity and QoL. QALY is used to calculate a score based on these two components of health. After calculating the number of QALYs gained, which can be easily done with the formula: utility value of a treatment multiplied by the duration of effect caused by the particular treatment, the cost-effectiveness of different types of treatment can be evaluated[20]. Thus, with optimization of effectiveness and durability of a procedure, the benefits as measured in QALYs increase. To accurately analyze the durability of an intervention, long-term follow-up studies are the most useful[15,20]. QALY is intervention-specific[21].

Cost-effectiveness analysis is a very common application of QALY, which is cost divided by the QALYs gained from the treatment of a specific disease state. With this calculation, the benefit of a given procedure or medical intervention is evaluated, which is comparable with various fields of application. Mathematically, QALYs can be expressed by the formula:

$$QALY = 1 \times Q$$

Q stands for a value given to a health-related state and ranges from 0 and 1. The maximum *Q* value of 1.0 represents a state of perfect health. *Q* decreases when the QoL decreases. Death is assigned a *Q* value of 0. However, some have suggested that there can be QoL states worse than death, which are assigned a negative value[22-25]. QALY is most often used to assess the effect on QoL following a particular intervention[22]. In some developed countries, policy makers have proposed that the cost per QALY gained should not exceed $50000-$100000 in order to consider an intervention cost effective[14,26,27]. Once an intervention has been linked to a certain amount of QALY, it is possible to compare the cost-utility of two treatment approaches for a given disease. This may be accomplished with the cost-effectiveness ratio (ICER), which is expressed with the equation:

$$ICER = (C1 - C2)/(Q1 - Q2)$$

C1 and C2 represent the costs of the two different treatments. Q1 and Q2 are the QALY values associated with two different treatments[15]. Interventions that lead to a better clinical outcome or are less expensive will be favored by these types of analyses and are considered "dominant"[24,28,29]. Cost effective interventions are those whose costs per QALY gained are less than or equal to the societal or patient willingness to pay[30]. When this type of analysis is applied to surgical procedures, a reduced rate of postoperative complications enhances the cost-effectiveness as complications can affect both cost and outcome of the procedures.

LUMBAR MICRODISCECTOMY

Hansson *et al*[31] compared the cost effectiveness of surgical *vs* conservative treatment for lumbar disc herniations in a non-randomized 2-year study. Total costs favored surgery over non-operative management due to greater work productivity as well as lower indirect costs in the surgery group. The QALY gained was tenfold higher in the surgery group[31]. A 1-year Dutch study compared early surgery *vs* prolonged conservative care in patients with symptomatic lumbar disc herniations[32]. The QALY analysis favored early surgery over conservative therapy[32]. The direct costs of the surgery exceed that for conservative care, but significant differences in non-healthcare costs (paid domestic help and monetary loss from decreased work productivity) favored the surgical group. This results in similar total costs between the two interventions[32]. A cost utility analysis demonstrated an 87% probability that surgery is more cost effective than conservative care at a willingness-to-pay of 80000 Euros per QALY gained, suggesting that early surgical intervention for lumbar disc herniation is cost effective[32]. In conclusion, surgery was able to confer additional clinical benefits in contrast to conservative care at reasonable economic prices in part due to greater improvements in patient work productivity. Tosteson *et al*[33] evaluated the cost effectiveness of surgery *vs* conservative treatment for lumbar disc herniations. They analyzed 2-year follow-up data from the multicenter spine patient outcomes research trial (SPORT). Standard open discectomy resulted in greater QALYs gained but, on the other hand, was associated with higher total costs compared to conservative treatment. The ICER for surgery relative to non-operative care was calculated to be $69403 per QALY gained for the general population. It was lower at $34355 per QALY gained in Medicare patients. Because of this, surgical treatment for lumbar disc herniations seemed to be cost effective and to be even more cost effective in Medicare patients[33]. Using 4-year follow-up data of the SPORT patient cohort, both the QALY gained and total costs were higher in surgical patients. The difference in total costs between surgery and conservative treatment groups over 4 years was $7006, which was lower than the difference in total costs at the end of 2 years ($14142). The four-year cost per QUALY gained was estimated to be $20600, leading to the conclusion that surgical intervention for lumbar disc herniations becomes more cost effective with longer follow-up[34]. In conclusion, the current literature provides a solid body of evidence that traditional microdiscectomy constitutes a cost effective treatment for symptomatic lumbar disc herniations.

In an attempt to limit access related tissue disruption, transforaminal endoscopic techniques for patients with symptomatic lumbar disc herniations have gained popularity in recent years. Various papers have been published, describing these new minimal-invasive surgical techniques, which allow the surgeon to approach the pathological site *via* an endoscopic uniportal access. The endoscope is entered *via* a posterolateral access, passing through the

intervertebral foramen between traversing and exiting spinal nerves[35-38]. Hermantin *et al*[39] conducted a prospective, randomized study on 60 patients to investigate the effectiveness endoscopic discectomy compared to traditional microdiscectomy. The clinical outcome of both procedures was comparable. Based on patient's self-evaluation, clinical findings and ability to return to work, 93% of patients treated with a traditional microdiscectomy compared to 97% of patients who underwent an endoscopic discectomy had a satisfactory outcome. Postoperatively, patients who underwent the endoscopic procedure had a lower use of narcotics compared to the traditional group. While this study did not carry out a cost effectiveness analysis, they report that patients who underwent a traditional microdiscectomy stayed for an average of 49 d out of the work force compared to 27 d of patients who underwent an endoscopic procedure. Mayer *et al*[40] conducted a study to investigate the effectiveness of endoscopic discectomy compared to microsurgical discectomy in a total of 40 patients. Two years after the procedure, sciatic pain had disappeared in 80% of patients who underwent an endoscopic procedure compared to 65% in the traditional group. Sensory deficits disappeared in 92.3% in the endoscopic group and in 68.8% in the open group. Motor deficits resolved in all affected patients in both groups. Mean duration of postoperative disability following an endoscopic surgery was 7.7 wk; in the microdiscectomy group 22.9 wk of disability were reported. Return to their previous occupation was achieved in 95% in the percutaneous endoscopic cohort and in 72.2% in the microdiscectomy cohort. Ruetten *et al*[41] conducted a prospective study in patients undergoing either full-endoscopic or traditional microsurgical discectomy, with 178 patients completing 2-year follow-up. At two-year follow-up, a similar improvement of leg pain was measured in patients treated with endoscopic [visual analoge scale (VAS) for leg pain: preoperative 7.1; follow-up 0.9] or traditional (VAS for leg pain: preoperative 7.6; at 2-year follow-up 0.8) technique. Recurrent disc herniations occurred at a rate of 6.2% both treatment groups. Ruetten *et al*[41] report a significantly lower rate of complications in patients who underwent endoscopic discectomy compared to traditional microdiscectomy. Importantly, the average duration of disability was 25 d in patients with endoscopic discectomy compared to 49 d in patients who had undergone traditional microdiscectomy.

In summary, the current literature suggests that endoscopic lumbar discectomy achieves similar clinical outcomes and similar patient satisfaction compared to traditional microdiscectomy. While, there is some data that endoscopic discectomy is associated with less disc space and concomitant foraminal collapse[42] long-term data on long-term sequele, such as degenerative disc disease or segmental instability of Endoscopic *vs* Microsurgical lumbar discectomy is lacking. Shorter operative times, shorter hospital stays and earlier return to work following endoscopic discectomy are consistently reported in the current literature. While, no cost-effectiveness analysis comparing endoscopic with microscopic technique is available to date, shorter hospital stays and earlier return to work may contribute to potential cost-effectiveness of endoscopic discectomies if their good clinical outcomes are maintained.

DECOMPRESSIVE SURGERY

Degenerative lumbar spinal stenosis typically manifests with lumbar radiculopathy or neurogenic claudication, which is impairment of walking due to pain or discomfort in the lower extremities. Neurogenic claudication typically is relieved by anteflexion of the trunk. Usually, nonoperative therapy does not result in sustained improvement[43]. Thus, patients are commonly offered a surgical intervention, the most traditional procedure being a decompressive laminectomy. The goal of this procedure is decompression of the narrowed spinal canal. Posterior elements, including lamina and interspinous ligaments, are removed, leading to the exposure of the lateral recess and lumbar foramina. Tosteson *et al*[44] conducted an analysis of the costs of traditional lumbar laminectomy to treat spinal stenosis, utilizing the prospective SPORT cohort. Among 634 participants, 394 suffered from spinal stenosis without spondylolisthesis and of these patients 320 patients underwent traditional decompressive surgery without arthrodesis. At 2 years a QALY gain of 0.17 was reported at a cost of $77600 per QALY gained. Importantly, more recent 4-year follow-up data confirmed cost effectiveness of traditional lumbar laminectomy for spinal stenosis without spondylolisthesis[34]. At 4 years, decompressive surgery resulted in a 0.23 QALY gain at a cost of $42800 per QALY gained. Katz *et al*[45] reported similar findings. Lumbar laminectomy resulted in a significant relief of leg pain from preoperative values (3.4 out of maximum 5 points) to 0.9 at 2 years follow-up in patients with spinal stenosis. Direct costs for laminectomy were $12615 for lumbar decompressive procedures and similar to $17688 reported by Tosteson *et al*[44]. However, the report of Katz *et al*[45] lacked a more complete cost effectiveness analysis due to the lack of primary patient-reported data or a validated EuroQol instrument. Adogwa *et al*[46] investigated cost effectiveness of revision decompression, performed in 42 patients[46]. The cumulative gain in QALY relative to preoperative baseline was 0.84 over a two-year period. Estimated costs were as high as $49431. Costs per QALY gained were calculated to be around $60000, which makes revision decompressions a cost effective treatment for recurrent lumbar stenosis.

In traditional open laminectomy, posterior elements

of the vertebral column are removed, including spinous processes and ligaments[30]. While the short-term outcome of traditional laminectomy is favorable[47,48] (Fu, 2008 #96), it has been proposed that 7-10 years after decompression, 33% of patients have severe back pain and 23% required reoperation[49]. Minimally invasive techniques for lumbar decompression aim to decrease the amount of tissue removal to minimize destabilization of the spine. Biomechanical studies propose that minimally invasive lumbar decompressive techniques cause significantly less hypermobility and less stiffness reduction compared to traditional laminectomy[50,51]. Fu *et al*[30] conducted a prospective study comparing two different decompression techniques ("Windows technique" laminoforaminotomy *vs* decompressive laminectomy) in patients with lumbar spinal stenosis. Results were good or outstanding in nearly 90% and acceptable in 11% 40 mo following less invasive laminoforaminotomy. There was no need for revision or secondary surgery in any case. In contrast, outcome in the open decompressive laminectomy group was good or excellent in 63% of cases, 30% of patients had acceptable outcomes, while outcome was poor in 7%. In this group, 6 cases of postoperative degenerative spinal instability with worsened back pain were found, which lead to secondary surgery in 4 patients due to recurrent stenosis and instability. Based on adequate long-term outcomes, few complications and low costs, the authors proposed the less invasive laminoforaminotomy as a possible standard method to treat degenerative spinal stenosis.

In a prospective, randomized study, Thomé *et al*[52] compared the clinical outcome of less invasive unilateral or bilateral laminotomy and traditional laminectomy. In all 120 patients adequate decompression was achieved and a massive decrease of pain was observed in each treatment group. The authors report that bilateral laminotomy resulted in significantly less pain compared to unilateral laminotomy or traditional laminectomy at the time of last-follow up 15.5 mo after the procedure. Similarly, SF-36 scores demonstrated marked improvement in all groups, but most pronounced in those patients undergoing bilateral laminotomy. Moreover, bilateral laminotomy exhibited a trend towards a lower rate of complications compared to the other groups. Based on these results, Thomé *et al*[52] propose that bilateral as well as unilateral laminotomy reliable and valid choices for decompressive surgery of lumbar stenosis, with the most crucial outcomes being relief of symptoms and improvement of QoL. While unilateral laminotomy and laminectomy seemed to be equal regarding clinical outcome, bilateral laminotomy enables more favorable results.

Parker *et al*[53] conducted cost-effectiveness study over a 2-year period, analyzing unilateral laminectomies using either a subperiosteal dissection *via* midline incision or tubular access *via* a paramedian incision. They especially focused on the utilization of medical resources provocated by back-related conditions, sickness absence rate and outcome measures like QALYs. The type of access did not affect direct, indirect or overall costs and both treatment arms presented with a cumulative gain of 0.72 QALYs at 2 years postoperative. Total costs averaged $23109 for a hemilaminotomy using a paramedian incision and $25420 for a hemilaminotomy using a midline incision. These results suggest that less invasive hemilaminotomies are a highly cost effective for the treatment of lumbar spinal stenosis. However, there is a paucity of literature comparing cost effectiveness of traditional open laminectomy to less invasive laminectomies. Knight *et al*[54] compared clinical outcome and cost in 104 patients with lumbar spinal stenosis following either traditional laminectomy or tubular decompression. Consistent with previous studies, the authors detected a similar degree of improvement of the ODI and VAS for back and leg pain following either open or tubular procedure. There was a trend towards more complications in patients treated with open laminectomy. While this study did no perform a complete cost effectiveness analysis it provides information regarding the direct cost of these procedures. Thus, the median cost for traditional laminectomy was $7305 compared to $4518 for tubular decompression.

In conclusion, several studies have demonstrated that traditional laminectomy is a highly cost efficient treatment for spinal stenosis. However, several controversies remain: While short-term outcome of laminectomy (without fusion) is satisfactory, concerns have been voiced regarding the long-term durability of clinical outcomes. Katz *et al*[49] reported that 7-10 years after decompression, 33% of patients have severe back pain and 23% already underwent reoperation. Moreover, it is not known if the use of less invasive decompression techniques with sparing of the posterior elements will decrease the occurrence of late symptomatic instability. The topic of increased instability is further complicated by coexisting spondylolisthesis. While spinal stenosis with concomitant spondylolisthesis is typically treated with decompression and arthrodesis, there is some emerging evidence that less invasive decompression techniques may be suitable even in the presence of mild spondylolisthesis. If less invasive decompression techniques achieve durable alleviation for spinal stenosis even in the setting of mild spondylolisthesis, abandoning the need for arthrodesis (in patients with only neurological symptoms) would certainly greatly enhance the cost effectiveness of less invasive decompression techniques. Further studies on the durability of clinical outcome and possible inclusion of spinal stenosis with mild spondylolisthesis as indication may dramatically increase the cost effec-

tiveness of less invasive decompression techniques.

SHORT SEGMENT FIXATION

Chronic low back pain, defined as pain lasting for more than three months[55], is a common health issue causing a significant healthcare burden. The cost from back pain is mainly due to indirect cost from loss of work productivity. Direct costs associated with the disability were estimated to be around £1.6 billion in the United Kingdom in 1998[56], and the condition is estimated to be responsible for close to 120 million United Kingdom work days lost per year[57]. Back pain may be caused by spondylolisthesis and/or degenerative disc disease, both of which may surgically be treated with arthrodesis. Tosteson *et al*[44] analyzed the cost-effectiveness of traditional fusion utilizing the prospective SPORT cohort. Among 634 participants, 368 suffered from degenerative spondylosis. Of these patients 344 underwent surgical decompression with spinal fusion. At 2 years a QALY gain of 0.19 was reported at a cost of $120000 per QALY gained. Importantly, the cost effectiveness for spinal arthrodesis for degenerative spondylolisthesis improved markedly 4 years after the procedure. At 4 years, decompressive surgery resulted in a 0.29 QALY gain at a cost of $66300 per QALY gained spondylolisthesis[34]. Fritzell *et al*[58] performed a prospective randomized controlled study evaluating the cost-effectiveness of lumbar fusion compared to nonsurgical treatment for chronic low back pain. A total of 284 patients were randomized to either fusion surgery (n = 217) or best medical management (n = 67). At 2 years, clinical outcome was improved in 60% of patients who underwent lumbar fusion compared to 34% who received non-surgical treatment. During 2 years, the societal costs per patient, consisting of direct and indirect costs were higher in the surgical group [704000 Swedish kroner (SEK)] compared to the control group (636000 SEK). With a difference of 60200 SEK, average hospital care costs were significantly higher in the surgical group. The most probable explanation for this finding is the higher cost associated with the fusion procedure itself, as well as the postoperative hospitalization. When using the noninstrumented posterolateral fusion as a reference, there was a 66% increase in costs when instrumentation was performed and a 103% increase if an interbody procedure was performed as well. In contrast to hospital costs, primary and private care seemed to be more expensive in the non-surgical group, with a difference of 1000 SEK, as were drug-associated costs with a difference of 1400 SEK. Another important finding was the significant difference in return-to-work-incidence: patients who had undergone surgery were able to return to work in 33%, while the only 16% of nonsurgical treated patients returned to work. Costs for production losses per patient on sick leave in the control group were: 460200 SEK. To conclude, health care costs and societal costs were higher with surgical treatment. Nevertheless, treatment efficacy clearly favored surgical treatment.

Fritzell *et al*[59] performed a cost-effectiveness analysis based on data from a 2-year randomized controlled trial. They compared lumbar arthrodesis with arthroplasty in patients with discogenic low back pain. Both cohorts experienced similar improvements in QoL 2 years following the procedure (0.45 QALY). This study found that lumbar fusion was associated with significant greater hospital and total healthcare costs. This was due to a higher rate of reoperations following lumbar arthrodesis (36%) compared to arthroplasty (10%). However, the gross majority of re-operations (77%) in the arthrodesis group were performed for implant removal as the implant was determined by the surgeon to act as pain generator. The authors also included an analysis with costs for re-operation removed from both groups, which eliminated the cost difference form the perspective of both the hospital and healthcare sector. After 2 years there was a nonsignificant cost difference of combined indirect and direct costs of lumbar arthroplasty compared to lumbar arthrodesis surgery. Thus, the authors concluded that both procedures were equally cost effective for society within a 2-year time frame.

Adogwa *et al*[60] performed a cost-effectiveness analysis on open transforaminal lumbar interbody fusion (TLIF) surgery for the treatment of degenerative spondylolisthesis. The mean length of hospital stay was 4 d. There were no surgical site infections, CSF leaks or hardware failures, but 4 cases of incidental durotomy. One patient suffered from perioperative hematoma and thus had to be returned to the operating room. A significant improvement in back pain VAS score, leg pain VAS score and Oswestry Disability Index was observed 2 years after TLIF. There was a cumulative health utility value of 0.86 QALY gained over 2-years. The mean total 2-year cost of TLIF was $36836. Surgery costs were $21311. Outpatient resource utilization costs were $3940. Mean direct medical costs were $25251. Indirect costs were $11584, and the mean 2-year cost per QALY gained associated with TLIF was $42854. There was a median amount of 60 d (IQR 30-120 d) missed workdays. TLIF improved pain, disability, and QoL in patients with degenerative spondylolisthesis-associated back and leg pain.

In summary, traditional open spinal arthrodesis procedures are associated with high direct procedural costs and hospital fees. However, the current literature suggests that lumbar spinal arthrodesis procedures produce stable clinical improvements, which leads to an accumulation of QALYs while only few additional medical costs incur. Therefore, surgical interventions become more cost effective with time[61]. In the SPORT

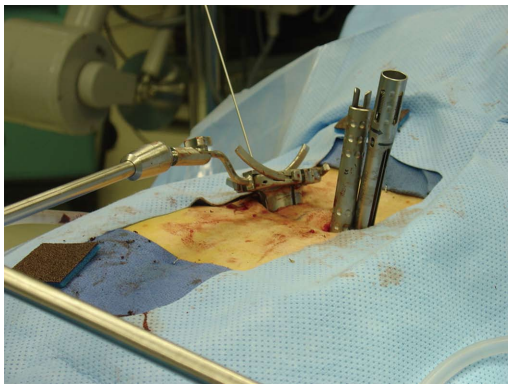

Figure 1 Minimally invasive transforaminal interbody fusion. An expandable tubular retractor is positioned *via* a paramedian approach. Note that the contralateral perdicle screws are in place.

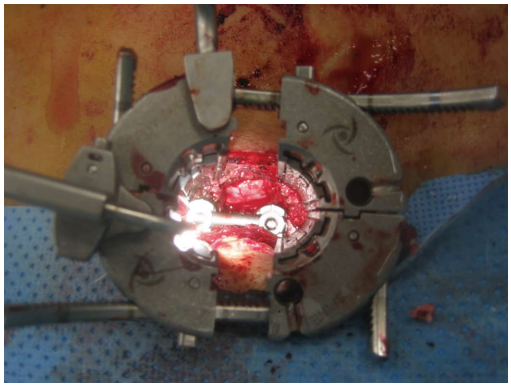

Figure 2 Intraoperative view of a pedicle-rod construct during the final stages of a minimally invasive transforaminal lumbar interbody fusion.

cohort cost effectiveness for spinal fusion surgery for spondylolisthesis was achieved 4 years following the procedure.

MIS arthrodesis procedures have been developed in order to achieve the same surgical goals compared to traditional surgery utilizing a smaller access corridor. The goal is to decrease intraoperative tissue trauma and disruption and hereby decrease perioperative morbidity and promote postoperative rehabilitation. In contrast to traditional TLIF which is performed *via* an open midline approach involving extensive soft tissue stripping and retraction of the paraspinous muscles[15], MIS TLIF utilizes a paramedian approach with muscle spreading (Figures 1 and 2). Parker *et al*[62] compared the clinical outcomes and conducted a cost-utility analysis of single-level MIS *vs* open TLIF procedures. While MIS TLIF's required longer operative times, they were associated with reduced blood loss and decreased length of hospitalization. Return to work was quicker with the MIS group, but postoperative complications were similar between both techniques. No significant differences in outcomes were noted between the two groups in this study. This study also included a cost-utility analysis to compare the MIS and open procedures 2 years following the intervention. They found a significant difference in total costs: Whereas MIS TLIF resulted in total average cost of $38563, open TLIF was $47858 ($P$ = 0.03). On the other hand, there were no statistically significant differences in the calculated QALYs (MIS = QALY gain of 0.77; open = QALY gain of 0.70). As the mean cost savings per MIS-TLIF procedure were $9295 with similar gain in QALYs, the MIS approach produced a higher value with a total cost per QALY of $122303[62].

Wang *et al*[63] conducted a retrospective analysis comparing acute hospitalization charges for 1- and 2-level MIS-TLIF *vs* open PLIF procedures. Patients having bilateral neurological symptoms were treated with open surgery; those with unilateral symptoms were treated with MIS. Blood loss was significantly reduced in MIS-TLIF procedures. Clinical outcomes did not differ significantly in single-level cases, but in two-level MIS-TLIF patients displayed a significant clinical improvement compared to 2-level open cases. Mean length of hospital stay was significantly lower in single-level MIS cases compared to open procedures. Those differences in length of hospital stay correlated with hospital charges: Single-level MIS-TLIF caused an average cost of $70159 compared to $78444 caused by the open approach. This results in average cost savings of $8285 per MIS-TLIF. For 2-level surgery, mean charges totaled $87454 for MIS *vs* $108843 for open surgery. Costs for implants and rhBMP-2 were nearly identical. The crucial factor for a cost-difference was the number of levels operated on[63].

Adogwa *et al*[64] conducted a study to compare narcotic use, return to work, disability, and QoL between MIS and open TLIF's. The duration of narcotic use was significantly less in the MIS TLIF patients and return to work was shorter for the MIS TLIF cohort. However, significant improvements were observed in all clinical measures in both groups, without a significant difference between both groups at 2 years. Wu *et al*[65] conducted a quantitative meta-analysis on studies reporting fusion rates after single-level or multi-level open or minimally invasive/mini-open TLIF procedures[65]. Recombinant bone morphogenetic protein was used in 50% of MIS TLIFs and in 12.18% of open procedures. Mean fusion rate for open TLIF (16 studies, 716 patients) was 90.9%, compared to a mean fusion rate of MIS TLIF was 94.8% (8 studies, 312 patients). Complication rates differed between both treatment groups as well, with 12.6% for open TLIF *vs* 7.5% for minimally invasive TLIF. To conclude, fusion rates for both procedures are in similar. Complication rates are also similar, but there is a trend of a lower complication rate in minimally invasive TLIF procedures.

Overall, MIS fusion procedures are associated with a reduction in utilization of inpatient resources as well as increased cost-savings in the acute perioperative period, predominantly due to reduced complication

rates[63]. Long-term cost-utility analysis of MIS *vs* open procedures is necessary to confirm the long-term clinical effectiveness of MIS procedures.

ADULT SPINAL DEFORMITY CORRECTION

Complex spine surgery is associated with high costs and performed with increasing frequency. It has therefore become a subject of intense economic scrutiny[66-68]. One of the fastest growing and most expensive areas of spine surgery is surgical correction of degenerative scoliosis and adult spinal deformity. Within 10 years (2000-2010) the total number of spine surgeries for the diagnosis of "curvature of the spine" (ICD-9), increased from 9400 to more than 20600[69]. In comparison, the number of all other ICD-9 spine primary diagnosis codes increased by 20% (from 675500 in 2000 to 813800 in 2010)[69]. Several publications have focused on this substantial topic, suggesting up to 32% of all adults being affected by scoliosis and a prevalence of up to 60% in the elderly[70-73]. Nationwide data from the healthcare cost and utilization project (HCUP) report that hospital costs for a principal diagnosis of curvature of the spine averaged $54000 in 2010, compared with $17000 for more common spine procedures (ICD-9 720-724)[69]. Costs for more complex multilevel fusions are estimated to be as high as $70000 (excluding overhead)[68]. Costs of readmissions subsequent to the initial surgery are estimated to range between $65000 and $80000 per readmission[74].

McCarthy *et al*[75] conducted a retrospective study to analyze the total per-patient hospital and operating room costs of adult spinal deformity surgery with minimum three levels fused through extended follow-up. Total hospital costs of surgical treatment averaged $120394. Primary surgery averaged $103143 and total readmission costs averaged $67262 per patient with a readmission (n = 130, 27% of all patients). Total costs in patients readmitted averaged $174629 compared to $100477 for patients without readmission. Average operating room costs were $70514 per patient, constituting 59% of total hospital costs. Due to prevalent readmissions, the average cost of spinal deformity surgery in adults rose by at least 70%, which illustrates the financial burden of revisions/reoperations. In another study, McCarthy *et al*[75] compared observed postoperative QALYs with predicted QALYs using observed preoperative health-related theoretical QALYs lacking operative treatment. One cohort consisted of surgical patients who completed 3-year follow-up and the other group of crossover patients with two preoperatively completed HRQOL (health related QoL) assessments. Average total hospital costs, with discounting and including readmissions, were $125407. At the 3-year follow-up assessment, there was an average QALY of 1.93. Average nonsurgical QALYs were supposed to be 1.6 at this same point of time. Three-years postoperative, the ICER was estimated to be $375000 and 5-year follow-up it was $198000. At the 10-year follow-up, the ICER was $80000. Based upon these calculations, McCarthy *et al*[75] proposed a cost-effectiveness of surgical spinal deformity treatment in adults after 10-years. This emphasizes the need for the durability of surgical treatment to assess the value of surgery.

Surgery for ASD definitely remains challenging. While marked clinical improvement may be seen following successful surgical correction of ASD, intra- and postoperative complications and morbidity remain probable. In a recently published report using data of the Spinal Deformity Study Group, the rate of minor complications was estimated to be 26.2% and the rate of major complications 15.5% in a cohort of 206 patients[76]. This has led spine surgeons all over the world to develop minimally invasive surgical techniques to address spinal deformities. During the last decade a multitude of minimally invasive techniques has evolved to correct coronal spinal deformities. Wang *et al*[77] presented their early experience with minimally invasive thoracolumbar surgery in 2010. They achieved internal fixation with an extreme lateral interbody fusion. RhBMP-2 was routinely used in all fusion sites and levels. Radiographic fusion was recorded in 84 of 86 operated levels. There was no pseudarthrosis. The patient cohort experienced significant improvement in leg and axial back pain (P < 0.01). Only 3 patients had minimal or no improvement of symptoms. Two patients had to be returned to the OR. One patient required extension of the construct and the other patient had a CSF leak. The majority of complications were associated with the transpsoas access. Thus, 30.4% of all patients experienced new postoperative neurological complications like thigh numbness or painful sensations, which lateralized to the side of the approach. Two of these patients had to be admitted to inpatient rehabilitation. In one patient neurological complications were severe, making the permanent use of assistive ambulatory devices mandatory.

Uribe *et al*[78] analyzed complications associated with 3 types of surgery: minimally invasive, hybrid and open. Blood loss was the least in the MIS group, while the open group had the shortest operating time. Length of hospital stay was similar among the groups. Oswestry disability index and visual analog scale scores improved significantly in all groups, except for leg pain, which was not significantly improved in the MIS group. Open surgery achieved significantly better correction of the pelvic incidence-lumbar lordosis mismatch compared to the MIS group postoperatively (P < 0.03). Complication rates were as follows: 30% in the MIS group, 47% in the hybrid group and 63% in the open group.

Wang *et al*[79] surveyed 3 different surgical methods to treat adult spinal deformity: stand-alone, 360° MIS and hybrid. The stand-alone procedure was

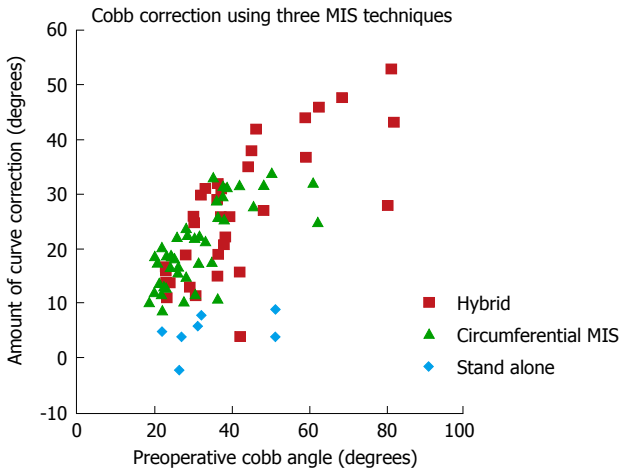

Figure 3 Scatterplot depicting scoliotic curve correction achieved at last follow-up as a function of peroperative curve severity.

least invasive; the hybrid group underwent the most substantial procedure. The circumferential MIS group was intermediate. Surgical time was lowest in the stand-alone group and highest in the hybrid group. Clinical improvement was seen in all 3 groups, without significant differences. The hybrid construct allowed for the highest degree of coronal curve correction (Figure 3), and was the only procedure that led to substantial correction of lumbar lordosis (16.6°). Major complications occurred in 29% of stand-alone procedures, 14% of circumferential procedures and in 40% of hybrid group patients. Wang *et al*[77] concluded that less invasive approaches are associated with specific limitations to coronal and sagittal plane deformity. More invasive procedures have the potential to result in comparable outcomes as open surgery, but are also associated with a higher morbidity.

In conclusion, MIS ASD surgery constitutes a rapidly evolving field which shows promise for certain types of deformities. Several studies have demonstrated that MIS deformity surgery leads to improvement of clinical outcomes and may reduce the rate of perioperative morbidity[80]. Current research is determining particular limitations for scoliotic curve correction utilizing specific less invasive surgical techniques. To date there is no data on the impact of minimally invasive surrey on the cost effectiveness of deformity surgery.

CONCLUSION

In the lumbar spine, MIS techniques are available for treating a variety of clinical indications. In general, clinical outcomes following MIS procedures compare favorably to traditional open surgery. MIS procedures appear to improve the cost effectiveness of lumbar spine procedures by decreasing hospital stay and rehabilitation time. Less invasive decompressive techniques such as endoscopic foraminal decompression and tubular spinal decompression also hold great promise to greatly reduce cost by replacing arthrodesis procedures in strictly selected indications. MIS ASD surgery is currently evolving and will potentially play an important role to make adult deformity surgery economically feasible in our aging society. Our current study identifies a great need for high quality cost-effectiveness studies comparing standard open lumbar spine surgeries with MIS techniques.

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P- Reviewer: Hyun SJ, Kasai Y, Park P **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i2.202

World J Orthop 2015 March 18; 6(2): 202-210
ISSN 2218-5836 (online)

REVIEW

Advanced concepts in knee arthrodesis

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Author contributions: Wood JH and Conway JD contributed equally to this work by analyzing the available literature and developing concepts to be presented; Wood JH wrote and revised the manuscript; Conway JD provided a framework for this review, provided critical content and expert opinion, revised the manuscript, and contributed collective patient experience.
Conflict-of-interest: Janet D Conway has received fees from Biomet and Depuy Synthes for serving as a consultant, has received royalties from the University of Florida, and has received research funding from Medtronic Sofamor Danek, Kinetic Concepts, Inc., and CD Diagnostics; Jennifer H Wood does not have any conflicts of interest to report.

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Received: September 6, 2014
Peer-review started: September 6, 2014
First decision: October 14, 2014
Revised: November 7, 2014
Accepted: December 16, 2014
Article in press: December 17, 2014
Published online: March 18, 2015

Abstract

The aim is to describe advanced strategies that can be used to diagnose and treat complications after knee arthrodesis and to describe temporary knee arthrodesis to treat infected knee arthroplasty. Potential difficult complications include nonunited knee arthrodesis, limb length discrepancy after knee arthrodesis, and united but infected knee arthrodesis. If a nonunited knee arthrodesis shows evidence of implant loosening or failure, then bone grafting the nonunion site as well as exchange intramedullary nailing and/or supplemental plate fixation are recommended. If symptomatic limb length discrepancy cannot be satisfactorily treated with a shoe lift, then the patient should undergo tibial lengthening over nail with a monolateral fixator or exchange nailing with a femoral internal lengthening device. If a united knee arthrodesis is infected, the nail must be removed. Then the surgeon has the option of replacing it with a long, antibiotic cement-coated nail. The authors also describe temporary knee arthrodesis for infected knee arthroplasty in patients who have the potential to undergo insertion of a new implant. The procedure has two goals: eradication of infection and stabilization of the knee. A temporary knee fusion can be accomplished by inserting both an antibiotic cement-coated knee fusion nail and a static antibiotic cement-coated spacer. These advanced techniques can be helpful when treating difficult complications after knee arthrodesis and treating cases of infected knee arthroplasty.

Key words: Arthroplasty; Knee; Arthrodesis; Nonunion; Limb salvage; Limb length inequality; Infection; Osteomyelitis; Bone lengthening; External fixator

Core tip: Knee arthrodesis nonunion can be treated effectively with autologous bone grafting and two modes of fixation such as a plate and intramedullary rod. The hardware in a well-fused but infected knee arthrodesis is surgically challenging to remove, but preserving the intact knee fusion is critical. Symptomatic limb length discrepancy after knee arthrodesis can

be treated with intramedullary lengthening devices or lengthening over a rod. Temporary knee arthrodesis provides a stable, durable solution to treat infection after total knee arthroplasty in an obese patient.

Wood JH, Conway JD. Advanced concepts in knee arthrodesis. *World J Orthop* 2015; 6(2): 202-210 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/202.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.202

INTRODUCTION

Knee arthrodesis has been performed for more than 100 years and is currently a treatment option for limb salvage in a failed total knee arthroplasty, unilateral post-traumatic osteoarthritis in a young patient, reconstruction after tumor resection, and knee joints that are unable to be reconstructed after severe trauma[1]. Techniques for knee arthrodesis are well documented, but the rates of complications range from 20% to 84%[2-6]. Although postoperative complications are commonplace, little information exists regarding treatment options for these complications.

This article will review how to evaluate a patient presenting with complications after knee arthrodesis. Surgical treatment options for nonunion, limb length discrepancy (LLD), and an infected but solidly united knee fusion will be discussed. In addition, we will discuss our indications and surgical technique for the treatment of infected total knee arthroplasty with a "temporary knee fusion".

PREOPERATIVE EVALUATION OF A PATIENT WITH COMPLICATIONS AFTER KNEE ARTHRODESIS

History and physical examination

A thorough patient evaluation is paramount when developing a treatment plan for nonunion, LLD, or infection in a united knee arthrodesis. Relevant clinical information regarding the affected extremity includes: the surgical history of the limb (number, type, and date of procedures), infection history (date, culture results, and treatment), and previous difficulties with wound or bone healing. History of draining wounds or constitutional symptoms such as fevers, chills, or weight loss should raise the suspicion of occult infection. Pain should be assessed by determining its location, duration, intensity, and associated alleviating or aggravating factors.

Comorbidities are optimized preoperatively, especially those affecting bone healing such as diabetes, vitamin D deficiency, calcium deficiency, hyperparathyroidism, hypothyroidism, nutritional deficiency, and peripheral vascular disease. Patients are advised to discontinue tobacco use and are informed of its detrimental effects on bone healing.

During the physical examination, the patient's gait pattern and overall strength are observed. Both lower extremities are inspected for conditions that affect wound healing including venous insufficiency (*e.g.,* edema, varicose veins, venous dermatitis), arterial disease (*e.g.,* cool skin, decreased peripheral pulses), and neuropathy (*e.g.,* hair loss, smooth shiny skin, sensation). The affected extremity is visually inspected for clinical signs of infection (*e.g.,* erythema, effusion, wound drainage, sinus tracts).

Particular attention is paid to the location of previous incisions, skin grafts, and flaps. Poor skin quality or soft tissue integrity is taken into account when developing the surgical plan, as both can lead to wound healing difficulties. Vascular supply to previous flaps must be known so that iatrogenic injury can be avoided.

If unequal limb length is suspected, the "block test" is performed to evaluate functional LLD[7]. To perform this test, 1-cm wooden blocks are placed under the short limb sequentially until the patient feels that the pelvis is level. Functional limb length discrepancy does not always correlate with the objective findings on radiographs.

Radiographic and laboratory studies

Radiographic studies should include a bilateral full length standing anteroposterior view and a full length standing lateral view of the affected extremity. A lift should be used to equalize limb lengths and prevent compensatory knee flexion or equinus, which can adversely affect the accuracy of the limb measurements. When radiographs are inconclusive for knee arthrodesis nonunion, the knee can be evaluated with a computed tomography (CT) scan with sagittal and coronal reconstructions.

Laboratory evaluation includes the erythrocyte sedimentation rate and an assessment of C-reactive protein to screen for infection as well as 25-hydroxy vitamin D, serum calcium, serum prealbumin, and serum albumin to identify vitamin or nutritional deficiencies known to affect bone and wound healing. Nutritional deficiencies are treated with high-protein supplements. Vitamin D deficiency is treated as per the Endocrine Society's Clinical Practice Guidelines[8]. Patients with a body mass index of less than 30 kg/m^2 are given oral supplements of 50000 IU vitamin D_2 or vitamin D_3 weekly for eight weeks, with a goal of increasing serum 25-hydroxyvitamin D to at least 30 ng/mL, with maintenance therapy of 1500 to 2000 IU/d given afterwards[8]. Because vitamin D is fat soluble, obese patients [body mass index > 30 kg/m^2] require two to three times more vitamin D than non-obese patients[8].

TREATMENT OF COMPLICATIONS AFTER KNEE ARTHRODESIS

Nonunion after knee arthrodesis

Nonunion rates range from 17% to 80%[2-5] and

are influenced by multiple factors including patient comorbidities, presence of active knee infection, and choice of implant. Nonunion after knee arthrodesis is typically asymptomatic until 6-9 mo after the arthrodesis procedure. Deconditioned and elderly patients are especially likely to have a delay in symptoms of nonunion as they are typically slow to mobilize. Plain radiographs normally confirm the diagnosis of nonunion, and a CT scan is ordered if plain films are indeterminate. If a nonunion is identified on radiographs but the patient is asymptomatic, surgical intervention is not required unless there is evidence of implant loosening or failure.

External fixation and exchange intramedullary nailing have been described as treatment options for nonunion of a knee arthrodesis[9,10]. An implant that no longer provides stable fixation due to failure or loosening should be removed. Nonunion often occurs when a short intramedullary (IM) nail is implanted in a limb with significant metaphyseal bone loss[3,11,12]. These patients always undergo revision from a short IM nail to a long IM nail, as long nails achieve stability through a diaphyseal fit and are capable of neutralizing the long lever arm and forces across the knee joint.

Surgical treatment options for nonunion of a knee arthrodesis with a retained long IM nail include bone grafting the nonunion site with graft harvested using the reamer/irrigator/aspirator (RIA) system (DePuy Synthes, West Chester, PA, United States) plus either exchange intramedullary nailing (EIN) or supplemental plate fixation (SPF). Implant failure, intramedullary canal diameter, soft tissue healing ability, and evidence of current infection must all be considered when deciding between EIN and SPF. In some cases, both EIN and SPF are used.

During EIN, the IM canal is reamed. The process of reaming the canal stimulates new bone formation[13] and also allows a larger diameter nail to be inserted, which provides additional rigidity and strength. Thus, EIN promotes bony healing through both biological and mechanical means.

SPF provides the mechanical advantages of increasing rotational stability, bending stiffness, and torsional stiffness[14]. The existing nail is left *in situ*. This technique can be helpful when a larger diameter IM nail either cannot be placed or would not provide additional stability at the nonunion site.

Surgical techniques

Supplemental Plate Fixation with Existing Intramedullary Nail, Harvest with the RIA System, and Bone Grafting.

Positioning: The patient is placed supine on radiolucent flattop table with the ipsilateral arm across the chest and a bump underneath the buttock to allow access to the existing IM nail. The draping should include the bilateral iliac crest, bilateral lower extremities, and previous IM nail entry point. The fluoroscope should be positioned perpendicular to the patient on the opposite side of the nonunion.

Description of procedure: Utilizing clean instruments, IM bone graft is harvested from the uninvolved femur using the RIA system. The RIA system can be used in an antegrade or retrograde fashion, and the technique is described in multiple papers[15-19]. After the bone graft harvest site is closed and sterile dressings have been applied, the graft is placed in a sterile cup on the back table. The authors prefer to obtain bone graft from the iliac crest only when the RIA system cannot be used to obtain bone graft from the uninvolved femur.

To insert the plate and apply the bone graft, a lateral or medial approach is used that is centered over the nonunion. The selection of an approach depends on two factors: soft tissue viability and bony contact. Soft tissue viability is the primary determinant in choice of surgical approach. Soft tissues that are suspicious for poor healing capability (*e.g.,* local scarring, areas of previous flaps, skin grafts) are noted and avoided. An anterior knee incision is not typically performed, as previous procedures often cause significant scarring and decreased soft tissue healing potential. Bony contact is the second most important consideration. The approach should allow the plate to be applied to the nonunion so that the plate has the greatest amount of bony contact and thus the greatest potential for gaining bony apposition, fixation, and stability with plate fixation.

After the incision is made, dissection proceeds directly to bone. The nonunion site is burred until there is bleeding, indicative of viable bone. Autograft, combined with bone morphogenetic protein (BMP) 2, is distributed along the nonunion site. A large fragment plate should be selected that is of sufficient length to allow four screws to be inserted both distal and proximal to the nonunion. The plate is bent to accommodate the flare of the proximal tibia and distal femur. The locking plate can be secured with locking or non-locking screws based on surgeon preference. The plate is centered over the nonunion site and placed either on the medial or lateral aspect of the distal femur and proximal tibia, depending on the surgical approach that was chosen. Strategic plate placement increases the likelihood that bicortical screw fixation will be achieved; typically this involves adjusting the plate to sit slightly anterior or posterior to midline on the bone. Bicortical purchase is not always possible, and in these instances, unicortical purchase is accepted.

The incision is closed using a standard multilayer closure. Deep drains and an incisional negative pressure dressing are utilized on an as needed basis. Weightbearing is typically restricted for 6 wk, after which gradual progressive weightbearing is allowed (Figure 1).

Exchange intramedullary nailing

Positioning: The patient is positioned supine on

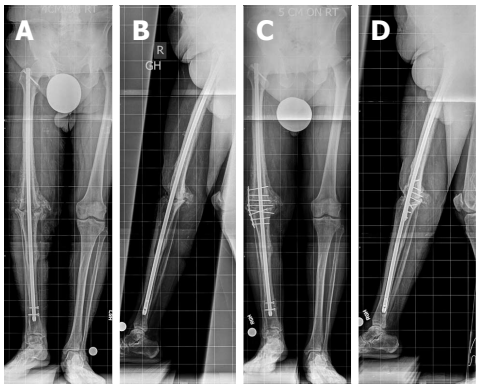

Figure 1 Radiographs of the knee. Anteroposterior (A) and lateral (B) view radiographs of the knee show nonunion of a knee arthrodesis with a long intramedullary nail, without evidence of implant failure or loosening. The intramedullary (IM) nail diameter has a good diaphyseal canal fit but poor canal fit at the arthrodesis site and surrounding metaphysis, which decreases bending and rotational stability provided by the IM nail in this region. Decreased stability increases motion at the arthrodesis site, which can impede bony healing. Anteroposterior (C) and lateral (D) view radiographs of the knee after supplemental plate fixation around the existing knee fusion nail and bone grafting of the nonunion site. Supplemental plate fixation provides additional stability at the nonunion site, which promotes bony healing and union of the knee arthrodesis. Bicortical screw fixation is achieved by aiming slightly posterior to the IM nail. Note the motion at the distal interlocking screws is now visible; however, the knee arthrodesis site has progressive consolidation (reprinted with permission from the Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore).

radiolucent flattop table. The draping includes bilateral iliac crest, bilateral lower extremities, and previous IM nail entry point. The fluoroscope is positioned perpendicular to the patient, on the opposite side of the nonunion. A non-sterile bump is placed under the sacrum to tilt the pelvis, which gives the surgeon access to IM nail entry portal and allows intraoperative lateral fluoroscopic views to be obtained.

Description of procedure: IM bone graft is harvested from the uninvolved femur using the RIA system. The graft is placed in a sterile cup on the back table. The original IM nail and interlocking screws are removed. The nonunion site is identified, and either a medial or lateral approach is performed as described previously in the supplemental plate fixation technique. A subperiosteal pocket is created to accommodate the bone graft. The femur and tibia are sequentially reamed until osseous tissue is noted on the reamer and there is good chatter. An appropriately sized nail is placed, with a goal of placing a new nail that is 2 to 4 mm larger in diameter than the one that was removed[20]. Interlocking screws are placed for rotational control, and the harvested autograft is combined with BMP-2 prior to placing it in the previously developed subperiosteal pocket. Surgical incisions are closed and sterile dressings placed. Postoperatively, partial weightbearing with a gradual increase to full weightbearing is allowed over the ensuing weeks (Figure 2).

LIMB LENGTH DISCREPANCY AFTER KNEE ARTHRODESIS

The goal after knee arthrodesis is a 1-cm LLD, with the fused side being shorter to allow for easier foot clearance when walking[21]. Multiple studies have reported an average LLD of greater than 2 cm[22-24], with some authors reporting an average LLD of greater than 5 cm[25,26]. If LLD is more than 1 cm, treatment may be needed. Nonoperative treatment consists of a shoe lift; however, balance issues occur more frequently as the lift height increases, especially when a lift height of 5 cm or more is required. Surgical intervention is considered for symptomatic LLD that cannot be satisfactorily treated with a shoe lift.

To select the appropriate shoe lift height or amount to lengthen, use the "block test" to determine functional LLD. In some cases, patients prefer not to have full correction of the limb length discrepancy. This is important to note so that the patient does not feel "over lengthened" when using the shoe lift or after the lengthening procedure.

If surgical intervention is needed, options for limb lengthening after knee arthrodesis include lengthening over a nail or exchange nailing with an internal lengthening device (*i.e.,* PRECICE, Ellipse Technologies, Irvine, CA, United States). Advanced age is not a contraindication to distraction osteogenesis[27]. Lengthening over an existing IM nail is a good option in patients whose limb would not tolerate rod removal, typically secondary to incomplete or inadequate healing of the knee arthrodesis. Options for the osteotomy level include the distal femur or the proximal tibia. A distal femoral osteotomy is easier because the fibula does not need to be cut and captured to protect the ankle (Figure 3). Lateral pins must be placed away from the nail. The proximal and distal metaphyseal bone around the knee are the best areas for fixator pins to be inserted.

Surgical techniques

Lengthening over a nail: Tibia.

Positioning: The patient should be positioned supine on radiolucent flattop table.

Description of procedure: A monolateral external fixator is used for this technique. External fixator pins are placed in the proximal and distal tibial metaphysis using the cannulated wire technique[28]. A total of four 6-mm hydroxyapatite-coated half-pins are used: two in the proximal segment and two in the distal segment. A fibular osteotomy is performed at the junction of the middle and distal 1/3 of the fibula. The fibula must be temporarily held at the level of the distal syndesmosis to protect the ankle joint with a screw. A tibial osteotomy is performed in the proximal tibial metaphysis through anterolateral and

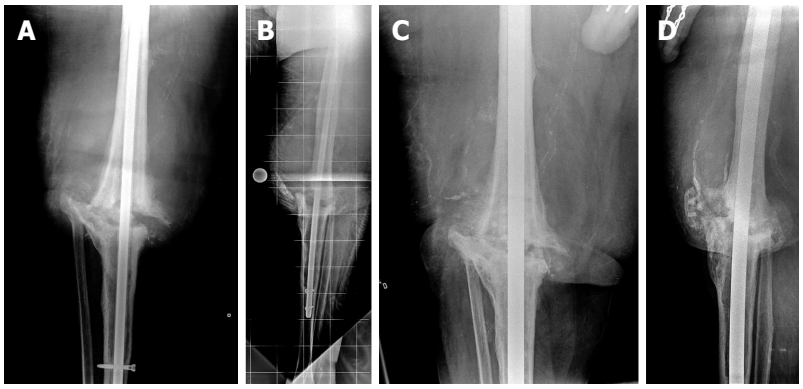

Figure 2 Anteroposterior and lateral view radiographs of the knee. Anteroposterior (A) and lateral (B) view radiographs of the knee show a nonunion of a knee arthrodesis following insertion of an antegrade knee arthrodesis rod with inadequate tibial length. In this case, the intramedullary (IM) nail is shorter than what is typically used in such cases. The distal end of the nail should be 2 cm above the ankle joint. Also, this IM nail diameter is too small to provide a good canal fit. The IM diameter is measured, and exchange nailing is planned. Anteroposterior (C) and lateral (D) view radiographs of the knee after exchange nailing and bone grafting of the nonunion site. Exchange nailing to a larger diameter rod improves canal fit, thus providing additional stability to the nonunion site. The IM nail length was also increased so that the distal end of the nail was 2 cm above the ankle joint. Increasing both the length and the diameter improves the biomechanical stability of the nail and decreases motion at the nonunion site, thus promoting bony healing (reprinted with permission from the Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore).

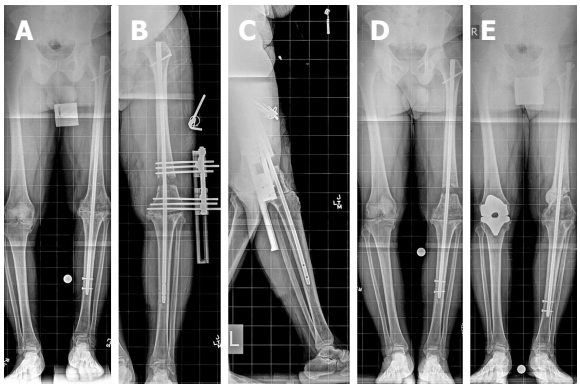

Figure 3 Knee arthrodesis. A: Anteroposterior view full length standing radiograph shows that the left limb has a 3-cm limb length discrepancy. Note the lift that is used under the left limb; B: Anteroposterior view full length standing radiograph shows the distal femoral osteotomy and lengthening over the existing knee fusion nail. Note that the distal interlocking screws are removed from the nail; C: Full length lateral view radiograph shows that the pins of the external fixator have been placed away from the intramedullary nail; D: Postoperative anteroposterior view full length standing radiograph shows that interlocking screws have been placed and the external fixator has been removed. Note the resolution of the limb length discrepancy; E: Anteroposterior view full length standing radiograph obtained 2 years after lengthening (reprinted with permission from the Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore).

posteromedial 1-cm incisions.

Distraction is begun 5 to 7 d after surgery at a rate of 0.75-1 mm/d. Pin-site infections are prevented by using hydroxyapatite-coated pins to decrease loosening. Pin care is performed daily with a saline solution to remove crust from pins. Pin sites are dressed with tightly wrapped Kerlix gauze (Covidien, Mansfield, MA, United States) to prevent soft-tissue pistoning on the skin, which is a major contributor to pin site drainage and infection. If pin-site infections do occur, the majority of cases are treated with 10 d of oral antibiotics.

Postoperatively, the patient attends three to five physical therapy sessions per week to maintain ankle range of motion. Touchdown weightbearing is allowed during the distraction phase and advanced to full weightbearing when consolidation of the regenerate bone has occurred (Figure 4).

Exchange nailing with a femoral internal lengthening device

Positioning: The patient is positioned supine on radiolucent flattop table. The draping should include the bilateral iliac crest, bilateral lower extremities, and previous IM nail entry point. The fluoroscope is positioned perpendicular to the patient and on the opposite side of the nonunion. A non-sterile bump is placed under the sacrum to tilt the pelvis, which helps the surgeon access the IM nail entry portal and obtain intraoperative lateral view fluoroscopic images.

Description of procedure: The diameter of the PRECICE is selected during preoperative planning and templating. Intraoperative fluoroscopy is utilized to identify the planned osteotomy site, which is typically performed in the subtrochanteric region of the femur. Retained implants are removed from the lower extremity if needed. A small lateral incision is made, and multiple drill holes are placed using the 4.8-mm drill bit at the osteotomy site. These holes allow for local deposit of bone graft during intramedullary reaming and venting of the femur to decrease risk of pulmonary embolism. The femur is then sequentially reamed with a reamer that is 1-2 mm larger than the planned diameter of the PRECICE. A percutaneous osteotome is then used to complete the osteotomy. The PRECICE is inserted into the femur and locked both proximally and distally. A fixator can help control

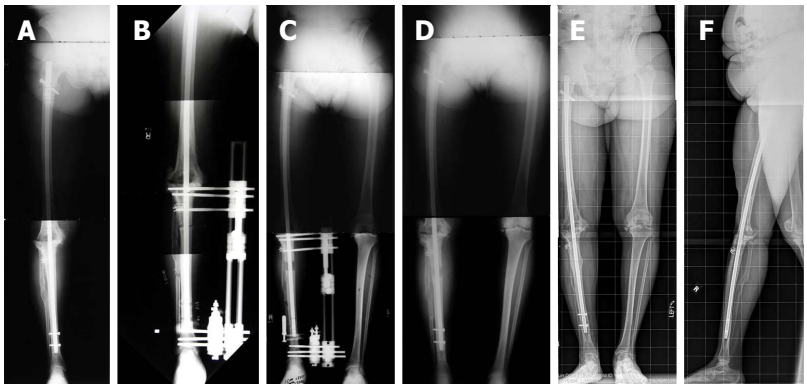

Figure 4 Sixty-four-year-old woman underwent total knee arthroplasty of the right knee and developed a chronic recurrent infection with loss of anterior soft tissue. The infection was treated and the knee was fused, but she developed limb length discrepancy (LLD) and nonunion of the right knee. She underwent resection of the nonunion, implantation of bone graft and bone morphogenetic protein-2, and gradual lengthening for the LLD. Proximal tibial and fibular osteotomies were performed, and external fixation was applied to the tibia. The antibiotic cement-coated rod was not removed. A: Preoperative anteroposterior view full length standing radiograph obtained at the time of nonunion and prior to lengthening; B: Anteroposterior view radiograph obtained during the distraction stage of treatment. Note that the distal fibula was captured with an anteromedial to anterolateral half-pin; C: Anteroposterior view full length standing radiograph obtained after the distraction stage of treatment was completed; D: Anteroposterior view full length standing radiograph obtained after external fixation removal and insertion of interlocking screws; E and F: Anteroposterior (E) and lateral (F) view full length standing radiographs obtained 12 mo after external fixation was removed. Note the complete and total regenerate healing at the level of the proximal tibia (reprinted with permission from the Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore).

rotation and alignment when inserting the PRECICE nail. The nail is tested intraoperatively to ensure that lengthening occurs. Postoperatively, weightbearing is limited to touchdown until the distraction phase is completed. After the regenerate bone has consolidated, the patient progresses to full weightbearing.

THE WELL FUSED BUT INFECTED KNEE ARTHRODESIS

Continued or recurrent infection following knee fusion with an IM nail typically requires nail removal to eradicate the infection. Both long and short IM knee arthrodesis nails are currently in use. Long IM nails are inserted in an antegrade fashion and can be rather easily accessed and extracted through their proximal femoral entry point. Short IM nails, including the Wichita fusion nail (Stryker Orthopaedics, Mahwah, NJ, United States) and the Neff femorotibial nail (Zimmer, Warsaw, IN, United States), are modular and are inserted through the knee. Removal of a short IM nail can be challenging, and preservation of the knee arthrodesis is not always possible. Preoperative evaluation should confirm knee fusion, as an infected nonunion requires a different surgical plan.

Surgical technique

Infected knee arthrodesis with retained short intramedullary nail.

Positioning: The patient should be positioned supine on a radiolucent flattop table.

Description of procedure: A sterile thigh-high tourniquet is employed when possible, and the previous anterior knee incision from nail insertion is used for the surgical approach. An anterior bony window is made at the fusion site, and the IM nail is identified.

For the Wichita nail, all interlocking screws and the compression screw must be removed, followed by transection of the nail with the a metal cutting burr such as the Midas Rex Legend Tool (Medtronic, Minneapolis, MN, United States) high speed cutting burr. This occurs through a bone window at the level of the knee. Do not make this window too large or it will be a stress riser at the anterior distal femur and the bone will break during weightbearing. This can be very time consuming as the Wichita nail is solid, thus more than one burr may be needed to transect the nail. Since the metal cutting sound is very abrasive, the author recommends that the surgical team wear earplugs. The separate sections of the nail are then removed through the anterior bony window. The infection is treated with a burr or careful intramedullary reaming and thorough irrigation and débridement. If the limb has only a small area of bone loss, a mixture of antibiotic cement, calcium triphosphate, and hydroxyapatite is placed in this region to help provide support. A long, antibiotic cement-coated IM nail can be placed if a large amount of bone must be débrided or if the fusion is disrupted.

The Neff nail is solid and long. The fusion must be taken down when a Neff nail is used and can be performed through a transverse incision. The knee must be completely flexed to access the canals and extract the rods. Three small screws hold the sections together, and each section can be 30 cm or longer. In these cases, a long antibiotic cement-coated nail is then inserted in an antegrade fashion through the piriformis fossa to repeat the fusion.

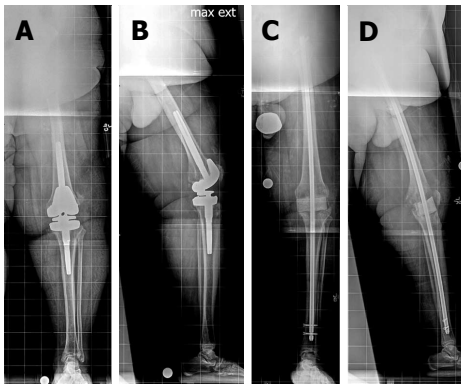

Figure 5 Temporary knee fusion is accomplished by inserting both an antibiotic cement-coated intramedullary knee fusion nail. Anteroposterior (A) and lateral (B) view radiographs of the left leg in a 71-year-old patient with an infected revision total knee arthroplasty. The patient was morbidly obese. A knee joint gap greater than 5 cm was expected after removal of the infected implants. Knee flexion contracture was also present (B). Temporary knee fusion was planned. Anteroposterior (C) and lateral (D) view radiographs of the left leg obtained postoperatively show the temporary knee fusion, including a long, antibiotic cement-coated intramedullary nail and a static antibiotic cement-coated spacer to fill the knee joint gap (reprinted with permission from the Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore).

TEMPORARY KNEE FUSION FOR TREATMENT OF INFECTED TOTAL KNEE ARTHROPLASTY

An infected total knee arthroplasty can be one of the more difficult conditions to treat[29]. In the United States, a chronic infection is commonly treated in a two-stage surgical fashion and articulating antibiotic cement-coated spacers are often used during the first stage of treatment[30]. In certain patients, however, an articulating antibiotic cement-coated spacer may not provide adequate stability and postoperative knee dislocation or inability to bear weight may be an issue. In these situations, the senior author has found that performing a temporary knee fusion provides sufficient stability to allow full weightbearing immediately postoperatively without concern for knee dislocation. A temporary knee fusion is accomplished by inserting both an antibiotic cement-coated IM knee fusion nail and a static antibiotic cement-coated spacer (Figures 5 and 6). Patients are considered for a temporary knee fusion if they are morbidly obese, lack an extensor mechanism, have significant soft tissue defects about the knee, or have extensive distal femoral or proximal tibial bone loss. Additionally, periprosthetic nonunion, especially infected nonunion, may warrant this procedure.

This procedure essentially has two goals: eradication of infection and stabilization of the knee. A double setup is utilized (*i.e.,* "clean and dirty") to remove the knee arthroplasty and resect necrotic bone and soft tissue followed by the reconstruction.

Surgical technique

Positioning: The patient is positioned supine on a radiolucent flattop table. A non-sterile bump is placed under the sacrum, slightly off midline towards the operative side. The operative hip and buttock region must be placed at the edge of the table. Positioning the patient with the affected hip at the edge of the table and placing a bump under the sacrum allows the gluteus musculature and associated adipose tissue to fall posteriorly. This facilitates access to the nail insertion site.

Description of procedure: Our double setup includes a Mayo stand positioned at the foot of the bed. Any instrument utilized during the first portion of the procedure is kept on the Mayo stand. The surgical technologist passes clean instruments kept on the back table to the surgical team but avoids physical contact with the surgical team and surgical field, including the Mayo stand.

A medial parapatellar arthrotomy is typically performed, and the total knee arthroplasty components are accessed and removed. A thorough débridement of the bone and soft tissue is performed, including intramedullary reaming of both the femoral and tibial canals. Ball-tipped guidewires and flexible reamers are utilized for retrograde femoral and antegrade tibial reaming that is 2 mm wider than the templated intramedullary nail diameter, including antibiotic coating. The nail length is calculated and includes the entire length of the femur, the knee joint gap (space between distal femur and proximal tibia), and the tibial length to approximately 2 cm above the ankle. Necrotic and infected bone is further débrided with a burr, and synovectomy is performed. The capsule, lateral gutter, and medial gutter are débrided; the Versajet Ⅱ Hydrosurgery System (Smith and Nephew, Largo, FL, United States) can facilitate posterior débridement. The femoral and tibial canals, as well as the knee joint, are then irrigated with 6 L of saline.

After removal of total knee components, irrigation, and débridement, the entire Mayo stand along with all instruments are removed from the surgical area. All contaminated items are removed from the surgical field *(e.g.,* tubing, bovie). The extremity is re-prepared and re-draped, and all surgical team members change their gowns and gloves. A Trigen knee fusion nail (Smith and Nephew, Memphis, TN, United States) is prepared with an antibiotic cement coating (utilizing silicone tubing as described by Thonse *et al*[31]) and a static antibiotic cement-coated spacer is fashioned to fit the knee joint gap.

Typically, while the extremity is being irrigated, a member of the surgical team breaks scrub, regowns, regloves, and begins making the antibiotic cement-coated fusion nail and spacer. This allows time for the antibiotic cement to cure so that both the nail and spacer will be ready for insertion after irrigation is completed and the extremity is re-prepared and re-draped.

The antibiotic cement-coated fusion nail is inserted

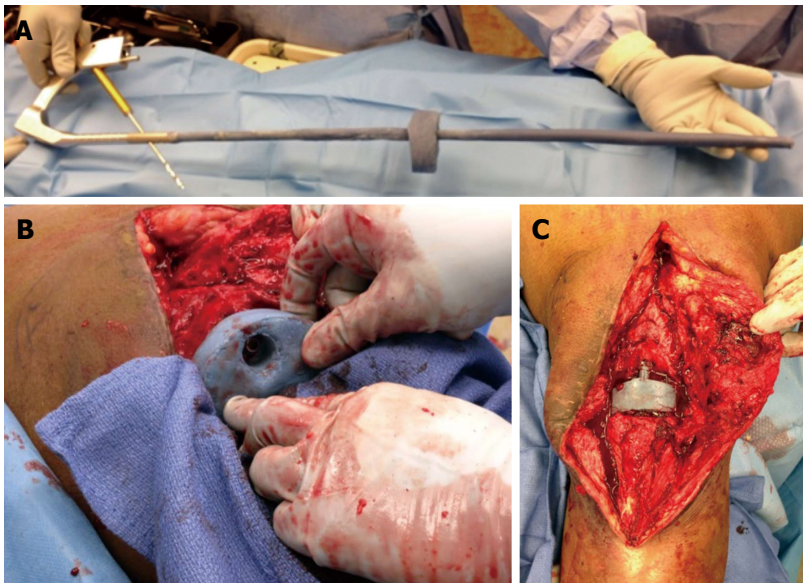

Figure 6 Intraoperative photographs of a temporary arthrodesis for an infected total knee arthroplasty. A: Photograph shows the long, antibiotic cement-coated intramedullary fusion nail and antibiotic cement-coated spacer prior to insertion. The static antibiotic cement-coated spacer was made with a hole placed centrally that was large enough to accommodate the antibiotic cement-coated nail; B: The nail was inserted to the level of the distal femur, was guided through the central hole in the static spacer, and was guided into the tibia. As the nail was inserted into the tibia, the tibia was held in proper alignment and rotation. When the nail reached the midshaft of the tibia, axial load was applied to the lower extremity to prevent distraction from occurring at the knee; C: The knee wound following spacer insertion and locking of the rod (reprinted with permission from the Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore).

antegrade to the level of the distal femur, the static knee spacer is placed, and the IM nail insertion into the tibia is completed. Interlocking screws are placed proximally and distally. Incisions are closed using non-braided suture, and dressings are placed per routine. Incisional negative pressure wound therapy can be utilized on the anterior knee incision to facilitate healing.

Postoperatively, the patient is allowed to weight bear as tolerated. Antibiotics are tailored based on growth from intraoperative cultures and are typically administered intravenously or orally for 6 wk. Typically, the patient also takes anticoagulation medication for 6 wk.

ACKNOWLEDGMENTS

The authors thank Amanda E Chase, MA, and Alvien Lee for their invaluable assistance with this manuscript.

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P- Reviewer: Babis GC, Fisher DA **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Liu SQ

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i2.211

World J Orthop 2015 March 18; 6(2): 211-220
ISSN 2218-5836 (online)

REVIEW

Factors affecting healing after arthroscopic rotator cuff repair

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Received: July 4, 2014
Peer-review started: July 4, 2014
First decision: July 18, 2014
Revised: September 29, 2014
Accepted: October 1, 2014
Article in press: October 10, 2014
Published online: March 18, 2015

Abstract

Rotator cuff repair has been shown to have good long-term results. Unfortunately, a significant proportion of repairs still fail to heal. Many factors, both patient and surgeon related, can influence healing after repair. Older age, larger tear size, worse muscle quality, greater muscle-tendon unit retraction, smoking, osteoporosis, diabetes and hypercholesterolemia have all shown to negatively influence tendon healing. Surgeon related factors that can influence healing include repair construct-single *vs* double row, rehabilitation, and biologics including platelet rich plasma and mesenchymal stem cells. Double-row repairs are biomechanically stronger and have better healing rates compared with single-row repairs although clinical outcomes are equivalent between both constructs. Slower, less aggressive rehabilitation programs have demonstrated improved healing with no negative effect on final range of motion and are therefore recommended after repair of most full thickness tears. Additionally no definitive evidence supports the use of platelet rich plasma or mesenchymal stem cells regarding improvement of healing rates and clinical outcomes. Further research is needed to identify effective biologically directed augmentations that will improve healing rates and clinical outcomes after rotator cuff repair.

Key words: Shoulder; Repair; Healing; Tendon; Rotator cuff tear

Core tip: Many factors, both patient and surgeon related, can influence healing after repair. Older age, larger tear size, worse muscle quality, greater muscle-tendon unit retraction, smoking, osteoporosis, diabetes and hypercholesterolemia have all shown to negatively influence tendon healing after rotator cuff repair. Smoking cessation and blood glucose and cholesterol control are methods to potentially improve healing rates. Slower, less aggressive rehabilitation programs may improve healing rates with no negative effect on final range of motion and are therefore recommended after arthroscopic repair of most full thickness tears. Finally, no definitive evidence supports the use of platelet rich plasma or mesenchymal stem cells regarding improvement of healing rates after rotator cuff repair. Routine use of these adjuvants is therefore not currently recommended.

Abtahi AM, Granger EK, Tashjian RZ. Factors affecting

healing after arthroscopic rotator cuff repair. *World J Orthop* 2015; 6(2): 211-220 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/211.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.211

INTRODUCTION

Rotator cuff tears are a common cause of pain and disability[1,2]. In patients meeting indications for surgery, rotator cuff repair has been shown to have good long-term clinical results[3,4]. Despite this, the literature suggests that a significant proportion of repairs fail to heal following rotator cuff repair. Reported healing rates vary from 91% for small tears to 6% for large and/or massive tears in some series[5-8]. Failure of tendon healing does not necessarily preclude satisfactory results, although improved results have been associated with intact repairs[9,10]. There is a large body of literature demonstrating that a number of different factors may influence the results following rotator cuff repair. In general, factors can be separated into patient-related (non-modifiable) and surgeon-related (modifiable). The purpose of this review is intended to provide a summary of the literature related to the major factors, both patient- and surgeon-related, influencing healing after rotator cuff repair.

PATIENT-RELATED FACTORS

Age

Increasing patient age has been associated with lower rates of tendon healing after rotator cuff repair in multiple studies[5,11-13]. The detrimental effect of age on rotator cuff tendon healing appears to be independent of the surgical technique utilized for repair. Boileau *et al*[5], in a series of 65 chronic full-thickness supraspinatus tears repaired *via* an arthroscopic single row technique, reported 43% healing in patients over 65% *vs* 86% healing in patients under age 65. Tashjian *et al*[11], in a series of 49 arthroscopic double-row rotator cuff repairs, reported that increased age was associated with lower rates of tendon healing. The average age of patients with unhealed repairs was 63.3 *vs* 55.1 for those with healed repairs[11]. Similarly, Cho *et al*[12], in a study of 123 arthroscopic double-row suture bridge repairs, demonstrated that increasing age was associated with lower rates of tendon healing. The average age of patients with unhealed repairs in their series was 60.1 compared to 53.8 in the healed group. Finally, Oh *et al*[13], in a study of 177 patients after arthroscopic and mini-open rotator cuff repairs of various techniques, also noted that increasing age was associated with lower rates of tendon healing. The average age of patients with unhealed repairs in their series was 63.7 compared to 58.4 in the healed group[13].

The detrimental effect of increasing age on tendon healing after rotator cuff repair may be due to other factors affecting tendon healing rather than to age itself. Chung *et al*[14], in a study of 272 patients after arthroscopic rotator cuff repair, found that bone mineral density, fatty infiltration, and retraction of the rotator cuff tendon were the only independent predictors of rotator cuff healing. Chung *et al*[15], in another study of 108 patients who underwent arthroscopic repair of massive rotator cuff tears, found that while several factors were associated with failure of cuff healing in the univariate analysis including age, only fatty infiltration was significantly related to healing failure in the multivariate analysis. Similarly, Oh *et al*[13] noted that age was not an independent predictor of tendon healing or functional outcome. Tear retraction and fatty atrophy were found to be the only independent predictors of tendon healing in their study[13]. Therefore, age may be a surrogate for other anatomical factors correlated with impaired healing after rotator cuff repair.

Tear size

Several studies have shown that tear size affects rotator cuff tendon healing. Larger tears have lower healing rates after rotator cuff repair compared to smaller tears. Failure rates after arthroscopic repair of large and/or massive rotator cuff repairs have been reported to range from 34%-94% in various series[6,16-19]. Despite poor healing rates in patients with large and/or massive rotator cuff tears, functional outcomes have generally been reported to be good following repair. Galatz *et al*[6] reported that despite failure of healing in 94% of patients at 1 year follow-up, excellent pain relief and improvement in the ability to perform activities of daily living was noted although these results did deteriorate somewhat at 24 mo follow-up. Chung *et al*[15] reported significantly improved functional improvement in a series of arthroscopically repaired massive cuff tears despite an anatomic failure rate of 39.8%. Despite this, not all patients with an unhealed repair do well clinically[18-21]. Namdari *et al*[21] reviewed a series of patients with structural failure after rotator cuff repair and reported a successful outcome in only 54% of patients. Those individuals with labor-intensive jobs were also found to be at high risk for poor outcome after a failed rotator cuff repair[21]. Kim *et al*[20] reviewed a similar group and determined younger age, lower education level and a workers' compensation claim were all risk factors for poorer outcomes after a failed repair.

Fatty infiltration and rotator cuff atrophy

Fatty infiltration and rotator cuff atrophy have been shown to affect healing and functional outcomes following rotator cuff repair[10,22,23]. Thomazeau *et al*[22] demonstrated that more severe preoperative atrophy was associated with worse postoperative repair integrity in 30 open repairs of chronic supraspinatus

tears. Liem *et al*[10], in a series of 53 arthroscopic repairs of isolated supraspinatus tears, reported that both supraspinatus atrophy and fatty infiltration were predictive of healing. Goutallier *et al*[23], in a series of 220 shoulders, demonstrated that the likelihood of recurrent tear was greater in patients whose muscle demonstrated more advanced degrees of fatty atrophy. Despite lower rates of cuff healing, patients with fatty infiltration and rotator cuff atrophy may still benefit from rotator cuff repair. Burkhart *et al*[24] reported on 22 patients with massive rotator cuff tears and Goutallier stage 3 or 4 fatty degeneration undergoing arthroscopic rotator cuff repair and demonstrated significant overall functional improvement. Patients with a greater degree of fatty degeneration, however, were less likely to benefit from surgical intervention than those with less fatty degeneration[24]. Other studies have also shown that patients with fatty infiltration and rotator cuff atrophy have lower rates of tendon healing associated with inferior clinical outcomes[10,25]. Goutallier grade 2 or higher degrees of fatty infiltration are significantly associated with poorer healing after repair[10].

Although rotator cuff atrophy and fatty infiltration are both considered part of the same process, they have been found to independently predict outcome following rotator cuff repair[25]. Most studies indicate that fatty infiltration is irreversible, even in the presence of a successful repair. In the presence of an untreated or failed repair, fatty infiltration continues to progress. In some studies, atrophy has been shown to improve to a small degree after successful repair. Fuchs *et al*[26] in a series of single tendon rotator cuff repairs reported that muscular atrophy did not decrease significantly after repair. However, fatty infiltration of the supraspinatus and infraspinatus, increased significantly despite repair. Rotator cuff atrophy was significantly worse in patients with re-tears than in those with intact repairs. Gerber *et al*[27], in a study of 12 patients, noted that within one year after successful tendon repair, fatty infiltration did not improve but rotator cuff atrophy improved partially. In the presence of a failed repair, atrophy and infiltration progressed significantly. In a separate study, Gerber *et al*[19] studied 29 patients who underwent arthroscopic repair of massive rotator cuff tears and noted a 34% retear rate. Supraspinatus atrophy was mildly reversed after repair. Infraspinatus atrophy, however, worsened even after successful repair. Fatty infiltration was not reversible but progressed less in patients with intact repairs. Chung *et al*[28] reported, in a series of 191 patients who underwent arthroscopic rotator cuff repair, that 42.4% of patients showed improvement of atrophy and 17.3% of patients showed worsening. The change in atrophy was related to repair integrity. For patients with worsened atrophy, the cuff healing rate was 48.5% compared with 22.2% in patients with improved atrophy. Gladstone *et al*[25], in a study of 38 patients after arthroscopic rotator cuff repair found that both atrophy and infiltration progressed regardless of rotator cuff healing. In cases in which the tendon had re-torn however, the progression was noted to be more significant compared to those patients that had healed. Liem *et al*[10] in a series of 53 consecutive patients who underwent arthroscopic repair of an isolated supraspinatus tear, reported that in patients with intact repairs fatty infiltration and atrophy did not progress whereas in those with recurrent tears fatty infiltration and atrophy worsened significantly. So overall, fatty infiltration may halt after a repair if it remains intact but will progress with re-tears. Atrophy has the potential to reverse after repair if the repair remains intact but will likely progress if it fails.

Muscle-tendon unit retraction

Tendon retraction, or the gap between the greater tuberosity and the tendon edge, is either due to tendon shortening or muscle retraction. Muscle retraction can be defined by utilizing the position of the muscle-tendon junction (MTJ) in relation to landmarks on the scapula. Meyer *et al*[29] evaluated 118 shoulder MRIs for the MTJ position in the setting of a rotator cuff tear. They concluded that increasing stages of fatty infiltration correlate with increasing tear size, tendon shortening and MTJ retraction. Initial stages of muscle-tendon unit retraction in the setting of rotator cuff tears with minimal fatty infiltration occurs through muscle shortening whereas tears with later stages of fatty infiltration shorten through tendon shortening[29]. Kim *et al*[30] reported similar results that showed with increasing tear size and tendon reaction, the tendon length shortens. These results support that initial retraction in smaller tears occur with muscle shortening but as tears enlarge and become more chronic the tendon shortens as well.

Meyer *et al*[31] also looked at the effect of MTJ shortening on rotator cuff repair healing. They determined that the muscle and tendon lengthened an average of 14 mm and 8 mm, respectively, after a successful rotator cuff repair. They also determined that a shorter preoperative tendon length correlated with worse overall healing rates although preoperative MTJ position had no effect[31]. Tashjian *et al*[32] evaluated MRIs of 51 patients after arthroscopic rotator cuff repair and did find a significant associate with preoperative MTJ position and postoperative tendon healing. If the preoperative MTJ was at the level of the glenoid or medial then 55% of tears healed whereas if the MTJ was lateral to the glenoid face then 93% of tears healed. Consequently, both greater preoperative MTJ retraction and greater preoperative tendon shortening negatively affect healing after rotator cuff repair.

Other patient-related factors (smoking, osteoporosis, hypercholesterolemia, diabetes)

Several other patient-related factors have been reported to affect rotator cuff tendon healing. Smoking not only increases the risk for rotator cuff tears, but

has been reported to influence rotator cuff tear size as well[33]. Smoking has been shown to delay tendon-to-bone healing in a rat model and clinical studies have demonstrated inferior clinical outcomes after repair in smokers[34,35]. Finally, Neyton *et al*[36] evaluated healing after arthroscopic double-row suture bridge repair for the impact of smoking. The authors determined healing rates were significantly worse in smokers (78%) compared to non-smokers (93%) after single tendon repair.

Both bone mineral density and vitamin D deficiency have been shown to affect rotator cuff tendon healing following surgical repair. Chung *et al*[14], in a study of 272 patients after arthroscopic rotator cuff repair, found that bone mineral density was an independent predictors of rotator cuff healing. In a rat rotator cuff repair model, Angeline *et al*[37] demonstrated that vitamin D deficiency negatively affects the biomechanical and histological properties of rotator cuff repairs during the early phase of healing. This effect was found to be independent of bone mineral density[37].

Other system diseases have been associated with rotator cuff tearing as well as rotator cuff healing. Abboud *et al*[38] collected serum cholesterol and lipid profiles on patients with full-thickness rotator cuff tears and compared them to a control population. They determined that total cholesterol, triglycerides and low-density lipoprotein cholesterol concentrations were higher in patients with rotator cuff tears. Consequently, patients with cuff tears are more likely to have hyper-cholesterolemia compared to controls. Beason *et al*[39] evaluated the effects of hypercholesterolemia on tendon healing in a rat rotator cuff tear model. These authors determined that there was a significant reduction in rotator cuff repair stiffness in hypercholesterolemic rats compared with controls[40]. This data would support hypercholesterolemia likely plays a role not only in the development of rotator cuff tearing but also on the ability for a tendon to heal after repair. Similarly, diabetes has been found to have a detrimental effect on tendon healing using a rat rotator cuff tear model[39]. Modification of serum cholesterol levels and blood glucose levels may play a role in improving healing after repairs.

SURGEON-RELATED FACTORS

Repair construct-single-row vs double-row

A number of surgical techniques are available to the surgeon treating tears of the rotator cuff. An ideal rotator cuff repair construct would provide high initial fixation strength and minimize gap formation during healing[41]. Biomechanical studies of double-row repairs have shown increased load to failure, improved contact areas and pressures, and decreased gap formation when compared to single row repairs[42-46]. These biomechanical studies have led to a number of clinical studies comparing single-row with double-row repair techniques. These studies have, in general, failed to demonstrate significant differences in functional outcomes with single *vs* double-row techniques. Grasso *et al*[47] in a prospective randomized study of single-row *vs* double-row arthroscopic rotator cuff repairs reported that arthroscopic rotator cuff repair with the double-row technique showed no significant difference in clinical outcome compared with single-row repair. In contrast, Park *et al*[48] reported that in patients with large to massive tears (> 3 cm), the American Shoulder and Elbow Surgeons Score, Constant scores and Shoulder Strength Index were all significantly better in the group that had double-row repair.

Despite the fact that most studies have failed to demonstrate clinical differences with singe *vs* double row repairs at short term follow-up, there appears to be a lower re-tear rate for the double-row compared with the single-row repairs[49-51]. Lapner *et al*[49], in a multicenter randomized controlled trial comparing single-row with double-row fixation in arthroscopic rotator cuff repairs reported that although double-row fixation was associated with higher healing rates, no significant differences in functional or quality-of-life outcomes were identified between single-row and double-row fixation techniques. In contrast, Burks *et al*[52], in a prospective randomized clinical trial comparing arthroscopic single- and double-row rotator cuff repair reported no clinical or MRI differences between single-row or double-row techniques.

A modification of the double-row technique is the double-row suture bridge technique[36,53-56]. Gartsman *et al*[54], evaluated the repair integrity of single-row *vs* double-row suture bridge arthroscopic rotator cuff repairs in a prospective, randomized study. They demonstrated that double-row suture bridge repair resulted in a significantly higher tendon healing rate compared to arthroscopic single-row repair. Mihata *et al*[53] demonstrated that in the subcategory of large and massive rotator cuff tears, the re-tear rate in the double-row suture bridge group was significantly less than those in the single-row group and the non-suture bridge double-row group. Several techniques have been described for double row suture bridge repair. Kim *et al*[55] compared three different methods including knotted and knotless techniques and demonstrated equivalence between techniques with regards to functional outcomes and repair integrity.

An alternative to double row repairs for improving fixation and healing is to increase the number of sutures per anchor. Jost *et al*[57] evaluated the effects of increasing suture number on rotator cuff healing strength in a sheep model and determined that increasing the number of sutures decreased cyclic gap formation and increased load to failure. Barber *et al*[58] determined that single row repairs utilizing triple-loaded anchors were more resistant to cyclic displacement

than double-row suture bridge repairs. Other authors have evaluated various suture configurations for rotator cuff repair. White *et al*[59], in a biomechanical study, reported no difference in biomechanical strength with 4 simple sutures, 2 mattress sutures, or 1 grasping suture. They concluded that this provides justification for the use of the simplest configuration with which the surgeon is comfortable.

Overall, the biomechanical data would support that double-row fixation is stronger than single row fixation using double-loaded suture anchors although increasing suture numbers per anchor (triple-loaded anchors) may offset any biomechanical advantage of double row repairs. Clinically, double-row repairs have improved healing rates compared to single row repairs using double-loaded suture anchors. Nevertheless, functional outcomes between double-row and single-row repairs are equivalent except in large and massive tears where double-row fixation may provide a functional advantage over single-row repairs.

Rehabilitation

A number of rehabilitation protocols have been described for use following rotator cuff repair. While some surgeons recommend early, aggressive rehabilitation programs, others recommend a more conservative rehabilitation program. Data are conflicting on which, if any, of these programs provides superior results. Early aggressive rehabilitation programs have been shown to result in better early outcomes, pain relief, and range of motion however most studies show no difference with regard to these parameters with longer-term follow-up[60-66]. One concern with early aggressive rehabilitation programs is that they may be associated with a higher incidence of tendon re-tear.

Immobilization has been shown to affect tendon healing although the data is conflicted. Galatz *et al*[67] and Hettrich *et al*[68] have shown that complete removal of load is detrimental to rotator cuff healing. In contrast, Gimbel *et al*[69] demonstrated that long durations of immobilization in rats result in enhanced mechanical properties of the healing supraspinatus tendon insertion site.

Like the basic science literature, the clinical literature is also conflicting as to whether the rehabilitation program utilized affects clinical healing rates after rotator cuff repair. While some studies show higher re-tear rates with early, aggressive therapy protocols, others show a trend or no difference in re-tear rates[62,63]. In a prospective randomized study of early aggressive *vs* delayed rehabilitation protocols, Cuff *et al*[63] demonstrated a slightly higher but non statistically significant re-tear rate at 1 year in the early group (15%) compared to the delayed group (9%). Lee *et al*[62] evaluated re-tear rates at 6 mo comparing aggressive with conservative rehabilitation protocols. They found that the re-tear rate was significantly higher in the more aggressive group (23.3%) compared with the conservative group (8.8%). They found no difference, however, in long-term functional outcomes between the two groups[62]. In contrast, Kim *et al*[61] evaluated early and delayed range of motion protocols after rotator cuff repair and found no statistically significant difference in healing rates between the two groups with a trend toward lower re-tear rates in the early range of motion group (12% *vs* 18%).

In summary, the literature shows that early aggressive rehabilitation protocols may result in a slightly higher incidence of re-tear compared with more conservative protocols. The benefits of early aggressive therapy protocols seen in the early postoperative period on pain relief and range of motion, however, are not observed with longer term follow up. The risk, therefore, may outweigh the benefits of such protocols in the majority of cases supporting the use of a slower rehabilitation protocol.

BIOLOGICS

Platelet rich plasma

Biologic augmentation of rotator cuff repairs has gained significant interest over the past several years as biomechanically improvements in repair constructs have maximized. Numerous growth factors have been shown to improve proliferation and collagen secretion of tenocytes *in vitro* including basic fibroblast growth factor, vascular endothelial growth factor, and transforming growth factor-β[70-74]. Platelet-rich plasma (PRP) is a fraction of whole blood containing high platelet counts that release these various growth factors when activated. Because these growth factors have shown a positive effect on healing *in vitro*, a large interest exits in the application of PRP to augment rotator cuff repair healing.

Several studies have been performed evaluating the effect of PRP on rotator cuff healing. There is currently no consensus on PRP application during rotator cuff repair as several studies have shown a positive effect on healing while others have shown no effect or a negative effect. Weber *et al*[75] performed a prospective randomized study evaluating the effects of platelet rich fibrin matrix (PRFM) on tendon healing and found no differences in healing rates in PRFM treated repairs compared to controls. Rodeo *et al*[76] reported similar results for PRFM in a randomized control trial where healing rates in the PRFM group were 67% compared to 81% in the non-augmented repairs (P = 0.2). Bergeson *et al*[77] actually reported significantly worse healing rates with PRFM application *vs* non-augmented repairs (38% *vs* 56%, P = 0.024).

Contrary to the findings reporting no effect of PRP on tendon healing, several authors have found beneficial effect of PRP on rotator cuff healing[78,79]. Barber *et al*[78] reported on a matched group of rotator cuff repairs treated with PRFM and non-augmented repairs and reported healing rates of 70% with PRFM augmentation and 40% without augmentation. Jo *et al*[79] performed a randomized control trial comparing PRP repair augmentation of large and massive rotator cuff tears and reported re-tear rates in the PRP

Table 1 Studies evaluating factors affecting healing after rotator cuff repair

Study	Study type	Number of patients/duration of follow up	Primary outcome	Conclusion	Level of evidence
Age					
Boileau *et al*[5]	Case series	65 pts/29 mo	CT arthrogram, MRI	Healing rate significantly lower in patients > age 65	Ⅳ
Tashjian *et al*[11]	Case series	48 pts/16 mo	US	Older age associated with lower tendon healing rate	Ⅳ
Cho *et al*[12]	Case series	120 pts/25.2 mo	MRI	Older age associated with lower tendon healing rate	Ⅳ
Oh *et al*[13]	Case series	177 pts/29 mo	CT arthrogram	Older age was related to poor postoperative repair integrity	Ⅳ
Tear size					
Galatz *et al*[6]	Case series	18 pts/36 mo	US	High rate of tendon healing failure	Ⅳ
Chung *et al*[15]	Case series	108 pts/31.7 mo	CT arthrogram, US	High rate of tendon healing failure	Ⅳ
Fatty infiltration/atrophy					
Thomazeau *et al*[22]	Case series	30 pts/21.1 mo	MRI	Supraspinatus atrophy was a strong risk factor for retear	Ⅳ
Liem *et al*[10]	Case series	53 pts/26.4 mo	MRI	Higher degrees of muscular atrophy and fatty infiltration preoperatively are associated with tear recurrence	Ⅳ
Goutallier *et al*[23]	Case series	220 shoulders/37 mo	CT arthrogram, MRI	The likelihood of a recurrent tear was greater for tendons whose muscle showed fatty degeneration greater than grade 1	Ⅳ
Chung *et al*[15]	Case series	108 pts/31.7 mo	CT arthrogram, US	Higher FI of the infraspinatus was the single most important factor negatively affecting cuff healing	Ⅳ
Tendon retraction					
Meyer *et al*[31]	Retrospective cohort	33 shoulder/24 mo	MRI	The combination of Goutallier grading and preoperative tendon length appears to be a more powerful predictor for the reparability of a tendon tear than Goutallier grading alone	Ⅲ
Tashjian *et al*[32]	Case series	51 pts/25 mo	MRI	The position of the MTJ with respect to the glenoid face can be predictive of healing, with over 90% healing if lateral and 50% if medial to the face	Ⅳ
Other patient factors					
Neyton *et al*[36]	Case series	105 pts/16.1 mo	MRI	Smoking was detrimental to healing	Ⅳ
Chung *et al*[14]	Retrospective cohort	408 pts/37.2 mo	CT arthrogram, US	Bone mineral density, as well as FI of the infraspinatus and amount of retraction, was an independent determining factor affecting postoperative rotator cuff healing	Ⅲ
Abboud *et al*[38]	Case-control	147 pts/NA	NA	Patients with rotator cuff tears were more likely to have hypercholesterolemia when compared with the control group	Ⅱ
Repair construct					
Lapner *et al*[49]	RCT	90 pts/24 mo	MRI, US	Smaller initial tear size and a double-row fixation technique were associated with higher healing rates	Ⅰ
Burks *et al*[52]	RCT	40 pts/12 mo	MRI	No clinical or MRI differences found between patients repaired with a SR or DR technique	Ⅰ
Mihata *et al*[53]	RCT	201 pts/38.5 mo	MRI, US	Retear rate in the compression double-row group was significantly less than in the single-row group and the double-row group	Ⅰ
Gartsman *et al*[54]	RCT	90 pts/10 mo	US	Arthroscopic double-row suture bridge repair resulted in a significantly higher tendon healing rate compared to single-row repair	Ⅰ
Kim *et al*[55]	Case series	79 pts/30.6 mo	MRI, US	The re-tear rate after suture-bridge repair was 15%	Ⅳ
Rehabilitation					
Lee *et al*[62]	RCT	64 shoulders/7.6 mo	MRI	More patients in the aggressive early passive rehabilitation group (23.3%) had retears compared to the limited early passive group (8.8%) although not statistically significant	Ⅱ
Kim *et al*[61]	RCT	105 pts/12 mo	MRI, CT arthrography	Early passive motion did not negatively affect cuff healing	Ⅰ
Biologics (PRP/MSCs)					
Weber *et al*[75]	RCT	60 pts/12 mo	MRI	Healing rates did not differ between groups	Ⅰ

Rodeo *et al*[76]	RCT	79 pts/12 wk	US	No differences in tendon-to-bone healing between the PRFM and control groups	II
Bergeson *et al*[77]	Prospective cohort	37 pts/27 mo in control group and 13 mo in PRFM group	MRI	No differences in retear rates between the PRFM and control groups	III
Barber *et al*[78]	Case-control	40 pts/31 mo	MRI	PRFM group had lower retear rates than control group	III
Jo *et al*[79]	RCT	48 pts/15.9 in PRP group and 17.3 in control group	MRI	Retear rate in the PRP group was significantly lower than in the control group	I
Hernigou *et al*[86]	Case-control	90 pts/10 yr	MRI	Higher rate of healing and reduced number of re-tears over time in the MSC groups compared to the control group	III

CT: Computed tomography; MRI: Magnetic resonance imaging; PRFM: Platelet rich fibrin matrix; MSC: Mesenchymal stem cell; PRP: Platelet-rich plasma; US: Ultrasound; MTJ: Muscle-tendon junction; DR: Double row; SR: Single row; FI: Fatty infiltration; NA: Not applicable; RCT: Randomized controlled trial.

augmentation group (20%) significantly lower than in the non-augmented group (56%) (P = 0.023).

At this point in time, it is unclear why certain studies have performed well with augmentation and others have found no improvement. Potential factors may be preparation mechanisms, timing of application and technique of repair to name only a few. Until further research is performed to elucidate which patients and through which technique PRP application may be beneficial, the use of PRP as an augmentation to rotator cuff repair to improve healing is experimental and of questionable utility.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have been explored as an option for biologic augmentation of rotator cuff repairs. Mazzocca *et al*[80] have demonstrated that MSCs can be isolated from the proximal humerus through the anchor tunnels created during arthroscopic rotator cuff repair. Utsunomiya *et al*[81] investigated multiple potential sources of MSCs that can be harvested during arthroscopic rotator cuff repair. They demonstrated that synovial cells harvested from the subacromial bursa are a good potential source of MSCs[81]. Gulotta *et al*[82] evaluated MSCs in an animal rotator cuff repair model and found that the addition of MSCs to the healing rotator cuff insertion site did not improve the structure, composition, or strength of the healing tendon attachment site despite evidence that they are present and metabolically active[82]. In a subsequent publication, however, the authors reported that bone marrow-derived MSCs transduced with scleraxis (a transcription factor that is thought to direct tendon development during the embryonic period) improved rotator cuff healing in a rat model[83]. Similarly, Mazzocca *et al*[84] have demonstrated that bone marrow-derived MSCs treated with insulin differentiated into tendon-like cells. Kim *et al*[85], in an animal model, demonstrated that MSCs increase type Ⅰ collagen production at the site of rotator cuff repair. Finally, Hernigou *et al*[86] evaluated forty-five patients that received concentrated bone marrow derived MSCs as an adjunct to single row rotator cuff repair compared to a matched control group and found that the healing rate at 6 mo was significantly higher in the MSC group. Furthermore, the authors found that at a mean follow-up of ten years there was a significantly higher re-tear rate in the control group compared to the MSC group[86]. Although use of MSCs demonstrates promise for biologic augmentation of rotator cuff repair, further clinical studies are necessary before their use can be recommended in clinical practice.

CONCLUSION

In summary, multiple factors have been shown to influence rotator cuff healing. Table 1 provides a summary of these factors and the relevant studies. Older age, larger tear size, worse muscle quality, greater muscle-tendon unit retraction, smoking, osteoporosis, diabetes and hypercholesterolemia have all shown to negatively influence tendon healing. Smoking cessation and blood glucose and cholesterol control are methods to potentially improve healing rates. Double-row rotator cuff repairs are biomechanically stronger and have better overall healing rates when compared to single-row repairs although clinical outcomes are equivalent between both repair constructs. Delayed rehabilitation after arthroscopic repair of most full thickness tears may improve healing rates with no negative effect on final range of motion therefore slower early rehabilitation can be recommended. Finally, no definitive evidence supports the use of platelet rich plasma regarding improvement of healing rates after rotator cuff repair therefore routine use is not currently recommended. Further research is required to identify effective biologically directed augments that will improve healing rates and clinical outcomes after rotator cuff repair.

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P- Reviewer: Drosos GI, Teresa Valenti M **S- Editor**: Song XX
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World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i2.221

World J Orthop 2015 March 18; 6(2): 221-235
ISSN 2218-5836 (online)

REVIEW

Fractal lacunarity of trabecular bone and magnetic resonance imaging: New perspectives for osteoporotic fracture risk assessment

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Author contributions: Zaia A designed and performed the study, analyzed data, designed and wrote the paper.
Conflict-of-interest: The author has no conflict of interest to report.

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Received: June 18, 2014
Peer-review started: June 19, 2014
First decision: July 10, 2014
Revised: November 5, 2014
Accepted: December 16, 2014
Article in press: December 17, 2014
Published online: March 18, 2015

Abstract

Osteoporosis represents one major health condition for our growing elderly population. It accounts for severe morbidity and increased mortality in postmenopausal women and it is becoming an emerging health concern even in aging men. Screening of the population at risk for bone degeneration and treatment assessment of osteoporotic patients to prevent bone fragility fractures represent useful tools to improve quality of life in the elderly and to lighten the related socio-economic impact. Bone mineral density (BMD) estimate by means of dual-energy X-ray absorptiometry is normally used in clinical practice for osteoporosis diagnosis. Nevertheless, BMD alone does not represent a good predictor of fracture risk. From a clinical point of view, bone microarchitecture seems to be an intriguing aspect to characterize bone alteration patterns in aging and pathology. The widening into clinical practice of medical imaging techniques and the impressive advances in information technologies together with enhanced capacity of power calculation have promoted proliferation of new methods to assess changes of trabecular bone architecture (TBA) during aging and osteoporosis. Magnetic resonance imaging (MRI) has recently arisen as a useful tool to measure bone structure *in vivo*. In particular, high-resolution MRI techniques have introduced new perspectives for TBA characterization by non-invasive non-ionizing methods. However, texture analysis methods have not found favor with clinicians as they produce quite a few parameters whose interpretation is difficult. The introduction in biomedical field of paradigms, such as theory of complexity, chaos, and fractals, suggests new approaches and provides innovative tools to develop computerized methods that, by producing a limited number of parameters sensitive to pathology onset and progression, would speed up their application into clinical practice. Complexity of living beings and fractality of several physio-anatomic structures suggest fractal analysis as a promising approach to quantify morpho-functional changes in both aging and pathology. In this particular context, fractal lacunarity seems to be the proper tool to characterize TBA texture as it is able to describe both discontinuity of bone network and sizes of bone marrow spaces, whose changes are an index of bone fracture risk. In this paper, an original method of MRI texture analysis, based on TBA fractal lacunarity is described and discussed in the light of new perspectives for early diagnosis of osteoporotic fractures.

Key words: Osteoporosis; Fracture risk; Trabecular bone microarchitecture; Fractal analysis; Fractal lacunarity

Core tip: High-resolution magnetic resonance imaging emerges as a useful tool for *in vivo* characterization of trabecular bone architecture (TBA). However, texture analysis is not frequently used as the large number of calculated parameters makes difficult their interpretation. Dealing with complexity and fractal properties of living beings, it is possible to quantify morpho-functional changes in aging and pathology with a limited number of parameters. In this context, fractal lacunarity appears the most suitable approach to TBA texture analysis as it describes discontinuity of bone network and sizes of bone marrow spaces, changes of which are an index of increased fracture risk.

Zaia A. Fractal lacunarity of trabecular bone and magnetic resonance imaging: New perspectives for osteoporotic fracture risk assessment. *World J Orthop* 2015; 6(2): 221-235 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/221.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.221

INTRODUCTION

Osteoporosis represents one major health condition for our growing elderly population[1,2]. It accounts for severe morbidity and increased mortality in postmenopausal women and it is becoming an emerging health concern even in aging men[3-5].

Despite a lack of well-known critical hormonal changes, responsible for a fast degenerative action on bone tissue[2,6], the male structure undergoes a slow progressive loss of bone mass and the risk of being affected by osteoporosis in late age is increasing even in men[7-9]. Nevertheless, perimenopausal female population still now shows the highest risk of early osteoporosis onset. The increased lifespan in the industrialized world accounts for the increasing incidence of osteoporosis and bone fractures with a perspective of additional years (at least 20) of disability osteoporotic women have to face in their later life.

Osteoporosis, as defined by World Health Organization, is a systemic disease of the skeleton characterized by low bone mineral density (BMD), and microarchitectural deterioration of bone tissue with consequent increased bone fragility that predisposes to fracture risk. Due to the silent progression of bone structure degeneration, osteoporosis diagnosis often follows a painful fracture event. To date, only a small percentage of individuals have been known to be osteoporotic while the condition of most pathologic people had remained undiagnosed until a fracture occurs[10-12]. It is worth noting that the first fracture event increases the risk and accelerates the onset of new ones[13].

Screening of the population at risk for bone degenerative processes and treatment of osteoporotic patients to prevent or reduce bone fragility fractures would improve quality of life in aging people. Early diagnosis of bone deterioration by tools sensitive to osteoporosis onset and progression would represent a promising approach to prevent disability and reduce mortality in osteoporotic patients.

OSTEOPOROSIS AND MEDICAL IMAGING

BMD estimate by means of dual-energy X-ray absorptiometry (DXA) is normally used in clinical practice for osteoporosis diagnosis. BMD alone, however, has been found to be not a good predictor for fracture risk[14]. Recently, detection of BMD by means of ultrasound techniques has been obtaining more attention as a possible less invasive diagnostic tool for bone degenerative disorders. At present, echographic investigation in clinical practice remains the "alternative" way to assess bone mass only in those subjects who cannot undergo X-ray irradiations. Quantitative ultrasound (QUS) detection of bone degeneration is becoming ever more promising and potentially useful mainly in screening studies[15]. This method, in fact, offers advantages over X-ray-based techniques, including low cost, portability, and non-ionizing radiation exposure[16-18]. In addition, it is known that ultrasound transmission depends not only on mineral content, but also on biomechanical properties of the bone, thus providing extremely useful information about bone structure properties. As a matter of fact, several studies have highlighted that bone parameters measured by QUS provide information about fracture risk independent of BMD[19-22].

The incidence of bone fractures is not always correlated to diminished BMD[23]. In fact, too high of a mineral content could predispose to a higher risk of bone fractures, probably due to an increased rigidity of the structure. Moreover, pharmacological treatment with agents acting by preventing and/or reducing bone loss is not always able to reduce bone fracture risk[24]. Bone microarchitecture has been found to be a determinant of bone fragility independent of bone density, thus representing an interesting aspect of bone strength to give insight into patterns of bone degenerative processes in both aging and osteoporosis. From a clinical point of view, understanding the role microarchitecture plays in the mechanisms of bone fragility as well as in the action of drugs to prevent fractures would improve clinical management of osteoporotic pathology[25].

For a long time, the unique font of information about bone microarchitecture in humans had been coming from studies on biopsies of bone tissue from autoptic samples.

In the last few decades, the impressive diffusion into clinical practice of medical imaging techniques has opened up new perspectives to characterize bone

structure *in vivo*. The rapid development of information technology together with advances in power calculation capacity has solicited proliferation of different new methods to assess bone microarchitecture changes with aging and pathology.

Several processing methods have been reported as suitable tools to quantify bone tissue in both classical sites at high risk of fracture, such as spine and femur head, and mirror sites, such as calcaneus, tibia, and radius[26,27]. Most of them uses axial radiographic images[28,29] or computer tomography, CT, projections[30] to *in vivo* characterize trabecular bone architecture (TBA).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has recently emerged as a suitable tool to measure trabecular bone structure *in vivo*[31]. In particular, MRI-based diagnosis of TBA deterioration could be used to complement standard BMD-DXA measurement for assessing osteoporosis onset and progression.

Several aspects of this technology, in fact, candidate MRI as a non-invasive, non-ionizing tool for *in vivo* study of bone tissue in human beings[32]. MRI is based on the interaction between a high-gradient magnetic field, radiofrequency pulse transmission, and protons in the tissues under investigation. Most clinical MRI systems have field strengths of 1.5 T, 3.0 T being quite rare. Bone tissue contains few mobile water and fat protons and appears as low signal intensity (hypointense) on MRI. Bone marrow, on the other hand, has abundant fat and water protons and appears as high signal intensity (hyperintense). Hypointense cortical and trabecular bone appear sharply outlined against hyperintense bone marrow and juxtacortical fat. High field strengths and improved coil technology have made it possible to achieve an in-plane resolution of about 150 μm[33]. However, because of current signal-to-noise constraints, minimal slice thickness is usually about 500 μm[34]. Although this resolution is larger than trabecular thickness, trabecular spacing (800-1000 μm) is still much larger than the size of a single MR voxel, so that trabecular parameters can be reasonably measured or estimated with MRI.

MR-derived structural dimensions are similar, but not identical, to histological or micro-computed tomography (CT) dimensions and a two-dimensional rather than three-dimensional approach is applied[34,35]. A magnetic susceptibility difference of about 3 ppm existing between bone and marrow leads to signal dampening at the bone-marrow interface and, as a result, an artificial overestimation of trabecular dimension occurs. This artefact, known as trabecular broadening, is responsible for an apparent increase in trabecular thickness that vary with pulse sequence applied and field strength[36]. MR pulse sequence strongly affects MR susceptibility artefact but it is not clear yet which pulse sequence is the best for trabecular bone imaging[37,38]. Interestingly, trabecular broadening is potentially advantageous to MRI since it enables visualization of small trabeculae that would not normally be seen due to partial volume effect. Most researchers currently use either gradient-echo or spin-echo imaging. Spin-echo technique has the advantage to reduce trabecular broadening artefact[38,39].

Trabecular structural parameters measured with 3.0 T are better defined than those at 1.5 T using micro-CT as a reference standard. Although correlations between 3.0 T and micro-CT are better than 1.5 T, increased trabecular broadening has been observed at 3.0 T due to an increase in susceptibility effect[36].

High correlation has been found also for trabecular number and spacing by comparing 3.0 T MR and high resolution pQCT. Histomorphometry and other different structural analysis techniques applied to both modalities provide different absolute values but high correlation ($r > 0.8$) for all bone structure parameters[34].

Micro-MR units with special high-field-strength (7 T, 11 T or higher) are used in experimental settings to obtain high-resolution MR images of small animals *in vivo* or bone specimens *in vitro*. Images obtained at about 90 μm yield TBA scalar parameters similar to those obtained with histomorphometry methods[40,41].

MRI AND CLINICAL ASSESSMENT OF BONE STRUCTURE

A recent review of osteoporosis imaging literature highlights that high-resolution MRI quantification of TBA deals with two different aspects of osteoporosis assessment: prevalence and incidence of osteoporotic fractures and TBA response to drug therapies. Early studies suggest that trabecular parameters as measured on MR images are able to separate patients with and without osteoporotic fractures better than BMD[42,43]. These two groups are better characterized by indices that quantify trabecular shape transformation from plate-like to rod-like by using structural model index method or plate-to-rod ratio method. Also finite element model produces good results. However, classic morphometric parameters such as bone volume fraction (BV/TV), trabecular number (Tb.N), and trabecular thickness (Tb.Th) show best results when compared to BMD[32,44].

Measuring the effect of drug therapies for osteoporosis, incidence of bone fragility fractures represents a crucial point as its assessment requires much time. BMD has then become the best single surrogate marker of bone strength. Nevertheless, it is widely demonstrated that BMD presents severe limitations. As a matter of fact, in the MORE study, including 7700 women treated with raloxifene, a 40% reduction of fracture risk has been highlighted with only 4% associated to increased BMD[45].

TBA parameters from MRI would monitor changes induced by antiresorptive therapies better than BMD. TBA analysis by using MRI has been demonstrated to be more sensitive than BMD even in monitoring several therapeutic effects: salmon calcitonin in different skeleton sites[46] testosterone at distal tibia[47]; alendronate in peripheral districts[48]. By comparing CT and MRI[32,49], CT has the advantage to visualize bone tissue with a higher space resolution while has the disadvantage to high doses of radiation when applied to central skeleton districts such as vertebras and femur neck, the two best sites to estimate fracture risk in primitive (postmenopausal and senile) osteoporosis. MRI with high field modalities (3, 7 T, and higher) have been introduced to significantly improve signal-to-noise resolution of the image; nevertheless, higher field strengths also increase magnetic susceptibility induced effects responsible for alterations in bone structure parameters[34,50]. However, bone structural parameters measured by means of MRI techniques have been widely correlated to *in vitro* histological ones. Therefore, MRI emerges as a promising non-invasive non-ionizing tool for *in vivo* characterization of TBA potentially useful in early diagnosis of fracture risk in osteoporosis. Its adoption and diffusion in clinical practice are limited because of texture analysis, mainly based on methods producing a set of numerous calculated parameters that make difficult their interpretation[51]. Most methods, in fact, are based on classical histomorphometric techniques that provide for a large number of measurements (up to 25) to be analyzed[51,52]. A promising MRI-based approach to define bone structure uses wavelet techniques[53]. Wavelet analysis is generally applied in functional medical imaging and finds successful application with MRI[54]. Several applications of wavelet techniques for texture analysis of different biological structures have been already described[55,56]. Attempts to reduce computational charge and speed up the methods are still under study; however, the time-cost remains too high for a routine application in clinical practice[55].

Recently, a method of MR image analysis has been proposed to provide a limited number of parameters sensitive to bone microarchitecture changes in aging and pathology[57-59]. The method has been developed taking into account biocomplexity of human beings and fractal properties of many physio-anatomic structures[60-66] and it is the result of a proper combination of image acquisition, texture analysis, and mathematical solution to the study of TBA.

A NEW APPROACH TO THE STUDY OF TRABECULAR BONE ARCHITECTURE

The introduction in biomedical field of paradigms, such as theory of complexity, chaos and fractals, suggests new approaches and provides innovative tools to the study of morpho-functional degenerative processes with aging and age-related pathologies, among is osteoporosis[61,65,67-72]. Combining biocomplexity analysis tools together with advanced techniques of image processing and image analysis, it is possible to develop computerized methods able to provide e limited number of parameters sensitive to age-related changes as well as to pathology onset and progression[65,66].

Recently, an original method of TBA analysis has been developed able to draw out one numerical index sensitive to physio-pathologic changes of the structure. The basic idea to build such a method stems from the complexity of living being and fractal nature of many physio-anatomic structures[31]. Several structures and functions of human body have got fractal properties[62,72,73]. Trabecular bone, in addition to be a good model for fractal analysis in biological structures, offers the opportunity of analyzing fractal lacunarity[74]. In this particular context, fractal lacunarity analysis appears the most suitable approach to define trabecular bone network. Fractal lacunarity, in fact, by measuring space-filling capacity of a complex object, has the potential to describe both bone network discontinuity and sizes of trabecular spaces (bone marrow), whose changes represent an index of increased bone fracture risk.

The method has been developed on MR images of lumbar vertebras. Spin-echo technique has been used to visualize the trabecular structure in the inner portion of vertebral body. The procedure adopted to set up the standard version of the method is described and discussed hereinafter and is schematically represented in Figure 1. It provides for fractal lacunarity analysis in a region of interest (ROI) after a pre-processing of the image to optimize trabecular network visualization. The parametric characterization of curvilinear graph, result of fractal analysis, is calculated by using our original bio-mathematical model based on hyperbola function model. In fact, hyperbola formula contains three coefficients (α, β, γ) that represent our suitable numerical indices, where α correlate with the fractal dimension, and β, related to the concavity, characterizes the lacunarity. The result is a triplet of parameters (α^* β^* γ^*) that univocally characterizes any single TBA analyzed[57,58].

Application of the method to several TBA from 25 female subjects with different age and physio-pathologic status (4 young, 5 pre-menopause, 6 post-menopause, 10 osteoporotic with an age-range of 31-37, 42-52, 51-81, and 59-75 respectively) has highlighted that, among the three coefficients, parameter β is particularly sensitive to both age and physio-pathologic changes. In particular, parameter β correlates with physio-pathologic status and assumes decreasing values from healthy young to perimenopausal to osteoporotic patients. Results also show that parameter β is statistically different (probability significance value $P \leqslant 0.5$ for Student-

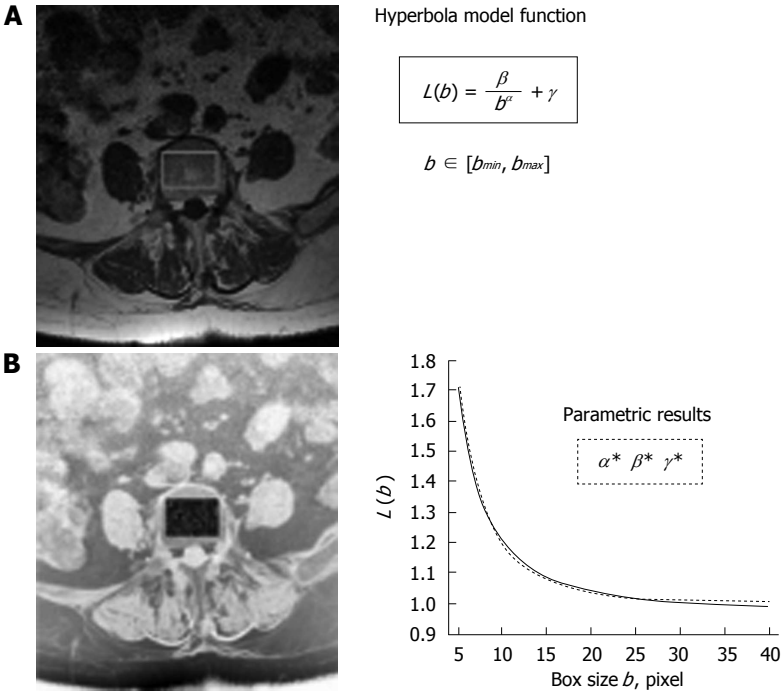

Figure 1 Schematic representation of fractal lacunarity analysis. A: 1.5 T MRI spin-echo image (512 × 512 pixel, pixel size equal to 0.469 mm) of fifth axial section of lumbar vertebra; B: Rectangular ROI within the inner perimeter of vertebral body in a intermediate step of binarization procedure on the reverse gray-scale image. The plot (right bottom) represents the result of gliding box algorithm application (dotted line) as fitted by hyperbola function (solid line) used to calculate the triplet of parameters α, β, γ. MRI: Magnetic resonance imaging; ROI: Region of interest.

Newman-Keuls multiple range test) in the three classes of TBA considered (healthy young, perimenopausal, and osteoporotic)[57,58]. A correlation between parameter β and age can also be observed with a decreasing trend of β values from young to old subjects[58]. It has to point out that the healthy old subject (in this context without clinical signs of osteoporosis) shows a β value higher than the younger osteoporotic patients. This evidence candidates parameter β as a standard for TBA characterization as well as an index of structure integrity, potentially predictive of bone fracture risk. Low values of β correspond to a decreased structural integrity linked to increased fracture risk[57,58,65].

Results from the application of three software prototype versions[57-59,66], differing in the pre-processing step, on the same set of TBA images confirm the potentiality of the proposed bio-mathematic model. Note that in Zaia *et al*[57,58] this method has been presented for binary images arising from a pre-processing step of image I by using image J program. The simple extension considered[58,59] can be used also for gray-scale images. The efficiency of such an extension is usually improved by a different pre-processing step through a sigmoid function (Figure 2). In particular, sigmoid function operates a sort of rescaling of gray tones by weighting the gray level of each single pixel: this procedure allows limiting information loss due to binarization procedure[59,66].

Figure 3 shows comparison of results from the first version of the algorithm, (described hereinafter) developed to work on binary images (black/white) obtained by pre-processing original gray-scale MR images in a different computational environment[57,58], and version 2 where the algorithm has been improved to directly work on original gray-scale images in a unique computational environment[66]. In both cases correlation of parameter β with both age and physio-pathologic changes is confirmed. It is worth noting that a fixed pair of values for parameters k and σ has been chosen such that for the triplet of coefficients α, β, γ, from lacunarity analysis we obtain results comparable with those of the previous studies[57,58]. In particular, k equal to 7 and σ equal to 0.7 have been used to obtain results reported in Figure 3. This procedure increases the sensitivity of the method as suggested by the large range of values parameter β can assume when compared with those from black/white version.

When version 2 of the method, more sensitive than the first one, is applied to a larger sample size (59 female subjects: 13 young, 17 pre-menopause, 14 post-menopause, 15 osteoporotic with an age-range of 23-39, 40-52, 50-81, and 57-78 respectively), a certain degree of overlapping of β values in osteoporotic and non-osteoporotic subjects can be observed (Figure 4). These results confirm the scientific evidence that TBA can represent a predictor of fracture risk independent of BMD.

Version 3 of the software prototype always works on original gray-scale images but, by omitting gray-scale inversion and introducing a different analysis of pixel gray levels by sigmoid function, allows

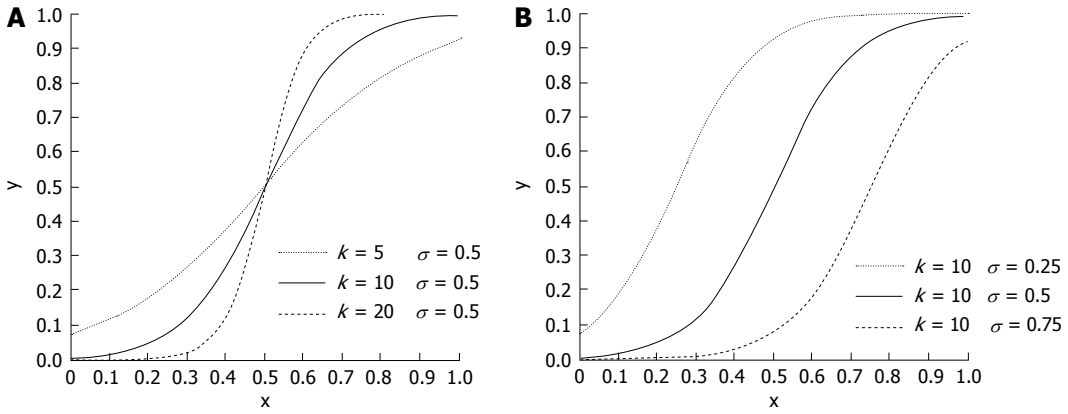

Figure 2 Representation of sigmoid function for different choices of parameters *k*, σ. A: Sigmoid graph obtained by varying values of parameter *k*; B: Graph obtained by varying values of parameter σ. This new pre-processing step prescribes to consider image J, in place of image I, where the pixels are defined as follows: $J(i, j) = 1/1 + \exp(-k\ (I(I,j) - \sigma))$, $i = 1,2,...M$, $j = 1,2,...N$, and k, $\sigma > 0$ are two given parameters. Note that the procedure goes toward a complete binarization by increasing parameter *k*, related to sigmoid rectangularization.

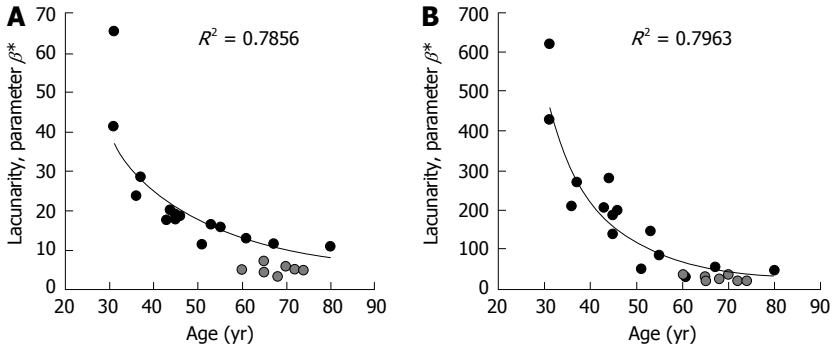

Figure 3 Representation of trabecular bone architecture changes with aging and osteoporosis from lacunarity texture analysis on binary and gray-scale images. Results are expressed as parameter β calculated on the same set of original images with two different software prototype versions: A: On binary images after a pre-processing step in a different computational environment; B: Directly applied to original gray-scale images. Black circles represent TBA lacunarity in non-osteoporotic subjects of different age. Gray circles represent TBA in osteoporosis (BMD-based diagnosis). Decreasing values of parameter β correspond to increasing lacunarity related to a higher microarchitecture deterioration. TBA: Trabecular bone architecture; BMD: Bone mineral density.

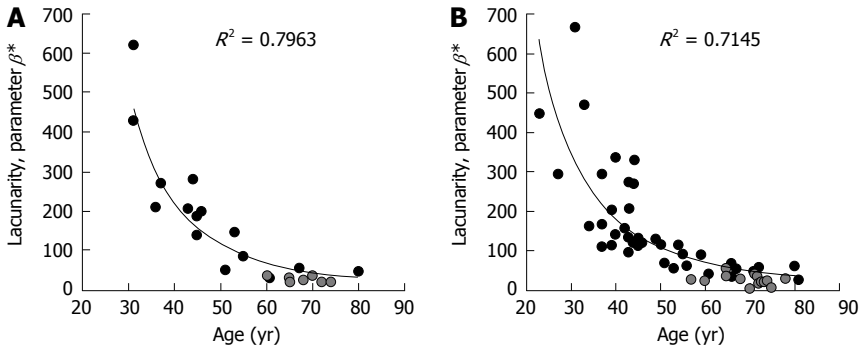

Figure 4 Effect of sample size on trabecular bone architecture changes with aging and osteoporosis. Results are expressed as parameter β calculated from lacunarity texture analysis with gray-scale version 2 of the method. Larger sample size (B) of 59 subjects comprises the smaller one (A). Black circles represent TBA lacunarity in non-osteoporotic subjects of different age. Gray circles represent TBA in osteoporosis (BMD-based diagnosis). Decreasing values of parameter β correspond to increasing lacunarity related to a higher microarchitecture deterioration. Overlapping of data from osteoporotic and "healthy" subjects (BMD-based diagnosis) stresses that TBA represents a determinant of bone fragility independent on BMD. TBA: Trabecular bone architecture; BMD: Bone mineral density.

correlating parameter β directly to fracture risk: that is, increasing β values correspond to increased TBA deterioration, index of increased fracture risk[59]. Lacunarity β values, shown in Figure 5, are such that a clear age-related healthy status trend can be drawn, osteoporotic-related values being much higher. In this case, parameter β ranges within a larger set of values and makes the method much more sensitive, such that it identifies three different clusters of values that can be related to three different levels of structural

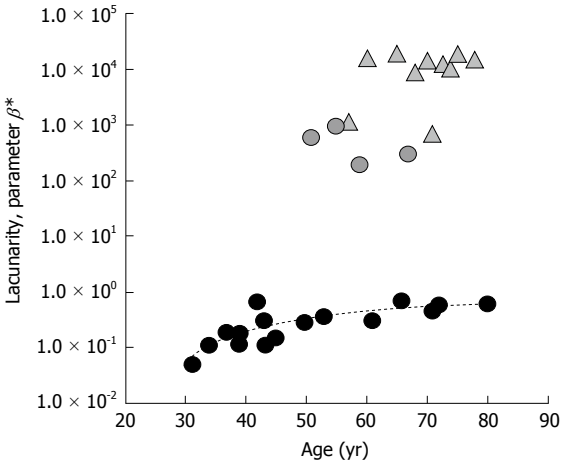

Figure 5 Results from trabecular bone architecture texture lacunarity analysis of magnetic resonance images with version 3 of the method. Lacunarity of TBA from 30 subjects differing in age and physio-pathologic status is expressed by parameter β. Circles: age-related alteration of TBA in "healthy" subjects; Triangles: pathologic-related changes of TBA in osteoporotic BMD-based diagnosis subjects. Parameter β values directly correlate with fracture risk. TBA: Trabecular bone architecture; BMD: Bone mineral density.

integrity: a lower cluster corresponding to healthy status (low fracture risk); a higher one corresponding to osteoporotic status (high fracture risk); an intermediate one where pathologic and non-pathologic subjects are mixed and can be associated to a similar fracture risk (Figure 5). Once again, it is stressed that TBA could predict fracture risk better than BMD alone. Note that four out of ten menopausal subjects show β values similar to the lowest osteoporotic ones. This intriguing observation suggests that these menopausal subjects could have a high risk of pathology onset while the osteoporotic patients could have a lower fracture risk than the other osteoporotic ones. Further studies enrolling a large number of subjects differing for both age and healthy status need to support this hypothesis.

From these preliminary studies, the proposed method emerges as a potential diagnostic tool for an improved characterization of osteoporotic pathology useful in early diagnosis of bone fragility fractures as well as in the assessment of therapy efficacy in preventing or decreasing fracture risk.

The methodological approach adopted to characterize TBA texture is highly innovative at both clinical and technological levels. The result from the proposed original mathematical solution is a triplet of parameters (α, β, γ); parameter β, particularly sensitive to TBA physio-pathologic alterations, emerges as a potential standard for TBA characterization as well as a parametric index for a best clinical management of osteoporosis[65].

The improved versions of the method, based on gray-scale texture analysis, has the advantage of being directly applicable to original trabecular bone MR images by working in a unique computational environment[59,66]. These easier and faster versions of the method would speed up its application in both research and clinical practice.

OUTLINE OF THE METHOD

The method for TBA texture characterization by lacunarity analysis is made up on three main steps: image acquisition by MRI spin-echo multislice technique; image processing of vertebral axial images to produce a binary representation of trabecular bone structure; quantitative lacunarity analysis of trabecular network by hyperbola model function approximation of the graph produced by gliding box technique (Figure 1). The method has been developed on real images to avoid surprises during clinical application. In fact, often it happens that methods built up on simulation models fail when applied to real clinical images. The procedure adopted to set up the method, described in Zaia *et al*[57,58] is reported and discussed below.

MR images acquisition

Lumbar vertebras images were obtained by means of a standard clinical MRI system (1.5 T whole-body imaging system-Gyroscan Intera; Philips Medical System, ACR-Nema 1.0). Spin-echo multislice technique was applied to acquired a set of 9 axial vertebral images (512 × 512 pixels, pixel dimension equal to 0.469 mm) once the fourth lumbar vertebra (L4) is spotted (Figure 6). Clinical application of spin-echo multislice technique is still quite rare; therefore, vertebral axial section images were obtained on purpose from female patients underwent MR assessment for injuries of the column. Twenty-five subjects were enrolled in this study and classified as follows: 4 healthy young (mean age 33.7 years, age range 31-37); 10 perimenopausal (mean age 51.7 years, age range 43-65); 10 osteoporotic, on the base of classical BMD-DXA diagnosis (mean age 68.4 years, age range 64-74); 1 "healthy" 80 years old woman, in this case without clinical signs of osteoporotic pathology.

Image processing and analysis of MR images

MRI spin-echo data set of lumbar vertebras was transferred to a personal computer for image texture analysis. The middle axial image of L4 was considered to build the method. Two main considerations solicited the choice of the fifth axial section image. A certain degree of both inter and intra-vertebral heterogeneity had to be expected; therefore, only one L4 section, namely the fifth one was considered to set up the method. This choice makes easier to compare results from different subjects. In addition, limiting analysis procedures to one image only would save time and facilitate technological transfer of the method into clinical practice. The goodness of this choice is supported by results from a pilot study: a certain degree of variability among the sections was observed in any data set produced by the application

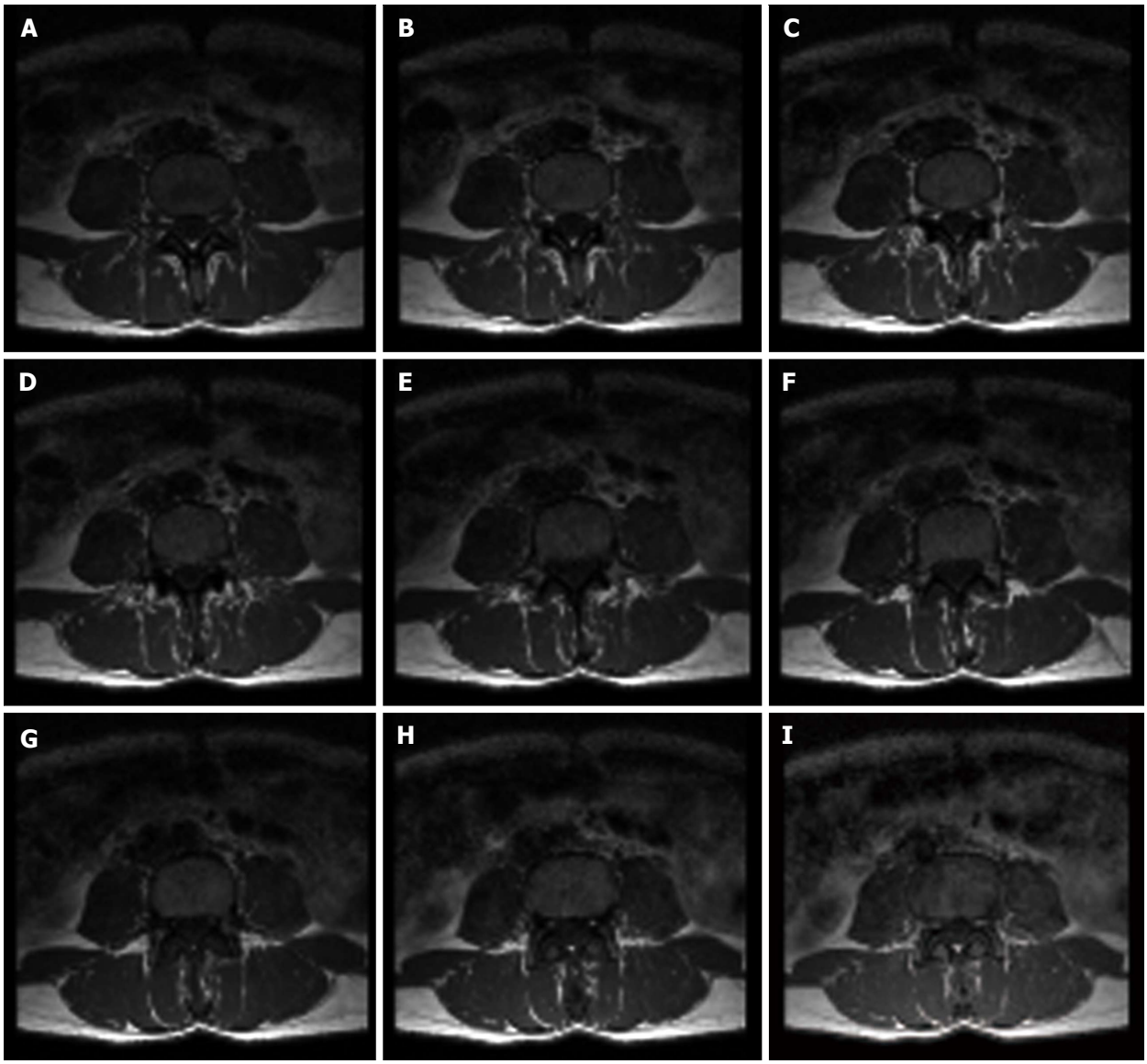

Figure 6 Set of images from magnetic resonance imaging spin-echo. Nine axial images of the fourth lumbar vertebra obtained by magnetic resonance imaging multislice technique. Acquisition of the set of axial images of vertebral body to visualize the inner trabecular bone portion is performed from bottom (A: lower base) to top (I: upper base).

of the method to the whole set of axial images of different vertebras. It is worth noting that the fifth section of any vertebra considered generally displayed intermediate values.

The algorithm for TBA characterization was developed on images pre-processed as described in Boutry *et al*[51] in a different computational environment by using ImageJ (version 1.26t), a software for image processing and image analysis available for free on the web. This pre-processing step, briefly described in Figure 7, generates a binary representation of TBA where the black regions represent bone marrow and the white ones represent bone. This binarization scheme has the advantage of keeping and/or excluding the "false-positive finding" of trabeculae in the black regions as well as of removing residual small artefacts.

Estimate of fractal lacunarity

Gliding box algorithm, GBA, is the most popular among the definitions and calculating procedures proposed to estimate lacunarity[75]. It is based on the analysis of mass distribution in the set and involves the variance of box mass, M, at each step, wherein the box is moved one by one space unit. A frequency distribution of box masses, $n(M,b)$, where b is the size of the gliding box, is produced by recounting the box mass throughout the whole region.

It is possible to consider only a discrete frequency distribution $n(M_j,b)$, $j=1,2,\ldots,\mu(b)$ by assuming that, for each b, only a finite number of masses M_j, $j=1,2,\ldots,\mu(b)$ are found in the various gliding boxes of size b. It is worth noting that this assumption is true for binary images, where the mass of a generic

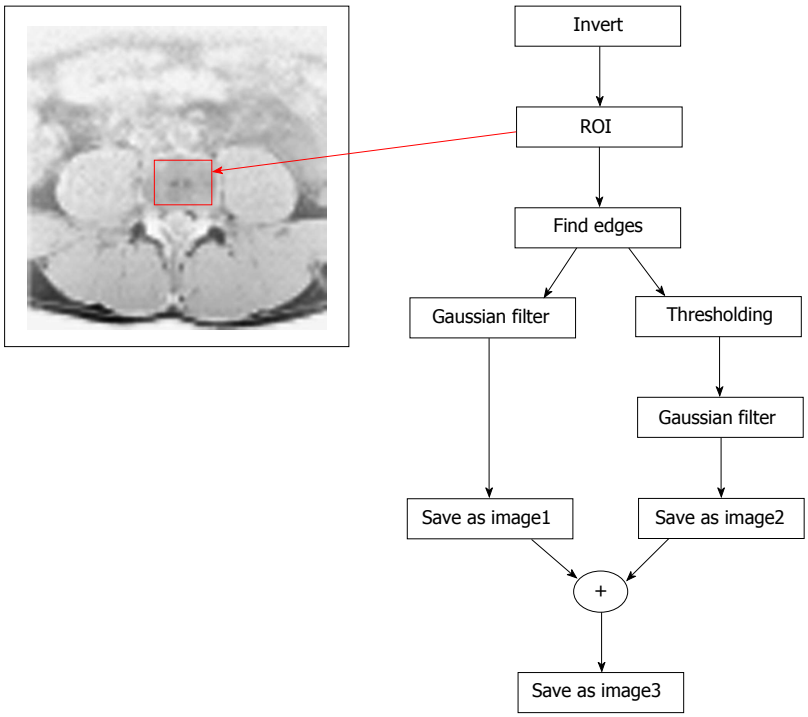

Figure 7 Schematic representation of the pre-processing step of magnetic resonance images with image J program used in trabecular bone architecture lacunarity analysis method-version1. Reverse grey-scale display of original images is used to ease visualization of trabecular network, a rectangular ROI is chosen as large as possible to fit the inner perimeter of trabecular bone. The boundary between cortical bone and soft-tissue background is defined by using an automatic contour detection algorithm. Trabecular bone is then extracted from bone marrow by using a Gaussian filter. This scheme generates a binary representation of the trabecular structure in which the dark regions represent bone marrow and the light regions represent bone. The Gaussian filter is applied first to the original ROI image and then to the thresholding one. The two resulting binary images are finally combined. ROI: Region of interest.

box on the image is given by the number of pixels associated to the value 1 in the box, that is, the white pixels. From standard arguments the moments of order q of M, through the GBA, are given by:

$$Z_q(M, b) = \frac{1}{N(b)} \sum_{j=1}^{\mu(b)} M_j^q \, n(M_j, b), \quad b > 0$$

where the division by $N(b)$ is necessary to convert $n(M_j, b)$, $j = 1, 2, \ldots, \mu(b)$ into a probability distribution. The definition of lacunarity function Λ is based on the first and the second moments of M only, that is

$$\Lambda(b) = \frac{Z_2(M, b)}{Z_1(M, b)^2}, \quad b > 0$$

The GBA method was implemented in a prototype software by using the MATLAB software package, version 6.1 (the MatWorks, Inc.). The program starts elaborating the binary image generated from the above mentioned binarization pre-processing step of MR lumbar vertebra images. It calculates lacunarity values, for each integer value of b comprised between b_{min} and b_{max}, where b_{min}, b_{max} are given integer multiples of the pixel size in the image considered. Once the lacunarity function $\Lambda(b)$ is calculated, the program displays the results as a graph.

It was observed that the curvilinear behavior of lacunarity function resembles the hyperbola one (Figure 4, plot) for all the images analyzed; therefore, the following model function:

$$L(b) = \frac{\beta}{b^{\alpha}} + \gamma, \quad b \in [b_{min}, b_{max}]$$

was chosen to approximate the curvilinear plot of lacunarity where the three coefficients α, β, γ are potential parameters to quantitatively define TBA.

Note that the theoretical behavior of lacunarity function Λ for both ideal fractals and other complex random sets further stresses this observation. In addition, for self-similar fractals parameter α is related to the fractal dimension and parameter β characterizes the fractal lacunarity of the set[75]. The best interpretation of lacunarity $\Lambda(b)$ by the hyperbola model function $L(b)$ is computed as a least squares problem solution. The three coefficients α, β, γ are the independent variables and minimizer of this problem is a triplet of parameters, $\alpha^* \beta^* \gamma^*$, of the hyperbola model function that better describes mass density variation of pixels in any image considered[57-59].

Parameter β as an estimate of lacunarity

The method was applied to different types of bone trabecular structure to test the robustness of the method. The subjects included in this study were women chosen to be representative for age and physio-pathologic status: women in their thirties were analyzed as bone loss begins approximately at that

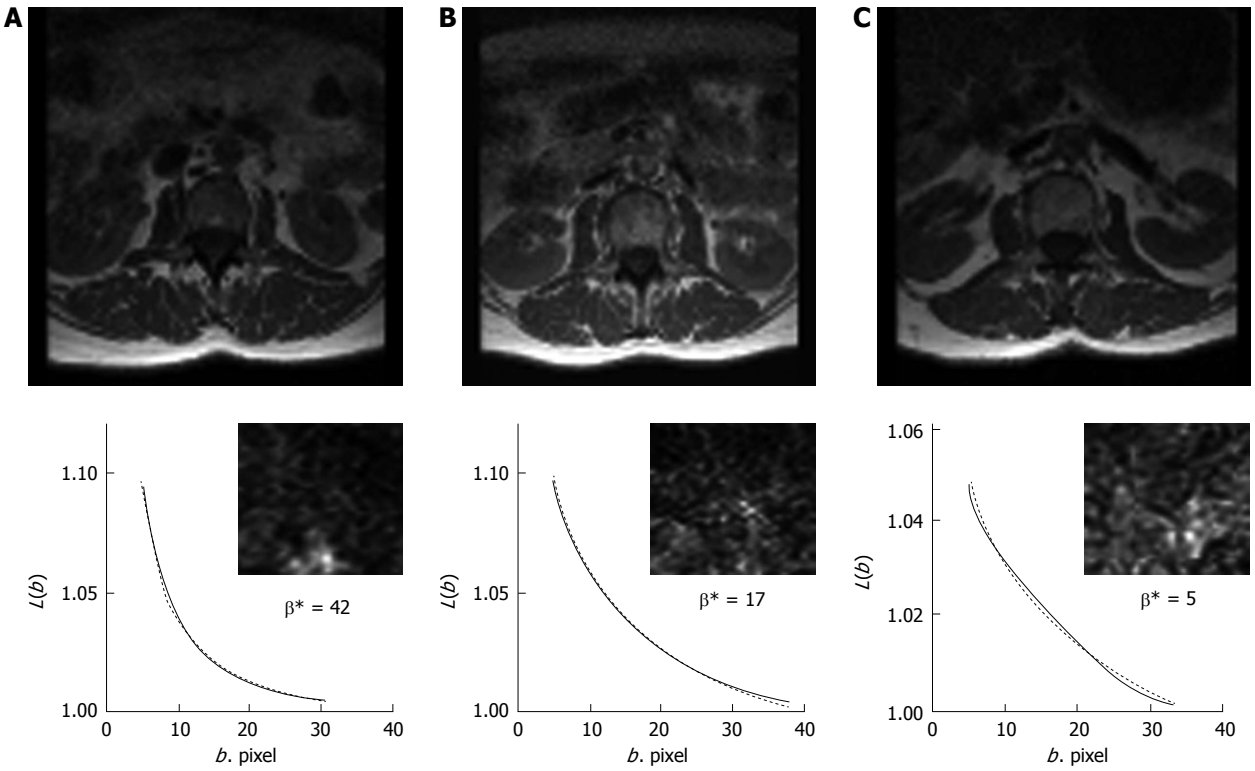

Figure 8 Example of results from lacunarity analysis of three types of trabecular bone different for age and healthy status. In the related plots, dotted lines represent the fitted hyperbola function. Goodness of the fitting represented by a almost complete overlapping of both theoric and experimental curve indicates that parametric lacunarity analysis by hyperbola model function is a proper choice. A: Young, 39s; B: Menopause, 53s; C: Osteoporosis, 74s.

age. Perimenopause subjects were also included in the study as they represent a condition characterized by a high risk of osteoporosis onset. Taking into account the possibility of a physiological aging, a healthy old woman (in this case without clinical signs of osteoporosis), was also considered. The pathologic patients were classified as osteoporotic on the basis of classical diagnosis based on BMD-DXA measurement. Application of the method to the same original image was repeated step by step for six times. Results from the fifth axial section image of L4 were obtained by fixing b_{min} equal to 5 pixels and b_{max} equal to 50% of ROI diagonal length, measured in pixels.

The three parameters ($\alpha^* \beta^* \gamma^*$) from our mathematical model define as univocal any lacunarity function, *L(b)* where α represents the order of convergence of *L(b)*, β defines the concavity of the hyperbola, and γ is the translation term on X-axis. Parameters α and γ assume quite similar small values in all bone structures analyzed while parameter β ranges within a larger set of values. A low β value defines a hyperbola function with a slight concavity (high lacunarity), whereas a high β value defines a hyperbola function with a deeper concavity (low lacunarity)[57,58] (Figure 8).

Improvements of the method are in progress to validate the goodness of lacunarity parameter β as a marker of TBA deterioration in both aging and pathology. In particular, we have been focusing on both thresholding and segmentation procedures. ROI size and shape are also under consideration to improve robustness and reliability of the method before approaching a clinical study on a large size sample of subjects at risk of bone fragility fracture.

PECULIARITY OF THE METHOD

Different potential benefits can be expected from clinical application of the above described method to assess osteoporotic fracture risk. First of all, it has been built on vertebral images. From comparative studies dealing with structural analysis in different sites, such as distal radius, calcaneus, and spine, or even in minor sites such as wrist or finger, spine represents the best site to early predict bone fragility fracture status[76]. Second, the method uses MRI system to acquire axial section images of the fourth lumbar vertebra, described as the best site to assess osteoporosis. MRI has been reported as ideally appropriate for TB texture analysis. In fact, MRI spin-echo scans of TB, where bone marrow appears with uniform hyperintense signal while bone has low background intensity, generate a binary tomographic system that simplifies TB network thresholding. Furthermore, using spin-echo technique to obtain axial sections of TB allows avoiding imaging artefacts of trabecular enlargement as it occurs with gradient-echo[51].

Fractal lacunarity analysis of TBA represents the most intriguing benefit of the proposed method. In fact, fractal analysis has been becoming a common tool to quantify TBA complexity; however, only fractal dimension is applied and generally measured by the Hmean parameter[26,28,51]. As mentioned above, fractal lacunarity appears the most suitable tool to analyze TB texture as it has the potential to describe both bone network discontinuity and sizes of trabecular spaces, changes of which are an index of increased bone fragility[58]. In addition, dealing with lacunarity analysis as a more general approach to analyze complex patterns with or without fractal properties[75,77,78], it allows overcoming biomedical limits of fractal analysis, responsible for misinterpretation if neglected. Lacunarity analysis of TB in human vertebras has been previously described only for micro-radiography and CT images of bioptic specimens[79,80]. Fractal lacunarity analysis of TB in MR spin-echo images of the vertebra, therefore, represents an original application of a non-ionizing, non-invasive method to assess TBA[57,58]. A MRI-based method to *in vivo* assess osteoporosis in men has been also proposed[51]. It is based on the gradient-echo technique, less precise than spin-echo[38,39], to acquire sagittal images of the calcaneus. Dealing with clinical application of medical imaging techniques to assess osteoporosis, the choice of mirror sites, such as the calcaneus, is justified only for invasive/ionizing methods. Furthermore, histomorphometric methods are used for texture analysis of TB in the cited study[51]: the result is a set of 20 parameters, 13 of which reported as significantly different in osteoporotic patients. In the last decades, a lot of studies have been performed in both central and mirror sites with different image acquisition techniques. Most of them always propose histomorphometric-based methods alone or combined with other methods for TB texture analysis, among are anisotropy, co-occurrence, gradient matrices, gray level histogram, and runlength[81,82]. All of them provide quite a few parameters to be checked and analyzed thus limiting their application in clinical practice. As a matter of fact, 8 parameters of 32 calculated in[29] and 9 of 24 in[52] have been reported as featuring TBA changes.

This observation highlights the last, but not least, advantage of the method, that is the result: a triplet of values, α^*, β^*, γ^*, corresponding to the three coefficients (α, β, γ) of the hyperbola model function which univocally characterize each single TBA pattern considered[57,58]. Among the three coefficients, parameter β, being highly sensitive to TBA changes with aging and pathology, is potentially candidate as a standard for TBA assessment and a parametric index useful in early diagnosis of osteoporosis and therapeutic assessment to prevent bone fracture risk[57-59,65].

DISCUSSION

Several clinical studies support the evidence that MRI-derived measurements of TBA are able to describe changes in both aging and pathologic status, and can discriminate patients with vertebral or hip fractures from fracture free individuals; the best featuring of patients with or without bone fragility fractures is achieved by combining structural parameters and BMD measurements. Nevertheless, very few data are available in literature on treatment-related changes of TBA, and no prospective studies can be found dealing with fracture risk prediction. Prospective studies on osteoporotic fractures on large scale therapeutic trials are necessary to give insight into the role of *in vivo* assessment of TBA. These studies are beneficial to define a set of diagnostic markers able to complement or improve fracture risk diagnosis based on BMD-DXA[83-85]. They would also give insights into the search for therapeutical approaches, such as antiresorptive drugs or fracture healing agents, more effective in preventing and/or curing osteoporotic bone fractures[24,86-89]. It is worth noting that Canadian Guidelines for the assessment of fracture risk in osteoporosis have been recently updated by introducing bone quality estimate[90] and last generation DXA devices start to be equipped with software for bone quality assessment[91-94]. Main obstacles to reach this goal are represented by limited technology dissemination in healthcare centers, a minimum standardization of protocols for image acquisition and processing, the number of parameters to characterize TBA. As a matter of fact, one most recent longitudinal study on alendronate therapy[48] uses a 3T-MRI system for image acquisition of peripheral bone districts such as distal tibia, distal radius, and proximal femur. The parameters measured to characterize TBA include BV/TV, Tb.N, Tb.Sp, Tb.Th, and seven parameters from topologic geodesic analysis (GTA). Only four GTA parameters and apparent Tb.N result significantly modified after 24 mo treatment in distal tibia when compared to BMD.

Efforts have been done for calibration and standardization; however, comparative multicentric studies are necessary to lay the bases for future multicentric clinical trials and prospective studies. These goals appear ever more unreachable dealing with the proposed methodologies, ever more sophisticate and developed without taking into account feasibility of their application in clinical practice. As the result, in 2013 we still find clinical studies on TBA characterization performed on bioptic specimens and analyzed by quantitative histomorphometric method in micro-CT images[95].

CT techniques represent a precious contribution to the knowledge of bone mechanical properties useful for a more precise evaluation of fracture risk. Studies on CT applications in this context are in

progress but they can be performed only in research centers as they require highly qualified personnel and sophisticated software and hardware systems. Diffusion of CT techniques into clinical practice is further limited by high dose irradiation when compared to DXA.

Many advantages can be obtained by widening MRI role in the assessment of bone fragility. MRI is a non-invasive/non-ionizing method that allows defining bone tissue structure *in vivo*. MRI data set acquisition can be performed in different arbitrary axes with an image acquisition time as quick as 10-15 min. Impressive advances in the development of MRI techniques to assess bone fragility have been done over the last few decades. Further progress has to be expected with improved image-processing and image-analysis methods. The advent of new high-resolution imaging techniques has introduced new stimuli to the study of bone tissue microarchitecture as it has been possible to overcome the limit of bi-dimensional analysis belonging to conventional techniques. The intrinsic three-dimensional nature of new instruments has allowed visualizing and analyzing bone specimens directly in 3D although this progress has not been associated with a proper standardization of investigated parameters. Frequently, classic histological indices have been simply mimicked or adapted, so that the new indices introduced and tested for new methodologies result inadequate for an exhaustive description of bone trabecular tissue structure and properties. New high-resolution MRI methods recently proposed to characterize TBA require ever more powerful and sophisticate instruments with high field strength modalities (3 T, 7 T, or 11 T) for both bi- and three-dimensional characterization of TBA and, once again, are based on classical histomorphometric analysis in peripheral bone districts[32,96,97]. It depends on the choice of micro-CT as the gold standard, thus alienating the introduction in clinical practice of non-invasive non-ionizing tools[98], even though promising.

The original and innovative method described, based on fractal lacunarity of vertebral TBA, appears particularly promising. The method uses images acquired by 1.5 T-MRI system, widely disseminated in most healthcare centers, and provides only one parameter highly sensitive to TBA changes thus representing a suitable method for an easy and fast applicability into both research and clinical practice. Currently, a study for clinical validation of the method is in progress in our Institute. The study has been designed to be observational, cross-sectional and prospective, and schedules the enrolment of women at risk of bone fragility fractures. From this study lacunarity parameter β could emerge as a standard for TBA characterization and as a marker candidate for osteoporotic fracture risk.

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P- Reviewer: Belaya ZE, Cheung WH, Specchia ML
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DOI: 10.5312/wjo.v6.i2.236

World J Orthop 2015 March 18; 6(2): 236-243
ISSN 2218-5836 (online)

Atlanto-occipital dislocation

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Received: February 14, 2014
Peer-review started: February 14, 2014
First decision: March 12, 2014
Revised: October 11, 2014
Accepted: October 23, 2014
Article in press: October 27, 2014
Published online: March 18, 2015

Abstract

Atlanto-occipital dislocation (AOD) is being increasingly recognized as a potentially survivable injury as a result of improved prehospital management of polytrauma patients and increased awareness of this entity, leading to earlier diagnosis and more aggressive treatment. However, despite overall improved outcomes, AOD is still associated with significant morbidity and mortality. The purpose of this paper is to review the biomechanical aspects, clinical features, radiologic criteria, and treatment strategies of AOD. Given that the diagnosis of AOD can be very challenging, a high degree of clinical suspicion is essential to ensure timely recognition and treatment, thus preventing neurological decline or death.

Key words: Atlanto-occipital dislocation; Cervical spine; Craniocervical junction; Occipitocervical fusion; Trauma

Core tip: Atlanto-occipital dislocation (AOD) is being increasingly recognized as a potentially survivable injury as a result of improved prehospital management, increased awareness, and more aggressive management. However, despite overall improved outcomes, AOD is still associated with significant morbidity and mortality. Given that the diagnosis can be very challenging, a high degree of clinical suspicion is essential to ensure timely recognition and treatment, thus preventing neurological decline or death.

Hall GC, Kinsman MJ, Nazar RG, Hruska RT, Mansfield KJ, Boakye M, Rahme R. Atlanto-occipital dislocation. *World J Orthop* 2015; 6(2): 236-243 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/236.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.236

INTRODUCTION

In a recent study of 300 patients with cervical spine trauma, 30% of injuries were located between the occiput and C2. Among these, acute spondylolysis of C2 (hangman's fracture), C1 ring fractures, odontoid fractures, and atlanto-occipital dislocation (AOD) were the most common[1].

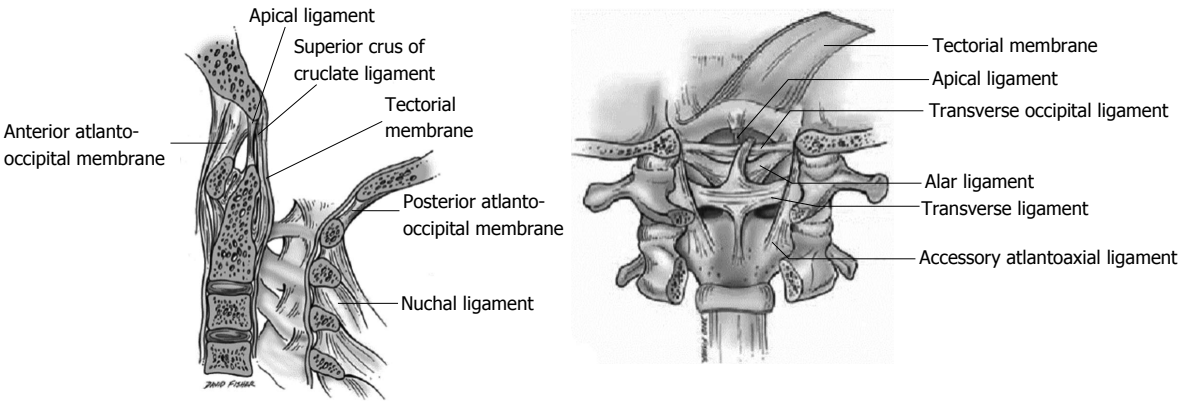

Figure 1 Anatomy of the craniocervical junction (reproduced with permission from Ref. [13]).

AOD is a highly unstable craniocervical injury, resulting from damage to ligaments and/or bony structures connecting the skull to the cervical spine. It is historically associated with significant neurological morbidity and mortality secondary to brainstem and upper cervical spinal cord injury. Although AOD represents roughly only 1% of all cervical spine injuries in the acute care setting, it has been reported to be the most common cervical spine injury in motor vehicle accident (MVA) fatalities. Modern case reports, however, have documented improved neurological outcomes, likely as a result of earlier diagnosis and surgical stabilization[2,3].

EPIDEMIOLOGY

AOD was first described by Blackwood[4] in 1908 and was long held to be a rare entity in comparison with other cervical spine injuries. Although rarely encountered and treated by spine surgeons, the incidence of AOD becomes much higher than historically assumed when non survivors of trauma are taken into account. In fact, AOD has been identified in 6%-10% of fatal cervical spine injuries from any mechanism[5,6]. When MVAs specifically are considered, the incidence of AOD among fatal cervical spine injuries may be as high as 35%[7,8].

AOD is more common among children and young adults. In fact, the injury is 3 times more common in children than in adults. This is thought to be secondary to a more horizontal plane of the articular surfaces and a relative laxity of the ligamentous structures, combined with the presence of a relatively large head and a higher effective fulcrum in the cervical spine[9].

AOD is generally associated with high-energy trauma, including high-speed MVAs or falls from heights, and thus should be considered as a possibility in any trauma involving large acceleration and deceleration forces[10]. As a result, AOD is frequently associated with severe traumatic brain injury, which can complicate initial identification of the injury as well as rehabilitation efforts after stabilization[10,11].

The advent of specialized emergency response systems and the evolution of Emergency Medicine as a specialty have served to alter the epidemiology of AOD over the last 3 decades. Improvements in field resuscitation, cervical immobilization, rapid transport, and increased recognition have resulted in more survivors of AOD, which is now being seen more often by clinicians in the acute care setting[3,8].

ANATOMY OF THE CRANIOCERVICAL JUNCTION

AOD is primarily an injury of the ligaments between the occiput and upper cervical spine, often without accompanying bony fractures. Thus, it can be missed more easily than traumatic fractures of the cervical spine. Proper identification and treatment of this injury requires a good understanding of the anatomy of the craniocervical junction (CCJ).

The junction between the skull and the cervical spine is stabilized by ligaments joining the axis and atlas to the clivus, occipital bone, and occipital condyle. The craniocervical junction must accommodate a wide variety of motions, which require many ligaments for stabilization (Figure 1).

The atlanto-occipital joint is formed by the superior articular facet of the atlas and the occipital condyle, which are stabilized by an articular capsule. This joint allows for 25 degrees of flexion and extension and 5 degrees of axial rotation[12,13].

The atlantoaxial segment consists of 3 joints, which together allow for 15 degrees of flexion and extension and 30 degrees of axial rotation. These include 2 lateral mass articulations and an atlantodental joint. The latter resists excessive extension, allowing only 10 degrees of extension in the average person[12,13].

The anterior atlanto-occipital membrane attaches from the anterior arch of the atlas to the anterior aspect of the clivus. It is a continuation of the anterior longitudinal ligament and serves to prevent excessive neck extension[12,13].

The alar ligaments attach from the lateral aspect of the odontoid process to the medial occipital condyle on

each side. These ligaments limit contralateral flexion and axial rotation at the atlanto-occipital joint[12-14].

The apical ligament attaches from the tip of the odontoid process to the basion, lying posterior to the alar ligaments and anterior to the superior band of the cruciate ligament. This ligament may be absent in 20% of cases and is often a rudimentary structure, with limited contribution to mechanical stability of the CCJ[12-14].

The Barkow ligament connects the tip of the dens to the occipital condyle, lying anterior and parallel to the alar ligaments. This ligament may assist in preventing excessive neck extension[12,13].

The transverse occipital ligament spans the foramen magnum, attaching to the medial aspect of the occipital condyles. This ligament sometimes joins the alar ligaments and may help prevent excessive lateral bending, flexion, and axial rotation[12,13].

The cruciform or cruciate ligament consists of a superior, transverse, and inferior bands centered just posterior to the odontoid. The superior band stabilizes the odontoid to the basion. The transverse band is the strongest portion of the cruciform ligament and stabilizes the odontoid to the lateral masses of the atlas. It limits lateral motion of C1 relative to the dens and prevents posterior displacement of the dens, thus limiting anterior C1-2 subluxation to 3-5 mm. The inferior band is a continuation of the superior band, which further strengthens the connection between the body of C2 and basion[12,13].

The tectorial membrane lies immediately posterior to the cruciate ligament. It attaches to the clivus lateral to the hypoglossal canals and continues through the spinal canal as the posterior longitudinal ligament. This ligament limits both excessive flexion and extension[12,13].

The accessory atlantoaxial ligament attaches from the posterior aspect of the body of C2 to the lateral masses of C1, lying anterior to the tectorial membrane. The role of this ligament is unclear[12,13].

The posterior atlanto-occipital membrane attaches from the occipital bone to the posterior arch of the atlas. It is a continuation of the ligamentum flavum[12,13].

The ligamentum nuchae is a continuation of the supraspinous ligament and spans from the external occipital protuberance to the spinous process of C7. This ligament serves to limit excessive neck flexion[12,13].

BIOMECHANICAL CONSIDERATIONS

AOD may be caused by different traumatic mechanisms, all having in common the transmission of excessive force to the CCJ, leading to widespread ligamentous disruption. Such mechanisms include hyperextension, hyperflexion, lateral flexion, or a combination of these[15-17].

Several predisposing conditions, including inflammatory, neoplastic, and congenital disorders, may increase the risk of AOD in the face of relatively minor trauma. Rheumatoid arthritis may involve the spine, particularly the CCJ, and cause weakening of the transverse ligament, thus increasing the risk of C1 subluxation. Down syndrome is associated with laxity of craniocervical ligaments in up to 30% of cases. Congenital cervical vertebral fusion syndromes may also predispose to AOD by creating a fulcrum-like effect[13].

CLINICAL FEATURES

Because of the relatively wide cross-sectional area of the spinal canal at the CCJ, spinal cord injury is less common than expected. However, when present, neurological injury from AOD can be devastating, often leading to sudden death secondary to brainstem injury. Neural injury may be direct, as a result of traction or compression mechanisms, or indirect, secondary to cerebrovascular injury leading to ischemia.

Survivors of AOD often have neurological impairment, including lower cranial nerve deficits, unilateral or bilateral weakness, or even quadriplegia. However, there is a wide range of presentations, with some patients being completely asymptomatic and others being dependent on advanced life support measures. Concomitant traumatic injuries to the brain, chest, abdomen, and extremities can further blur the clinical picture, masking weakness, apnea, or neurogenic shock.

Up to 20% of patients with AOD may have normal neurological examination at presentation. Severe neck pain may be the only symptom in such patients[18]. The lack of localizing neurological findings can delay the diagnosis of AOD. However, the majority of patients present with unconsciousness and respiratory arrest. Lower cranial nerves, such as abducens, vagus and hypoglossal, may also be involved in AOD.

More severe cases of AOD can present with spinal cord injury, including sensory and motor deficits, hyperreflexia with clonus, positive Babinski sign, and abnormal sphincter tone. Neurological deficits may be unilateral or bilateral, and typically include the entirety of the affected side from shoulder to foot. Reflex examination should be interpreted cautiously, given the possibility of spinal shock.

Autonomic dysregulation, including neurogenic shock, may also be a presenting symptom. The ensuing hemodynamic instability may cause trauma teams to undertake negative exploratory laparotomies, which may increase the risk of neurological deterioration during transfers and may delay the diagnosis of AOD.

Finally, symptoms of AOD may be caused by cerebrovascular injury. It is fairly common for vertebral dissections to occur with AOD, as well as carotid dissections. These injuries can lead to ischemic strokes, further clouding the clinical presentation[11].

Thus, until radiologic evaluation with computed tomography (CT) or magnetic resonance imaging (MRI) can be performed, any patient involved in

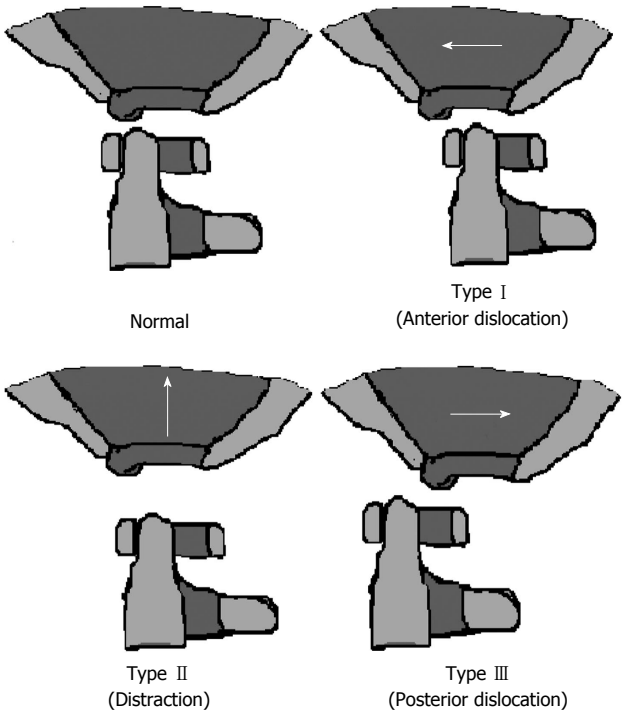

Figure 2 The Traynelis classification.

high-energy trauma should be suspected of having AOD, irrespective of clinical findings, and appropriate precautionary measures should be taken.

RADIOLOGIC CRITERIA

Given the complex anatomical and biomechanical factors involved in AOD, a single measurement or abnormality on imaging studies cannot universally define AOD. Over the years, many different and complementary methods have been developed to help diagnose this often overlooked entity, each having its own strengths and weaknesses. All methods seek to assess for damage to the structures stabilizing the occipital-atlanto-axial unit. These include the Traynelis classification[19], Powers' ratio[20], X-line method[21], basion-dens interval (BDI) and basion-axis interval (BAI) (*i.e.*, Harris lines)[22,23], and occipital condyle-C1 interval (CCI)[24,25]. Care should be taken when applying these various techniques to adult *vs* pediatric patients, as there are significant anatomic and biomechanical differences between these 2 populations.

The Traynelis classification[8,19] (Figure 2) divides AOD into 3 groups: (1) Type Ⅰ is an anterior displacement of the occiput relative to the atlas; (2) Type Ⅱ is a distraction of the occiput from the atlas; and (3) Type Ⅲ is a posterior displacement of the occiput relative to the atlas.

Traction is sometimes used to realign types Ⅰ and Ⅲ, but remains controversial. Unfortunately, this classification scheme does not take into consideration the presence of coronal misalignment. Thus, a clinician depending solely on this method may miss an AOD with pure coronal distraction. Nevertheless, this system still provides a useful framework when assessing for AOD and may help guide management.

Powers' ratio[8,20] compares measurements relating the skull base to C1 (Figure 3A). The distance from the basion (B) to the midpoint of the anterior cortex of the posterior arch of C1 (C) is measured. The distance from the opisthion (O) to the midpoint of the posterior cortex of the anterior arch of C1 (A) is measured. If BxC/OxA exceeds 1, then AOD should be suspected. Normal values are typically < 0.9. Powers' ratio was originally described to detect anterior dislocation injuries and, as such, is less sensitive to distraction or posterior dislocation injuries, *i.e.,* Traynelis types Ⅱ and Ⅲ. Nevertheless, it remains one of the earliest reliable and reproducible published methods and often stands as the benchmark to which other methods are compared.

The X-line method[8,21] involves drawing a line from the basion to the spinolaminar junction of C2 and a line from the opisthion to the posteroinferior corner of the body of C2 (Figure 3B). The result is considered abnormal if both the first line does not intersect C2 and the second line does not intersect C1. Because of its more anatomic definition of normality, the X-line method is more sensitive than Powers' ratio in detecting Traynelis types Ⅱ and Ⅲ injuries.

The Harris method[8,22,23] combines 2 previously developed measures: the BDI and the BAI (Figure 3C and D). BDI measures the distance between the basion and the tip of the dens. Values above 10 mm in adults and 12 mm in children are considered abnormal. BDI is particularly sensitive to Traynelis type Ⅱ injuries. BAI measures the distance between a line drawn tangentially to the posterior cortical surface of C2, *i.e.,* the posterior axial line, and a second parallel line drawn through the basion. Normal values range from 12 mm (basion anterior to dens) to -4 mm (basion posterior to dens) in adults and from 12 mm to 0 mm in children. BAI is most sensitive to Traynelis type Ⅰ and Ⅲ injuries. Using BDI and BAI in combination, Harris *et al*[23] demonstrated increased diagnostic accuracy compared with Powers' ratio.

The CCI or condylar gap method is a measurement used and validated in the pediatric population[8,24,25]. It is the only method that directly assesses structural elements of the atlanto-occipital joint. Specifically, the distance between the occipital condyle and its articulating surface on C1 is measured (Figure 3E), making this technique highly sensitive for Traynelis type Ⅱ injuries. The measurement is made on coronal CT images. A distance of more than 2 mm in adults or more than 5 mm in children, or gross asymmetry between the 2 joints is highly sensitive and specific for AOD, with good interrater reliability[24,25]. While this technique was initially validated in the pediatric population, it is rapidly becoming the gold standard

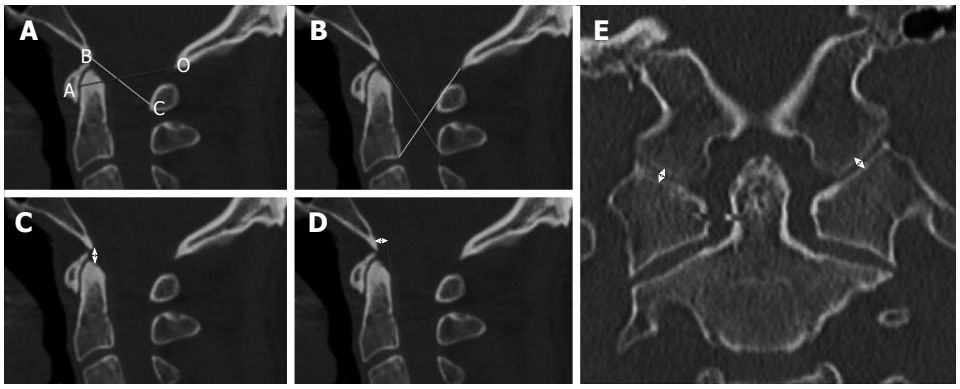

Figure 3 Diagnostic methods for atlanto-occipital dislocation (see text for details). A: Powers' ratio; B: X-line method; C: Basion-dens interval; D: Basion-axis interval; E: Occipital condyle-C1 interval.

for diagnosing AOD in adults as well, as recent studies suggest similar accuracy in that population[26].

Based on level Ⅲ evidence, the "Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries"[27] recommend applying the BDI-BAI (Harris lines) method on a plain lateral cervical X-ray in adults. If this is nondiagnostic and there is high clinical suspicion or significant prevertebral soft tissue swelling, CT and/or MRI are recommended. In children, the CCI determined on CT has the highest diagnostic sensitivity and specificity for AOD[27]. Signs that should raise concern for AOD include: enlargement of the predental space, high cervical spinal cord deficits, respiratory dysfunction or apnea, subarachnoid hemorrhage at the CCJ, cranial nerve deficits, and signal abnormalities affecting the tectorial membrane, alar and transverse ligaments, or occipitoatlantal joint capsule on MRI[25].

Ultimately, none of these diagnostic methods is perfect and each has limitations. For instance, none maximally tests for all 3 Traynelis types and few assess for coronal plane displacement. Also, the diversity of these methods and measurement techniques may cause confusion among clinicians. There is still no gold standard technique to diagnose AOD and the large number of available methods reinforces the notion that this diagnosis can be easily missed. We recommend utilizing at least 2 complementary methods to help compensate for the shortcomings of any single method. Also, clinicians should take into account the patient's clinical presentation and suspected mechanism of injury when assessing for AOD, since no radiographic measures can completely rule out the diagnosis.

TREATMENT

Treatment of AOD begins in the field. Hemodynamic and respiratory instability should be immediately dealt with at the scene and given utmost priority. Inline stabilization of the neck and cervical spine injury precautions, including the proper application of a rigid cervical collar at the trauma scene, are also critical to prevent this potentially recoverable injury from becoming a lethal one. In the emergency department, careful documentation of the patient's neurological exam may help raise clinical suspicion for AOD. A rapid, yet thorough assessment, followed by appropriate radiologic imaging, is essential to ensure timely diagnosis and treatment of this injury. Once the diagnosis of AOD is confirmed, halo immobilization should be performed, followed by internal occipitocervical fixation and fusion. Cervical traction should be avoided, since it is associated with a 10% risk of neurological deterioration[27].

Anterior approaches to the CCJ have been well described and are typically used for pathology anterior to the spinal cord. Such approaches are more suited for decompression rather than stabilization and are often technically challenging. Because of this, they tend to be less useful for AOD, where stabilization is the major goal of surgery and where patients are often critically ill and unable to tolerate long and morbid procedures. Conversely, the posterior approach can be used to achieve both decompression and stabilization of the CCJ. While the approach itself has not changed over time, fusion technology has evolved from cable wiring to laminar clamps to screw fixation, resulting in improved stabilization results[28-31].

Posterior fixation was historically accomplished with sublaminar wiring. C1-2 sublaminar wiring and facet fusion was described as early as 1939[28]. In the 1980s, techniques combining C1-2 cable wiring with occipital bone wiring through burr holes were developed[29]. Cable-wired metal rods, such as modified Steinmann pins, were introduced as a way to maximize stabilization[30]. These craniocervical stabilization techniques were often used in adjunction with spinal traction and halo immobilization throughout the 1980s[29]. As experience and technology progressed, wiring techniques were largely abandoned in favor of screw fixation techniques, which provide better biomechanical stability[31].

In the modern era, patients with strictly occipitoatlantal joint instability and no other associated cervical injuries may be treated with an O-C1 or O-C2

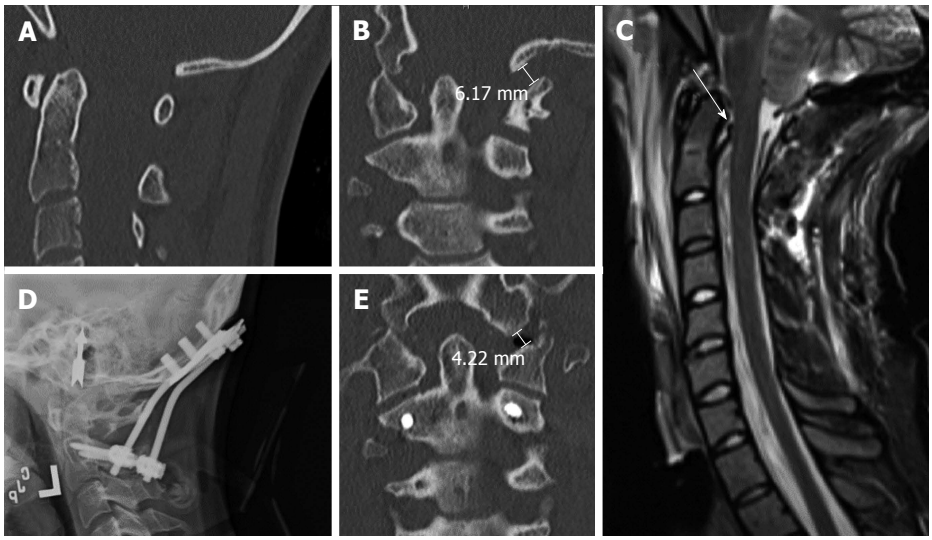

Figure 4 Nineteen years old woman with traumatic atlanto-occipital dislocation following high-speed motor vehicle accident. A and B: CT of the cervical spine demonstrates no significant abnormalities in the midsagittal plane (A), but clear asymmetry of the occipito-atlantal joints in the coronal plane (B). The left occipital condyle-C1 interval is increased, measuring 6 mm; C: MRI of the cervical spine (T2WI) reveals abnormal signal suggesting disruption of the cruciate ligament; D: Post-operative cervical radiographs show O-C2 fusion using bicortical occipital screws and C2 pedicle screws; E: Post-operative CT of the cervical spine demonstrates reduction of the left occipital condyle-C1 interval to 4 mm. CT: Computed tomography; MRI: Magnetic resonance imaging.

screw fixation. The former has the benefit of sparing the atlantoaxial motion segment. Occipitocervical fusion can be performed using either transarticular or lateral mass screws, although C2 pedicle or laminar screws have also been successfully used[8,11,29]. At the cranial level, instrumentation options include bicortical occipital screws and occipital condyle screws. Transarticular screws have excellent purchase when placed bicortically, leading to high biomechanical stability, and can be placed even when posterior elements are absent or incompetent. However, transarticular techniques place the vertebral artery at risk for injury. Thus, the patient's individual anatomy must be taken into account[8,29]. In our institution, C1-2 transarticular screws have been largely abandoned in favor of C1 lateral mass and C2 pars screws, given the lower risk of vascular injury with this technique (Figure 4).

AOD is often associated with concomitant cervical injuries below C1, necessitating the extension of fusion to the lowest disrupted level[32]. When such an extension is needed, lateral mass or pedicle screws can be placed at the remaining levels[8]. An important factor in the viability of these constructs is ensuring a strong fusion. Involved facet joints should be abraded and exposed bony surfaces should be decorticated in preparation for autograft application. Appropriate options for autograft include: iliac crest, locally harvested bone (lamina, spinous process), and rib graft. In addition, calvarial bone may be used in children[8].

Even in this modern era, halo fixation may still play a role in the treatment of AOD. In fact, some authors have proposed halo immobilization as a treatment option for patients with normal CT findings, *i.e.*, no bony distraction, but equivocal changes on MRI, including mild signal changes at the occipitoatlantal joint[11]. However, halo devices are not frequently used for a number of reasons. First, the halo device is often ineffective in adequately stabilizing the CCJ. Second, halo immobilization is a cumbersome and potentially morbid procedure. It prevents early patient mobilization and limits daily activities, and has been associated with increased mortality rates in the elderly. Finally, AOD is an essentially ligamentous injury and, as such, is unlikely to spontaneously heal well over time, even after prolonged external immobilization[11,33]. In our institution, the use of halo immobilization for AOD is essentially limited to temporary preoperative stabilization pending definitive occipitocervical fusion. In such cases, care is always taken to avoid significant cephalad traction during halo application, which could easily exacerbate the injury and lead to neurological decline.

Special considerations apply when treating AOD in children, including smaller dimensions, syndromic anatomic variations, and the risk of limiting normal bony development and growth[8,34]. In a review of over 750 CCJ fusions in children, Ahmed *et al*[34] found lower morbidity rates with rib grafts compared with iliac crest grafts. The authors recommended using rib grafts alone in children 6 years of age or less, contoured rod-wire constructs in children between 7 and 10 years of age, and rigid instrumentation in children over the age of 10 years. No cervical spine growth abnormalities were observed in patients fused before the age of 5 years[34]. However, alternative fixation methods at C1 and C2, such as transarticular screws, lateral mass screws, and translaminar screws, have been successfully used in pediatric patients with atlantoaxial and occipitocervical instability, ranging in age from 1

to 17 years[35]. Moreover, in a recent pediatric study (age range 1-19 years), O-C2 fusion without C1 instrumentation had similar fusion rates compared with constructs incorporating C1[36]. Therefore, it seems that, irrespective of age, a successful fusion in children with upper cervical instability can be obtained using a variety of different instrumentation methods.

OUTCOME

Previous autopsy reports have documented AOD as cause of death in 6%-8% of traffic fatalities[8]. However, not every case of AOD will result in fatality or severe disability. Unfortunately, outcome analysis is biased by the high rate of misdiagnosis, particularly among asymptomatic patients. Outcome analysis is also complicated by the heterogeneity of treatment groups in the published literature, including variable mechanisms of injury, concurrent injuries, and comorbidities.

The natural history of asymptomatic AOD is unknown, since current standards of care mandate immediate stabilization. Earlier studies had documented a 54% rate of neurological worsening and 15% mortality among untreated AOD patients[27]. Some information is also available on initially asymptomatic patients that exhibit subsequent neurological worsening. A literature review in 2002 identified 9 such patients with an initially missed diagnosis of AOD. Half of these never returned to their baseline neurological condition, even after surgical stabilization[33].

Early aggressive surgical stabilization is associated with improved outcomes after AOD[33]. A study of 40 patients treated conservatively with external immobilization alone demonstrated a 30% rate of continued craniocervical instability and neurological worsening on follow-up[33]. Following early occipitocervical fusion in 19 patients, neurological improvement was seen in 15 patients, clinical stability in 3, and a new cranial nerve palsy in only 1[33]. Likewise, no neurological worsening was observed in a group of 8 patients who underwent delayed occipitocervical fusion after temporary external immobilization without traction[33].

CONCLUSION

AOD is an uncommon, yet increasingly recognized traumatic injury, which can be difficult to diagnose and may be easily overlooked on routine cervical spine radiographs. Despite advances in pre-hospital and hospital care and improved overall outcomes, AOD remains a potentially lethal and disabling injury. A high index of suspicion is critical for early diagnosis and to avoid neurological deterioration secondary to delay in care. AOD may initially be temporarily treated with external halo immobilization, but early surgical stabilization is required to confer long-term craniocervical stability and facilitate neurological recovery.

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P- Reviewer: Anderson RCE, Singh H **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i2.244

World J Orthop 2015 March 18; 6(2): 244-251
ISSN 2218-5836 (online)

MINIREVIEWS

Use of scoring systems for assessing and reporting the outcome results from shoulder surgery and arthroplasty

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Author contributions: Booker S and Alfahad N researched the scoring systems and collated the data on the scoring systems; Alfahad N, Scott M and Gooding B supervised the development of the database of scoring systems; Gooding B and Wallace WA carried out the shoulder arthroplasty operations and edited the final article which was approved by all authors.

Conflict-of-interest: This article focuses on shoulder scoring systems used world-wide. None of the authors have any conflict of interest in relation to any of these shoulder scoring systems. The shoulder replacement results reported are for the Vaios shoulder replacement (marketed by JRI Orthopaedics Ltd) and are the results for a consecutive series of primary shoulder replacements carried out by the Senior Author (WAW) who was the co-designer of the Vaios shoulder replacement and has a Consultancy agreement with JRI Orthopaedics Ltd. None of the other co-authors have any conflict of interest in relation to shoulder replacement surgery.

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Received: March 11, 2014
Peer-review started: March 12, 2014
First decision: April 30, 2014
Revised: December 9, 2014
Accepted: December 18, 2014
Article in press: December 19, 2014
Published online: March 18, 2015

Abstract

To investigate shoulder scoring systems used in Europe and North America and how outcomes might be classified after shoulder joint replacement. All research papers published in four major journals in 2012 and 2013 were reviewed for the shoulder scoring systems used in their published papers. A method of identifying how outcomes after shoulder arthroplasty might be used to categorize patients into fair, good, very good and excellent outcomes was explored using the outcome evaluations from patients treated in our own unit. A total of 174 research articles that were published in the four journals used some form of shoulder scoring system. The outcome from shoulder arthroplasty in our unit has been evaluated using the constant score (CS) and the oxford shoulder score and these scores have been used to evaluate individual patient outcomes. CSs of < 30 = unsatisfactory; 30-39 = fair; 40-59 = good; 60-69 = very good; and 70 and over = excellent. The most popular shoulder scoring systems in North America were Simple Shoulder Test and American shoulder and elbow surgeons standard shoulder assessment form score and in Europe CS, Oxford Shoulder Score and DASH score.

Key words: Shoulder joint; Arthroplasty; Replacement; Scoring methods; Operations; Surgery; Surgical therapy; Assessment; Patient outcomes; Classification

Core tip: We have identified the most commonly used shoulder scoring systems used when results of surgery are published. The constant score (CS) can be used to categorize the outcomes after shoulder arthroplasty into unsatisfactory; fair; good; very good; and excellent. This be carried out using both the original CS and the Adjusted (for age and sex) CS. For the majority of

orthopaedic surgeons the reporting of outcomes in this way is clearer than providing the mean and standard deviation of one of the commonly used shoulder scoring systems.

Booker S, Alfahad N, Scott M, Gooding B, Wallace WA. Use of scoring systems for assessing and reporting the outcome results from shoulder surgery and arthroplasty. *World J Orthop* 2015; 6(2): 244-251 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/244.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.244

INTRODUCTION

Functional shoulder disabilities are frequently reported by patients with a wide variety of conditions, such as arthritis, rotator cuff disease, breast carcinoma, trauma and radiation therapy[1]. Upper limb disabilities may include pain, stiffness, decreased range of movement, lymphoedema and reduced activity tolerance. There are a myriad of scoring systems used in everyday orthopaedic practise and research, and a number of scoring systems have been developed and established to assess the function and limitations of the shoulder. None of these are ideal methods for correlating both the physician's and the patient's perspective[2] as some are more inclined towards the opinion of the physician while others are more centred on the patient's self-assessment. A review of four popular journals (see below) showed that in their 2012 volumes 16 different scoring systems were commonly used to evaluate shoulder conditions. This can make it difficult to compare outcomes between studies and interventions, and makes it more problematic for practising orthopaedic surgeons to decide which of their treatment options is providing the best outcomes if the scoring systems used are different. This review aims to evaluate the evidence behind the scoring systems, and will provide some guidance as to which to rely on.

Many shoulder scoring systems are used in-appropriately without being tested for their sensitivity, reproducibility and validity[3]. In order to apply any scoring system, their complete validation must be documented. Over the last 5 years the use of patient reported outcome measures (PROMs) have been promoted as they are considered to place a greater emphasis on the quality of life perceived by the patient[4]. There is therefore a need to develop questionnaires or shoulder scoring outcome measures which can address specific conditions or abnormalities of the shoulder so that they can fulfil both the patient's and clinician's perspective[5]. Above all, shoulder scoring systems need to be evaluated and modified for specific condition to produce a valid, sensitive and reproductive outcome.

COMMONLY USED SCORING SYSTEMS

Constant score

The constant score (CS)[6] is one of the most commonly used shoulder scoring systems[7], and is considered the gold standard in Europe[8]. It is comprised of 4 parts - Pain reported by the patient (15 points); Activities of Daily Living reported by the patient (20 points); Range of Movement - assessed by the examiner (40 points) and strength - assessed by the examiner (25 points), with the better functioning shoulders having a greater number of points up to a maximum of 100 points. It has a long history and is easy to apply, hence it is used very extensively[7,9]. Because of its long term use since it was formally published in 1987, it is likely to remain popular so that treatment outcomes previously reported in the literature can be compared with more modern surgical or non-surgical treatments. Authors have criticised the CS, suggesting its level of standardisation is poor[10,11]. It does not evaluate shoulder instability and this is a weakness[12], as is the non-standardised strength evaluation[13] although Bankes *et al*[14] have described the fixed spring balance modification (fixed to a desk or to the floor) as a low-cost technique, which gave similar and equally reproducible values for power when compared with an electronic measuring device[15]. However, it does reliably detect improvements in shoulder function after intervention[16]. Some concerns have been expressed about the different results reported for males and females and the reduction of scores with increasing age[15] but these have been addressed by the use of the modified CS, which corrects for both age and gender[17].

Oxford shoulder score

The oxford shoulder score (OSS)[18] is a joint specific scoring system that is patient assessed, and scored out of 48. It is an outcome measure based on the patient's perspective of their outcome and using standard questions where 4 of the 12 questions are related to pain. The OSS is a reliable, easy to use outcome measure which is sensitive to surgical outcome and clinical changes[19,20]. It has good correlation with clinical findings. Again the OSS does not assess shoulder instability[21] and, as a consequence the oxford instability score (OSIS) has been developed subsequently[22] (see below). Olley *et al*[20] concluded that the OSS can be used for audit purposes, however, they have suggested that larger prospective studies should be carried out to identify whether OSS varies with age, gender, and size of rotator cuff tear or not. Frich *et al*[23] studied the Danish version of the OSS, reporting that the OSS psychometric properties are valid and reliable. They also reported that the OSS is appropriate to evaluate individuals suffering from degenerative or post-traumatic shoulder diseases.

OSIS

The OSIS[22] is based on a 5-option response (Likert scale) for each item, with each response scored from 0 to 4, with 4 being the best outcome. All questions are laid out similarly with response categories denoting least (or no) symptoms being to the left of the page (scoring 4) and those representing greatest severity lying on the right hand side (scoring 0). The overall OSIS score is reached by simply summing the scores received for individual questions. This results in a continuous score ranging from 0 (most severe symptoms) to 48 (least symptoms).

Disability of the arm, shoulder and hand

The disability of the arm, shoulder and hand (DASH) score is a 30-item patient-reported tool to assess symptoms and physical disability in the arm. The DASH parameters are symptoms, physical, social and psychological functions. The score evaluates pain, physical disability and sleep disturbance. The pain score and physical disability assessment make a large part of this outcome measure. The DASH score has been shown to assess improvement after surgery [Lewis (2012)], and multiple authors have found it to be a valid and reliable score [Slobogean *et al*[24] (2010) Huisstede *et al*[25] (2009) Bilberg *et al*[26] (2012)]. As with the OSS, the DASH score has also been used cross-culturally and has provided similar results (Jianmongkol *et al*[27] 2012). However, as the name suggests, it is not a shoulder specific scoring system, and being a patient self-reported scoring system, DASH may fall victim to patient bias. In addition the DASH score results are inverted with the higher scores (maximum = 100) representing a greater disability and the lower scores occurring in a good functioning arm.

Simple shoulder test

The simple shoulder test (SST) was developed by Rick Matsen, initially in San Antonio and later in Seattle at the University of Washington Shoulder and Elbow Service. It has been reported as simple, valid, highly reliable and free practical patient self-assessment tool. The SST is a questionnaire with 12 questions designed for "yes/no" answers. It is validated for pre and post-operative shoulder function, and, is popular in North America[28]. However, it has also been validated in a number of other countries[29], including Brazil[30], Holland[16] and Italy[31] and is considered to be user friendly[16]. Drawbacks associated with the SST are perhaps its generosity (high scores when significant disability is present), and the different effects of age and type of injury or disease on the scores.

American shoulder and elbow surgeons standard shoulder assessment form

The American shoulder and elbow surgeons standard shoulder assessment form (ASES)[32] is easy to apply and consists of an assessment of the patients activities of daily living and a patient self-evaluation. It can be applied to all shoulder patients regardless of diagnosis. Some authors report it has good reliability, high constructive validity and high responsiveness[32]. However, Bafus *et al*[33] have reported that the ASES is not a valid and reliable scoring system for shoulder pathology as there are questions like "do usual sport" and "throw ball overhand" which are not easy for some patients to answer as they do neither. Although ASES is a highly accepted shoulder scoring system, it does contain several shortcomings in its construction.

Western ontario shoulder instability index

The Western ontario shoulder instability index (WOSI)[34] is a specific instability score designed to address the lack of validity of other scores in assessing shoulder instability symptoms. It is a self-assessment shoulder scoring tool that is disease-specific and also assesses the quality of life of patients with symptomatic shoulder instability. It is highly accepted by patients and surgeons because of the perceived importance of the items questioned, and has been found to be valid and reliable[35,36]. The disadvantages of the WOSI are that it has 21 questions each scored using 100 mm visual analogue scales, and its research usability is moderate as it is specific to instability conditions.

Japanese orthopaedic association shoulder score

The Japanese orthopaedic association (JOA) shoulder score is extensively used throughout Japan but it is not commonly reported outside that country. It is a much more complicated scoring system. For each of the 36 questions, patients are asked to self-interpret their symptoms using a scoring system divided into five levels (0 to 4) in which the larger values mean a better shoulder. The grades are: I have no difficulties (= 4); I have minor difficulties (= 3); I have some difficulties but I can manage on my own (= 2); I have major difficulties and require help from someone (= 1); and I cannot do it at all (= 0). These are very similar to the answers to the OSS questions, but 32 questions are used by the JOA while only 12 are used for the OSS. However the complex part is the final calculation which involves transferring scores from one domain to another, and as a result, it has not found popularity outside Japan.

Short form-36, short form-12, EQ-5D and short form-6D for general health

The short form (SF)-36 and the shorter SF-12 have become the most widely used measures of general health in clinical studies throughout the world. The SF-36 currently generates eight dimension scores and two summary scores for physical and mental health. Whilst such scores provide an excellent means for judging the effectiveness of health care interventions, they have only a limited application in economic

Table 1 Shoulder scoring systems used in 2012 and 2013

Shoulder scoring system	No. of times used in articles in 2012	No. of times used in articles in 2013	No. of times used in articles in 2012 and 2013
CS	47	44	91
American shoulder and elbow surgeons evaluation form	41	32	73
The disability of the arm, shoulder and hand score	22	13	35
SST	16	13	29
University of California/Los Angeles shoulder score	15	13	28
Western ontario osteoarthritis score	6	0	6
The OSS	4	6	10
SF-12 general health	3	7	10
Western ontario rotator cuff score	3	5	8
SF-36 general health	1	8	9
Penn shoulder score	1	2	3
Shoulder pain and disability index	1	4	5
Western ontario shoulder instability score	1	2	3
Rowe shoulder instability score	1	2	3
Single assessment numeric evaluation score	1	7	8
Kerlan-Jobe orthopaedic clinic overhead athlete score	1	2	3
Hospital for special surgery shoulder score	0	0	0
OSIS	0	2	2

CS: Constant score; SST: Simple shoulder test; OSS: Oxford shoulder score; SF-12: Short form-12; OSIS: Oxford instability score.

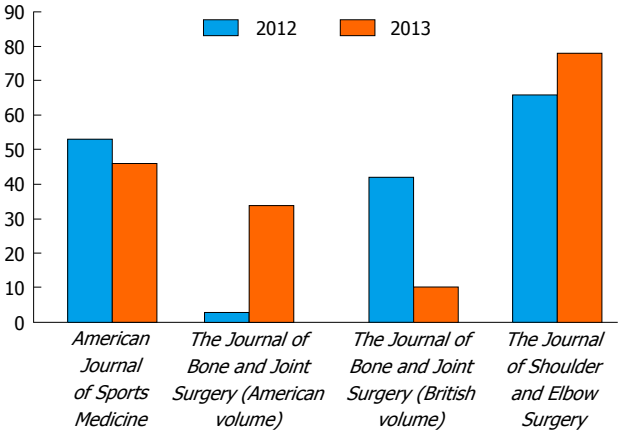

Figure 1 Number of articles that used different shoulder scoring systems during 2012 and 2013.

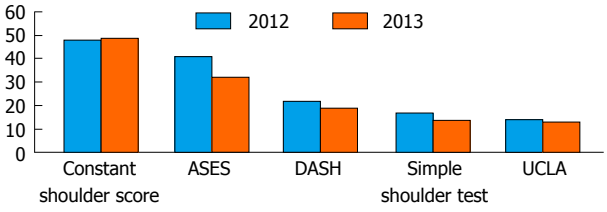

Figure 2 Most popular shoulder scoring systems during 2012 and 2013. ASES: American shoulder and elbow surgeons standard shoulder assessment form; DASH: Disabilities of the arm, shoulder and hand; UCLA: University of California-Los Angeles shoulder scale.

evaluation because they are not based on preferences. The SF-6D[37] provides a means for using the SF-36 and SF-12 in economic evaluation by estimating a preference-based single index measure for health from these data using general population values. The SF-6D allows the analyst to obtain quality adjusted life years from the SF-36 for use in cost utility analysis. The EQ-5D is a similar, five-dimension, questionnaire and is now becoming popular in evaluating cost utility analysis and changes in general health after surgical operations in the United Kingdom and Europe.

REVIEW OF THE MOST COMMONLY USED SHOULDER OUTCOME SCORES IN EUROPE AND AMERICA

A review was carried out of all the articles in the 2012 and 2013 volumes of four major MEDLINE/PubMed referenced journals: The Journal of Bone and Joint Surgery (Am); The Journal of Bone and Joint Surgery (Br - now called the Bone and Joint Journal); The Journal of Shoulder and Elbow Surgery; and the American Journal of Sports Medicine. That review is summarised in Figures 1 and 2 and Table 1. The CS and the ASES are those most frequently used. This may be because of their long history, and the tradition of combining both objective and subjective assessments of patients. Both have also been extensively validated. However, there is evidence that patient self-reported scoring is not only easier and cheaper, but may also be a more accurate method of assessing orthopaedic outcomes[38-40]. Other popular scoring systems include the DASH, the SST and the university of California-Los Angeles shoulder scale (UCLA). The remainder are used far less commonly, sometimes for specialised situations (*i.e.*, the Kerlan-Jobe Orthopaedic Clinic - KJOC overhead athlete score). Different shoulder scoring systems appear to be used in different countries. In Europe the CS, DASH and the OSS appear to be the most common, while in North America, the ASES, SST, and UCLA are used to assess the shoulder most often. All of

Table 2 Estimated normal constant scores for age and sex[15]

Age (yr)	Men	Women
50-59	95 ± 2	88 ± 2
60-69	92 ± 2	85 ± 2
70-79	89 ± 2	82 ± 2
80-89	86 ± 2	79 ± 2

these scoring systems either test different things or features in different ways to assess shoulder function. However, one would presume some kind of inter-correlation might be found between the scoring systems used in Europe and those being performed in United States as all of them intend to evaluate the shoulder function.

EQUIVALENCE OF SHOULDER SCORING SYSTEMS

A number of papers have evaluated whether different scoring systems are comparable. The CS is a combination of both a clinically-based and patient assessment outcome measure for patients with shoulder problems, while most other scores focus on more patient-based outcome measures. One would therefore suspect that the CS cannot be interchanged or merged with the other scoring systems which are based on self-assessment by the patients. In contrast, OSS, DASH, SST and WOSI scoring systems can be compared and interchanged to some extent. However there are confounding factors which will influence these scores. All the patient-based assessment outcome measures may be affected by personal or patient response biases. Scott *et al*[41] have compared the CS and OSS, and found that using the OSS gave a higher proportionate overall score for the shoulder patient than the CS and that the agreement between the scores was poor. However, other studies have revealed that OSS is more stable than CS in terms of outcome measures[18,42]. Skutek *et al*[43] have also shown only moderate correlation between the CS and SST. Hirschmann *et al*[13] suggested that CS is poor at measuring shoulder strength and should be re-evaluated for its sensitivity and reliability. Lewis[44] reviewed patients with subacromial impingement, and measured CS, DASH and the EuroQol (EQ-5D) quality of life measurement. He found that CS and DASH were both significantly improved in the intervention exercise group, but CS improved more than DASH, suggesting poor agreement between the two systems.

As the OSS and DASH are patient self-assessment measurement outcomes they could be expected to be interrelated to each other but may sometimes be used combined. Studies have reported that OSS is better to assess the surgical outcome in patients with rheumatoid arthritis as compared to the DASH and SF-36[45].

In order to check the reliability and validity of DASH and SF-6D, Slobogean *et al*[24] studied patients with treated proximal humeral fractures. They reported that DASH and SF-6D questionnaires were adequate in assessing psychometric properties, and suggested that these scoring systems are appropriate to assess the outcome in patients treated for proximal humeral fractures. Interestingly, van de Walter *et al*[46] reviewed five scoring systems-CS, -OSS, -DASH, -UCLA and a Subjective Shoulder Value following proximal humeral fractures and concluded that currently available shoulder scoring systems may not offer significant value for assessing functional improvement after such fractures.

Godfrey *et al*[29] conducted a study on 1077 patients suffering from shoulder instability to assess the reliability, validity, and responsiveness of the SST. They found that the SST is significantly correlated with the ASES score and both responded to change in shoulder function. However, they reported that the results were different for different age groups and different types of shoulder injury. The study conducted by van Kampen *et al*[16] also revealed that the SST is highly correlated with the DASH, OSS and SF-36 in terms of physical subscales; however, it did not correlate well with the CS.

WHEN TO USE SCORING SYSTEMS

Many surgical and non-surgical shoulder interventions take months to gain full benefit after shoulder treatment, so any follow up has to be measured over months and years to evaluate longer term outcomes. Our preference is to score all our patients preoperatively, then at 6 mo and 1 year if the patient continues to be followed up. For shoulder joint replacement patient's scores are then repeated at 3, 5 and 10 years unless the patients are scored more regularly as part of a research protocol.

USING THE CONSTANT SCORE TO EVALUATE THE OUTCOME FOLLOWING SHOULDER ARTHROPLASTY

It has been standard practice in our unit for 20 years to use the CS to evaluate the outcome from shoulder operations and, in particular shoulder arthroplasty. Previous studies, reported in 2007[15] have highlighted the changes in the CS in normal people with increasing age and between the sexes. Table 2 shows the estimated normal CSs for age and sex.

As a practical example from our unit, in 2013 we evaluated the outcomes from all our primary anatomic and inverse (or reverse) shoulder replacements using a new Vaios shoulder replacement design[47] and the results are shown in Table 3 for anatomic shoulder arthroplasty and Table 4 for reverse shoulder arthroplasty. However these means and standard deviations are difficult to understand for most orthopaedic surgeons but they

Table 3 Constant and oxford shoulder scores for the vaios anatomic shoulder replacements

Outcome measure	No. of shoulders	Oxford score (/48)	Pain (/15)	ADL (/20)	ROM (/40)	Strength (/25)	Total CS (/100)	Constant score adjusted for age and sex (%)
Pre-op mean (SD)	49	16.8 (7.8)	4.8 (3.2)	6.7 (3.7)	10.1 (5.1)	1.0 (2.2)	21.9 (9.7)	29.2 (12.4)
Post-op 1 yr mean (SD)	49	33.0 (12.8)	11.3 (4.1)	13.3 (4.7)	20.0 (11.3)	4.0 (4.8)	44.6 (17.6)	59.6 (24.0)
Post-op 2 yr Mean (SD)	30	36.5 (12.3)	12.0 (3.9)	14.0 (6.0)	20.5 (10.7)	6.7 (6.0)	47.2 (19.4)	62.1 (22.8)
Post-op 3 yr mean (SD)	8	38.4 (10.6)	10.8 (2.9)	11.8 (4.0)	16.4 (6.2)	6.4 (3.6)	45.4 (10.4)	63.6 (21.0)

ADL: Activities of daily living; CS: Constant score.

Table 4 Constant and oxford shoulder scores for the vaios inverse shoulder replacements

Outcome measure	No. of shoulders	Oxford score (/48)	Pain (/15)	ADL (/20)	ROM (/40)	Strength (/25)	Total CS (/100)	Constant score adjusted for age and sex (%)
Pre-op mean (SD)	63	18.9 (9.0)	6.6 (4.0)	8.0 (4.2)	11.2 (8.1)	0.8 (2.1)	25.9 (13.1)	37.0 (18.2)
Post-op 1 yr mean (SD)	63	35.4 (11.7)	12.3 (3.7)	13.5 (5.4)	22.8 (10.5)	4.7 (5.3)	49.4 (18.1)	69.0 (25.5)
Post-op 2 yr mean (SD)	28	34.4 (13.8)	12.4 (3.7)	13.7 (5.5)	23.9 (11.5)	5.6 (4.3)	49.8 (19.0)	69.7 (27.7)
Post-op 3 yr mean (SD)	6	33.0 (10.6)	11.8 (4.7)	16.3 (3.9)	24.0 (9.8)	7.8 (0.5)	59.8 (17.0)	81.6 (23.5)

ADL: Activities of daily living; CS: Constant score.

Table 5 Categories of outcome after shoulder arthroplasty using the constant score

Category	Total CS (/100)	Age and sex adjusted CS (%)
Average shoulder function before arthroplasty	< 30	< 40
Post-op unsatisfactory	< 30	< 40
Post-op fair outcome	30-39	40-49
Post-op good outcome	40-59	50-69
Post-op very good outcome	60-69	70-79
Post-op excellent outcome (*i.e.*, a virtually normal shoulder)	⩾ 70	⩾ 80

CS: Constant score.

Table 6 Stratified outcome for the vaios primary total shoulder replacements using the adjusted constant score (adjusted for age and sex)

Post-op outcome	Adjusted CS (%)	No. of anatomic TSRs n = 46	% anatomic TSRs using adjusted CS	No. of inverse TSRs n = 58	% Inverse TSRs using adjusted CS
Unsatisfactory outcome	< 40	10	22	9	16
Fair outcome	40-49	9	20	5	9
Good outcome	50-69	9	20	14	24
Very good outcome	70-79	3	7	5	9
Excellent outcome	⩾ 80	15	33	25	43
Totals		46	100	58	100

CS: Constant score.

become more meaningful if they are converted into different grades of improvement.

We have therefore developed a meaningful grading system for assessing the outcomes following arthroplasty using either the CS as shown in Table 5 or the age and sex adjusted CS as shown in Table 6. These results are more meaningful than means and standard deviations and allow us to appreciate that 60% of patients achieve a good, very good or excellent result after anatomic Total Shoulder Replacement while 76% achieve a good, very good or excellent result after Inverse or Reverse shoulder replacement using the age and sex adjusted CS.

CONCLUSION

It is difficult to choose the best scoring system as a "best choice of outcome measurement tool" for patients with shoulder problems. There remains a need to develop a comprehensive outcome measurement tool that can adequately deal with both the clinician's and the patient's perspective. None of the scoring systems ideally fulfil this criterion. For instance, the clinically-based outcome measuring tool may not satisfy the patient, and the patient self-assessment tools may not provide the information that the clinician believes is important. Patient-based assessment tools

may fall a victim to bias as the patient may under or over report symptoms: under-reporting if they wish to please the surgeon or over-reporting for secondary (or compensation related) gain. Similarly, physician-based tools may not truly reflect what the patient feels about their outcome. Therefore it makes sense to combine scoring systems when collecting data for outcome measures, and we would recommend using multiple scores, including clinically - based and patient self-assessment tools. We currently use the CS and OSS in our unit for the majority of our patients but the SST has also been proven to be a valuable outcome assessment in North America. These assessment do need to be carried out at the appropriate time and our policy in Nottingham is to always carry out a pre-operative assessment and then to carry out the first post-operative evaluation at 6 mo after surgery when the patient's condition is reaching a plateau. The United Kingdom health service has become much more focused on using PROMs and many are moving towards using the OSS as their preferred PROM for general shoulder assessment.

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P- Reviewer: Juneja D **S- Editor**: Ji FF
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DOI: 10.5312/wjo.v6.i2.252

World J Orthop 2015 March 18; 6(2): 252-262
ISSN 2218-5836 (online)

Review of evolution of tunnel position in anterior cruciate ligament reconstruction

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Author contributions: All authors contributed to this paper.
Conflict-of-interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Telephone: +44-78-60454942
Received: May 28, 2014
Peer-review started: May 29, 2014
First decision: August 18, 2014
Revised: December 1, 2014
Accepted: December 16, 2014
Article in press: December 17, 2014
Published online: March 18, 2015

Abstract

Anterior cruciate ligament (ACL) rupture is one of the commonest knee sport injuries. The annual incidence of the ACL injury is between 100000-200000 in the United States. Worldwide around 400000 ACL reconstructions are performed in a year. The goal of ACL reconstruction is to restore the normal knee anatomy and kinesiology. The tibial and femoral tunnel placements are of primordial importance in achieving this outcome. Other factors that influence successful reconstruction are types of grafts, surgical techniques and rehabilitation programmes. A comprehensive understanding of ACL anatomy has led to the development of newer techniques supplemented by more robust biological and mechanical concepts. In this review we are mainly focussing on the evolution of tunnel placement in ACL reconstruction, focusing on three main categories, *i.e.*, anatomical, biological and clinical outcomes. The importance of tunnel placement in the success of ACL reconstruction is well researched. Definite clinical and functional data is lacking to establish the superiority of the single or double bundle reconstruction technique. While there is a trend towards the use of anteromedial portals for femoral tunnel placement, their clinical superiority over trans-tibial tunnels is yet to be established.

Key words: Anterior cruciate ligament; Anatomy; Biomechanics; Isometry; Tunnel

Core tip: We are mainly focussing on the evolution of tunnel placement in anterior cruciate ligament (ACL) reconstruction especially on three main categories, *i.e.*, anatomical, biological and clinical outcomes. The importance of tunnel placement in the success of ACL reconstruction is well researched and still ongoing. Due to the nature of the intervention it is difficult to attain definite clinical and functional data to establish the superiority of the single or double bundle reconstruction technique.

Rayan F, Nanjayan SK, Quah C, Ramoutar D, Konan S, Haddad FS. Review of evolution of tunnel position in anterior cruciate ligament reconstruction. *World J Orthop* 2015; 6(2): 252-262 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/252.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.252

ANTERIOR CRUCIATE LIGAMENT - ANATOMICAL PERSPECTIVE

The anterior cruciate ligament (ACL) is an intracapsular but extra synovial structure. It is the primary static stabilizer in the anterior translation of the tibia in relation to the femur and helps in preventing extreme tibial rotations. The ACL originates from the posteromedial aspect of the lateral femoral condyle in the intercondylar notch and attaches to anterior aspect of the tibial plateau. The femoral attachment of the ACL is oriented along the long axis of femur. The centre of the ACL lies about 9 mm posterior to the intermeniscal ligament and 7-8 mm from the PCL, nearly 6 mm anterior to a projected line from the apex of the medial tibial eminence[1,2]. The tibial attachment lies parallel to the anteroposterior axis of tibia.

The ACL is divided into two bundles based on their insertion on the tibial footprint, namely anteromedial (AM) and posterolateral (PL)[3]. The two bundles were first described by Weber *et al*[4] and Longo *et al*[5]. These bundles are seen as early as in the fetal life[6]. The AM and PL bundles differ in their length, width and the insertional area on femur and tibia. In 90 degrees of knee flexion, these insertion points are horizontal to each other whereas in extension, they are oriented vertically. The AM and PL bundles are oriented parallel in extension and change to being crossed in flexion. The average intra-articular length is 33 mm (range 22-41 mm). The width of ACL ranges from 7 to 17 mm with an average of about 11 mm. The average length of AM bundle is 33 mm and PL bundle is 18 mm. While the average cross-sectional area is 47 mm in males, it is about 37 mm in females[3].

In knee flexion, the larger AM bundle tightens and PL bundle relaxes. In extension, the PL bundle tightens while the AM bundle relaxes. As different portions of the bundles tighten throughout the range of motion, the ACL remains functional throughout the range of motion[7]. The principal blood supply to the ACL is from middle genicular artery, which is a branch of popliteal artery. It reaches ACL by piercing the posterior capsule[7]. The inferomedial and inferolateral genicular arteries supply ACL from the fat pad. The posterior articular nerve, a branch of the tibial nerve, supplies the ACL. The ACL has proprioceptive nerve fibres, which helps protect the knee joint. There are several mechanoreceptors within the ACL, which contributes to proprioception[8-12]. The ACL is mainly composed of highly organized matrix of type Ⅰ collagen 1 which constitutes about 90% of the fibres and the rest is predominantly type Ⅲ collagen. As the ACL has inherent viscoelasticity, it can stretch and return to its normal resting length without suffering any significant structural damage[7].

EVOLUTION OF TUNNEL PLACEMENT IN ACL RECONSTRUCTION

Incorrect positioning of either tibial or femoral tunnel has remained the most common reason for suboptimal outcome or failure of the ACL reconstruction[13,14]. Anterior placement of femoral tunnel could lead to restriction of knee flexion and tightness of the graft in flexion. Placing the tibial tunnel slightly anteriorly may cause graft impingement subsequently leading to failure. Single bundle ACL reconstruction has been used successfully for the last few decades with good outcomes. It clearly has certain advantages in terms of surgical time, technical ease, low cost, fewer complications, ease of revision and less tunnel widening[6]. But recent long term studies have shown the long term sequelae of arthritic changes and persistent instability (especially rotatory) and inability to return to previous level of activity[15,16]. With the ever improving techniques in arthroscopic surgery, double bundle ACL reconstruction was recommended to reconstruct AM and PL bundles separately to imitate the normal anatomy of the native ACL, thus helping the restoring knee stability more effectively and theoretically eliminating the "Pivot Shift". Recent studies have shown better biomechanical stability (antero-posterior and rotational) and clinical outcome with double bundle compared to single bundle ACL reconstruction[17-20]. The double bundle ACL reconstruction may have the added advantage of better graft-bone healing because the increased graft-bone contact area[21]. However, some studies have shown no difference in the clinical outcome between the single and double bundle ACL reconstruction and the controversy related to single and double bundle technique still remains[5,6,18-20,22]. ACL has been reconstructed using various tunnel techniques (for example single tibial tunnel with single femoral tunnel, single tibial tunnel with double femoral tunnel or double tibial tunnel with double femoral tunnel). A survey among the 20 panellists worldwide suggested that one of the most common techniques used was 2 femoral and 2 tibial tunnels, hamstring graft being the most common graft. There was greater disparity among them about the AM bundles in femur but were consistent in their femoral antero-lateral bundles[23].

Transtibial tunnel drilling often results in non-anatomic placement of the femoral tunnels[24]. In the recent years, the transtibial tunnel drilling has been increasingly replaced by anatomic femoral tunnel as such tunnels are believed to offer increased rotational stability, translational and tensioning patterns similar to the native ACL[25,26]. There is evidence is the literature about the high revision rates in non-anatomical placement of ACL[27]. This could represent inadequacy of transtibial tunnel drilling technique for placement within the native femoral and tibial footprints of the

ACL[28,29]. Placing the femoral tunnel in the anatomical femoral footprint of the ACL results in closer knee joint kinematics closer to the intact knee than a tunnel suited for the best graft isometry[30]. Integrity of the posterior cortex of the femur is of paramount importance (at least 2 mm of the posterior rim of the femoral tunnel to the posterior edge of the notch roof) for a successful outcome of the surgery.

CONCEPT OF ISOMETRY

The ligaments in the body are taut and maintain their length during the range of movements of the joint concerned. This cannot be strictly being applicable to all the ligaments in the body. This "concept of isometry" is important in ACL, as full range of movements (ROM) can be achieved without causing significant long term deformation. Isometry in ACL does not exist as there is no one point on femur that maintains a fixed distance from a single point on the tibia during the range of motion of the knee. The AM bundle tightens in flexion and slack in extension. The fibres of AM bundle which has relatively vertical attachment on the femur are more isometric.

In order to achieve graft isometry the optimal position of the femoral tunnel was thought be 11'-o clock (right) or 1 clock position (with respect to the apex of the notch, modified femoral clock wall model) which places the graft high and posterior in the lateral femoral condyle[18]. (However, the o'clock terminology is not favoured by everybody, as they argue that femoral notch is a three dimensional structure and placing the tunnel according the clock may lead to non-anatomical placement). If the graft is placed anterior to this position, it will be tight in flexion, thus restricting the full ROM. If the graft is placed posterior to this position, the graft will tighten with knee extension[31].

CONCEPT OF ANATOMICAL TUNNELS

While the initial literature proposed ACL reconstruction with graft isometry, the subsequent literature proved that "graft isometry" is not the most crucial factor in ACL reconstruction but it is the graft placement in the "anatomical attachment" of the ACL[32]. As the anatomical placement of the femoral tunnel better resists the rotational force it may reduce the risk of later osteoarthritis[25,33]. The footprint of the femoral attachment of the ACL and "Lateral Intercondylar Ridge" (Resident's Ridge) serve as useful landmarks for the placement of femoral tunnel. It is better visualized with a 70 degree scope (helps in avoiding the parallax error while using 30 degree arthroscopic camera) and through anteromedial portal[34-36] (Table 1).

Resident's Ridge is commonly located just anterior to the femoral attachment of the ACL. Awareness of "Resident's Ridge" is important as it can mislead the inexperienced surgeons to place the femoral tunnels in incorrect positions[34]. "Lateral intercondylar ridge" and the "lateral bifurcate ridge" serve as the bony landmarks for the femoral attachments[35]. At knee in 90 degree flexion, lateral intercondylar ridge runs from proximal to distal through the entire length of ACL foot print. No ACL fibres attach superior to the ridge. Lateral bifurcate ridge when present, separates the AM and the PL bundles femoral insertions and it runs almost perpendicular to the lateral intercondylar ridge. In the absence of consistent intra-operative soft tissue or osseous land marks, "Ruler method" can be used to determine the mid-bundle femoral tunnel positioning[37]. Radiographic quadrant method using Blumensaat's line can be used to locate optimal femoral footprint of ACL[38].

TIBIAL TUNNEL

Correct placement of the tibial tunnel is vital for successful surgery and to avoid complications such as anterior knee pain, loss of knee extension, instability and graft impingement. An ideal position for the tibial tunnel would at the centre of the footprint of the ACL in the intercondylar area. This position is located using multiple bony and osseous landmarks[1,2,39,40]. The outside entry in to the tibial tunnel is often at 4 cm from tibial joint line and 2 cm medial to the tibial tubercle. Several radiographic methods have been employed to locate the ideal place for a tibial tunnel[41,42]. An ideal tibial tunnel should avoid the PCL impingement. This can be done by performing notchplasty, drilling the tibial tunnel at about 60-65 degree angle with respect to medial joint line and by placing the lateral edge of the tibial tunnel through the lateral tibial spine[6].

BIOMECHANICAL STUDIES ON TUNNEL POSITIONING

There have been several biomechanical studies that have studied the effects of different tunnel positioning and graft placement in ACL reconstruction (Table 2). These studies have mainly compared graft placement in the femur at the standard 11-o'clock more vertical position for the right knee (or 1-o'clock position for the left knee) with grafts placed at the more oblique or lateral 9.30 to 10-o'clock position[43-45]. Other studies have analysed the effect of anatomic graft placement and isometric positions[30,46,47].

TEN-O'CLOCK OR ELEVEN-O'CLOCK POSITION?

ACL reconstruction should re-create the coronal and sagittal obliquity of the graft similar to the orientation of the intact ACL. Increasing the coronal plane obliquity of the femoral tunnel has gained popularity over the last decade as biomechanical studies have shown it to be superior to vertical tunnel placement[43,45]. Loh *et al*[43] tested 10 human cadaveric knees with

Table 1 Anatomy and evolution summary

Ref.	Study type	Results/conclusion
Petersen *et al*[1]	Anatomical	Describes the anatomy of ACL with histology. Describes definite landmarks of ACL attachments
Ferretti *et al*[2]	Cadaveric	The medial tibial eminence and the intermeniscal ligament may be used as landmarks to guide the correct tunnel placement in an anatomical ACL reconstruction
Schultz *et al*[8]	Histological	In this first histological demonstration of mechanoreceptors in human ACL, it seemed likely that mechanoreceptors provide proprioceptive information and contribute to reflexes inhibiting injurious movements of the knee
Schutte *et al*[9]	Histological	Three morphological types of mechanoreceptors and free nerve-endings were identified: two of the slow-adapting ruffini type and the third, a rapidly adapting pacinian corpuscle. Rapidly adapting receptors signal motion and slow-adapting receptors subserve speed and acceleration. Free nerve-endings, which are responsible for pain, were also identified within the ligament. These neural elements comprise 1 percent of the area of the anterior cruciate ligament
Adachi *et al*[11]	Histological	Positive correlation between the number of mechanoreceptors and accuracy of the joint position sense, suggesting that proprioceptive function of the ACL is related to the number of mechanoreceptors. Recommended preserving ACL remnants during ACL reconstruction
Georgoulis *et al*[12]	Anatomical and histological	In patients with an ACL remnant adapted to the PCL, mechanoreceptors exist even 3 yr after injury
Mae *et al*[17]	Cross over trial using cadaveric laboratory study	The ACL reconstruction *via* 2 femoral sockets using quadrupled hamstring tendons provides better anterior-posterior stability compared with the conventional reconstruction using a single socket
Strauss *et al*[24]	Descriptive laboratory study	During hamstring ACL reconstructions, the constraints imposed by a coupled drilling technique result in nonanatomic femoral tunnels that are superior and posterior to the native femoral insertion. Clinical relevance: Anatomic femoral tunnel placement during hamstring ACL reconstructions may not be possible using a coupled, transtibial drilling approach
Zavras *et al*[26]	Controlled laboratory study	Laxity was restored best by grafts tensioned to a mean of 9 ± 14 N, positioned isometrically and 3 mm posterior to the isometric point. Their tension remained low until terminal extension. Grafts 3 mm anterior to the isometric point caused significant overconstraint, and had higher tension beyond 80 degrees knee flexion
Musahl *et al*[30]	Controlled laboratory study	Neither femoral tunnel position restores normal kinematics of the intact knee. A femoral tunnel placed inside the anatomical footprint of the ACL results in knee kinematics closer to the intact knee than does a tunnel position located for best graft isometry
Siebold *et al*[18]	Cadaveric dissection Laboratory study	Clinical relevance: This study provides an anatomic description of the femoral AM and PL insertions including gender differences, landmarks, and arthroscopic orientation models for DB bone tunnel placement
Hefzy *et al*[31]	Cadaveric	Study found that altering the femoral attachment had a much larger effect than had altering the tibial attachment. The axis of the 2 mm region was nearly proximal-distal in orientation and located near the center of the ACL's femoral insertion. Attachments located anterior to the axis moved away from the tibial attachment with flexion, whereas attachments located posterior to the axis moved toward the tibia
Hutchinson *et al*[34]	Cadaveric	The phenomenon of "resident's ridge" is accounted for by a distinctive change in slope of the femoral notch roof that occurs just anterior to the femoral attachment of the ACL. The density change apparent at the time of notchplasty is probably caused by the transition between normal cortical thickness just anterior to the ACL and the cortical thickness of the ACL attachment. No distinctive increased cortical thickness can be identified as "resident's ridge"-
Ferretti *et al*[35]	Histological and cadaveric anatomic study	The ACL femoral attachment has a unique topography with a constant presence of the lateral intercondylar ridge and often an osseous ridge between AM and PL femoral attachment, the lateral bifurcate ridge. Clinical relevance: These findings may assist surgeons to perform ACL surgery in a more anatomic fashion
Purnell *et al*[36]	Descriptive cadaveric study	Clinical relevance: Bony landmarks can be used to aid in anatomical anterior cruciate ligament reconstruction
Bernard *et al*[38]	Cadaveric anatomic study	By using this radiographic quadrant method combined with fluoroscopic control during surgery, authors were able to reinsert the ACL at its anatomic insertion site. This method is independent of variation in knee size or film-focus distance, easy to handle, and reproducible.
Colombet *et al*[40]	Cadaveric study	The Retro Eminence Ridge provides an easily identifiable and accurate reference point that can be used clinically. On a lateral radiograph, the positions of the tibial attachments can be referenced to Amis and Jakob's line. This method, different from Blumensaat's line, is independent of knee flexion
Amis *et al*[41]		A study of knee anatomy and graft placement concluded that the tibial attachment must be posterior enough to avoid graft impingement against the femur, and methods to attain this were presented

ACL: Anterior cruciate ligament; AM: Anteromedial; PL: Posterolateral.

Table 2 Biomechanics summary

Ref.	Study type	Femoral tunnel positioning	Anatomic or isometric graft placement	Tibial tunnel positioning	Results
Loh *et al*[43]	Controlled laboratory study	Reconstructed bone-patella tendon-bone graft at the 10 and 11-o'clock position	-	-	Both the tunnel positions were equally effective under an anterior tibial load, the 10-o' clock position more effectively resists rotatory loads when compared to the 11-o'clock position
Scopp *et al*[45]	Controlled laboratory study	Reconstructed bone-patella tendon-bone graft at standard or oblique tunnel position	-	-	The group with the standard 30° from vertical reconstruction had significantly more laxity in internal rotation. The oblique 60° femoral tunnel more closely restored normal knee kinematics
Markolf *et al*[44]	Controlled laboratory study	Compared the ACL graft placed at the 11-o'clock and 9:30- to 10-o'clock femoral tunnel positions during a simulated pivot shift event	-	-	There were no significant differences in tibial rotations or tibial plateau displacements during the pivot shift between standard and oblique femoral tunnels
Musahl *et al*[30]	Controlled laboratory study	-	Tested cadaveric knees in response to a 134 N anterior load and a combined 10 Nm valgus and 5 Nm internal rotation load	-	A femoral tunnel placed inside the anatomical footprint of the ACL results in knee kinematics closer to the intact knee than does a tunnel position located for best graft isometry
Driscoll *et al*[46]	Controlled laboratory study	-	Compared femoral tunnels that were reamed through the anteromedial portal and centred alternatively in either the AM portions of the femoral footprint or the centre of the femoral footprint		Femoral tunnel positioned in the true anatomic centre of the femoral origin of the ACL may improve rotatory stability without sacrificing anterior stability
Abebe *et al*[47]	Controlled laboratory study	-	Compared femoral tunnels that was placed near the anterior and proximal border of the ACL and another near the centre of the ACL footprint	-	Grafts placed anteroproximally on the femur were in a more vertical orientation and therefore less likely to provide sufficient restrain. Normal orientation of the graft was better achieved with anatomical placement of the graft ultimately resulting in a more stable knee
Bedi *et al*[50]	Controlled laboratory study	-	-	Evaluated the effect of 3 tibial tunnel positions on restoration of knee kinematics after ACL reconstruction: over the top (non-anatomic positioning), anterior footprint and posterior footprint with a standard central femoral tunnel position at the femoral ACL footprint	Anterior positing of the tibial tunnel either in the over the top position or at the anterior foot print produces favourable kinematics than posterior positioning of the tibial tunnel. However, there is a risk of causing secondary notch impingement leading to graft attrition and failure

ACL: Anterior cruciate ligament; AM: Anteromedial.

reconstructed bone-patella tendon-bone graft at the 10 and 11-o'clock position. They compared two external loading conditions: anterior tibial load of 134 N with the knee at full extension, 15°, 30°, 60° and 90° of flexion and a combined rotatory load of 10 Nm valgus and 5 Nm internal tibial torque with the knee at 15° and 30° of flexion. The authors concluded while both the tunnel positions were equally effective under an anterior tibial load, the 10-o'clock position more effectively resists rotatory loads when compared to the 11-o'clock position[43]. These findings were further supported by a similar experimental study by Scopp

et al[45]. The authors measured the anterior tibial translation with a 100N load and external and internal tibial rotation with a 6.5 Nm torque applied at 30° and 90° of flexion in 10 matched pairs of human cadaveric knees. They found that the group with the standard 30° from vertical reconstruction had significantly more laxity in internal rotation, therefore concluding that ACL reconstruction using the oblique 60° femoral tunnel more closely restored normal knee kinematics[45].

Markolf *et al*[44] however questioned the rationale for placing an oblique femoral tunnel. They compared the abilities of an ACL graft placed at the 11-o'clock and 9:30- to 10-o'clock femoral tunnel positions to limit tibial rotation and lateral tibial plateau displacement during a simulated pivot shift event. For each specimen, the authors found a unique combination of valgus moment and iliotibial band tension that caused the ACL deficient knee to pivot. The same combination of loads was then applied to the ACL reconstructed knee. They believed that their test methodology better simulates the pivot shift that occurs during clinical examination compared to the previous two studies by Loh *et al*[43] and Scopp *et al*[45]. They concluded that moving the femoral tunnel from the standard location to a more oblique position in the notch did not significantly alter pivot shift kinematics.

ANATOMIC *VS* ISOMETRIC GRAFT PLACEMENT?

The anatomical footprint of the ACL is located in a different position than one positioned for best graft isometry. Femoral tunnel position for best isometry (over-the-top position) is located high in the femoral notch whist the anatomical footprint of the ACL is located lower[30]. The concept of isometric graft placements is to avoid changes in graft length and tension during knee flexion and extension to avoid graft failure by overstretching[26,48]. However, there are concerns that the isometric placement of the graft will result in a more vertically orientated graft in the sagittal plane and therefore less effective at resisting motions in the transverse plane. Furthermore, basic science studies have shown that the normal ACL is not isometric with the anteromedial bundle of the ACL experiencing higher stress during flexion and the posterolateral bundle experiencing higher stress during extension[49].

Several studies have shown that positioning the femoral tunnel position inside the anatomical footprint of the ACL results in knee kinematics closer to the intact knee than does a tunnel position located for best isometry[30,46]. Musahl *et al*[30] tested 10 cadaveric knees in response to a 134 N anterior load and a combined 10 Nm valgus and 5 Nm internal rotation load and found a significant difference between these 2 tunnel positions[30]. In another study, Driscoll *et al*[46] compared femoral tunnels that were reamed through the anteromedial portal and centred alternatively in either the AM portions of the femoral footprint or the centre of the femoral footprint[46]. They concluded that a femoral tunnel positioned in the true anatomic centre of the femoral origin of the ACL may improve rotatory stability without sacrificing anterior stability[46]. These findings were further supported in a more recent study conducted by Abebe *et al*[47] who compared femoral tunnels that was placed near the anterior and proximal border of the ACL and another near the centre of the ACL footprint. The results of their study showed that grafts placed antero proximally on the femur were in a more vertical orientation and therefore less likely to provide sufficient restrain. Normal orientation of the graft was better achieved with anatomical placement of the graft ultimately resulting in a more stable knee[47].

TIBIAL TUNNEL POSITIONING

Bedi *et al*[50] evaluated the effect of tibial tunnel position on restoration of knee kinematics after ACL reconstruction. Ten paired cadaveric knees were subjected to standardized Lachman and mechanized pivot shift examination[50]. Biomechanical testing was performed on ACL reconstruction using 3 tibial tunnel positions- over the top (non-anatomic positioning), anterior footprint and posterior footprint with a standard central femoral tunnel position at the femoral ACL footprint. The results of their study demonstrated that tibial tunnel positioning of a single bundle ACL graft has a critical influence on knee stability and impingement. Anterior positing of the tibial tunnel either in the over the top position or at the anterior foot print produces favourable kinematics than posterior positioning of the tibial tunnel. However, the authors warned that these biomechanical advantages have a risk of causing secondary notch impingement leading to graft attrition and failure. Therefore, the authors recommended that the tibial tunnel should be positioned in the central aspect of the native ACL footprint may offer the best compromise.

CLINICAL STUDIES ON TUNNEL POSITIONING

There have been relatively fewer studies looking at the clinical outcomes of different tunnel positions in ACL reconstruction. Anatomic *vs* non-anatomic tunnel placement is still debated though there is some evidence to support the anatomic approach. Most studies compare the two main techniques for drilling the femoral tunnel, the transtibial technique and the use of a separate anteromedial portal (Table 3) Overall, most studies agree that the anteromedial portal technique allows a more anatomic femoral tunnel position when compared to the transtibial technique[51,52]. Some studies have compared the

Table 3 Clinical studies summary

Ref.	Year	Study type	Study size	Graft type	Femoral tunnel positioning	Tibial tunnel positioning	Follow-up time	Outcome measures	Results
Adebe *et al*[57]	2011	Retrospective cohort	22 patients	Hamstring and (BPTB)	Anatomic *vs* non-anatomic	-	6-36 mo	Tibial translation and rotation	Anatomic tunnel more stable in terms of anterior and medial translation and internal rotation
Alentorn-Geli *et al*[65]	2010	Cross-sectional comparative	47 patients	BPTB	Transtibial *vs* anteromedial portal techniques	-	2-5 yr	IKDC score; knee stability; ROM; one-leg hop test; mid-quadriceps circumference; VAS for satisfaction with surgery; Lysholm score; Tegner score; SF-12	From AMP technique, significantly lower recovery time from surgery to walking without crutches, return to normal life, return to jogging, training and play. Significantly better knee stability values but no difference in other functional scores surgery
Avadhani *et al*[69]	2010	Prospective cohort	41 patients	BPTB	-	AP position of tunnel	Minimum 2 yr	IKDC score; modified lysholm score	Placing the tibial tunnel in the anterior 25% of the tibial plateau was associated with poor knee outcomes
Behrend *et al*[59]	2006	Retrospective cohort	50 patients	BPTB	Position assessed using quadrant method of bernard and hertel	Position assessed using criteria of staubli and rauschning	Mean 19 mo	IKDC score	More anterior the femoral canal, highly significant correlation with poorer IKDC score. Position of the tibial tunnel had no statistically significant effect on IKDC score
Duffee *et al*[61]	2013[6]	Prospective cohort	436 patients	Hamstring and BPTB	Transtibial *vs* anteromedial portal techniques	-	6 yr	KOOS	No difference between the techniques in terms of predicting functional outcome with KOOS
Fernandes *et al*[60]	2014	Prospective cohort	86 patients	Hamstring and BPTB	Anteromedial footprint (anatomic) and high anteromedial position	-	6 and 12 mo	IKDC score; tegner score; lysholm scale; return to sports	Femoral tunnel positions at AM footprint and high AM position associated with earlier return to sports on previous Tegner score level and better functional outcomes at 12 mo
Franceschi *et al*[62]	2013	Retrospective cohort	94 patients	Hamstring	Transtibial *vs* anteromedial portal techniques	-	Minimum 5 yr	IKDC score; Lysholm scale; KT-1000 arthrometer; Lachman test; Pivot shift test; radiographic assessment	No difference between the two techniques in terms of functional scores (lysholm and IKDC) though the anteromedial portal technique provided better rotational and anterior translational stability
Hatayama *et al*[68]	2013	Prospective cohort	60 patients	Hamstring	-	AP position of tibial tunnel	2 yr	Pivot shift test; stress radiographs; 2nd look arthroscopy	Anterior placement of the tibial tunnel inside the footprint led to better anterior knee stability
Hosseini *et al*[58]	2012	Retrospective cohort	26 patients	Hamstring, BPTB and allograft	Non-anatomic	Non-anatomic	-	Patients undergoing revision ACL surgery: MRI based 3D modelling	Both the tibial and femoral tunnel positions in the failed ACLR were non-anatomic compared to native ACL values
Jepsen *et al*[55]	2007	Prospective randomised trial	60 patients	Hamstring	High (1 o'clock) *vs* Low (2 o'clock) positions	-	1 yr	Laxity; IKDC Evaluation and Examination forms; radiograph assessment	No significant difference in the laxity at 25 degrees and 70 degrees or scores on the IKDC examination form. Significant difference in the scores on the IKDC evaluation form
Koutras *et al*[64]	2013	Prospective cohort	51 patients	Hamstring	Transtibial *vs* anteromedial portal techniques	-	3 and 6 mo	Lysholm score; isokinetic tests; functional tests	AMP technique had significantly better suggesting a quicker return to function and performance
Noh *et al*[52]	2013	Prospective randomised trial	61 patients	Allograft	Transtibial *vs* anteromedial portal techniques	-	Mean 30.2 mo	Lachman test; pivot shift test; IKDC score; lysholm score; tegner activity scale; radiograph and MRI assessment	AMP technique resulted in a more posterior femoral tunnel position than the TT technique and knees with this technique were more stable with a higher lysholm score

Ohsawa *et al*[67]	2012	Retrospective cohort	121 patients	Hamstring	-	Posterior tibial landmark *vs* anterior tibia landmark	Minimum 2 yr	3D CT; 2nd look arthroscopy + EUA; Lachman, pivot shift and side-side stability tests; lysholm score	Pivot shift and side to side stability tests and knee flexion were significantly better in the anterior landmark group
Park *et al*[54]	2010	Cross-sectional	70 patients	Allograft	High (1 o'clock) *vs* low (2 o'clock) positions	-	Intraoperative	Intraoperative anterior and rotational knee stability at differing degrees of flexion	The low femoral tunnel group showed significantly better intraoperative internal rotational stability at 0° and 30° of flexion
Rahr-Wagner *et al*[63]	2013	Prospective cohort	9239 patients	-	Transtibial *vs* anteromedial technique	-	4 yr	Need for revision; pivot-shift and instrumented objective test	Increased risk of revision ACL surgery when using the AM technique compared with the TT technique
Sadoghi *et al*[56]	2011	Prospective cohort	53 knees	Hamstring and BPTB	Anatomic *vs* non-anatomic	Anatomic *vs* non-anatomic	1 yr	3D CT; Tegner score;WOMAC score; IKDC score; KT-1000 arthrometer measurements; pivot-shift test	Significantly superior clinical outcome in anatomic ACL reconstructions in terms of higher clinical scores (tegner and IKDC), higher anterior posterior stability, and less pivot shift
Seon *et al*[53]	2011	Prospective cohort	58 patients	Allograft	High (1 o'clock) *vs* low (2 o'clock) positions	-	Minimum 2 yr	Lysholm; Tegner; Clinical and radiographic stability	Low tunnel group had significantly better internal rotational stability at 0 and 30 degrees of knee flexion
Seo *et al*[66]	2013	Retrospective cohort	89 patients	Allograft	Transtibial *vs* "outside in" techniques	-	Minimum 1 yr	3D CT; pivot-shift; lachman; IKDC; lysholm; tegner; ROM	A more anatomical femoral tunnel with better knee joint rotational stability on pivot shift test
Taketomi *et al*[51]	2013	Case series	34 patients	Hamstring	Anatomic	-	2 yr	Lysholm score; IKDC score; KT-2000 arthrometer; lachman test; reverse pivot-shift test	Excellent short-term using the anatomic femoral tunnel objectively, subjectively and in terms of knee stability

ACL: Anterior cruciate ligament; AM: Anteromedial; TT: Transtibial; KOOS: Knee injury and osteoarthritis outcomes score; ACLR: Anterior cruciate ligament reconstruction; SF-12: Short form 12; VAS: Visual analogue scale; AP: Anter posterior; TT: Transtibial; AMP: Antero medial portal; ROM: Range of movements.

clinical outcomes of high (1 o'clock/11 o'clock) femoral tunnel position *vs* low (2 o'clock/10 o'clock) position[53-55].

ANATOMIC *VS* NON-ANATOMIC FEMORAL TUNNEL POSITION

Excellent short-term outcomes using the anatomic femoral tunnel have been reported objectively (IKDC Knee score, Lachman and pivot shift tests and a KT arthrometer, Tegner score, WOMAC score, IKDC score), subjectively (Lysholm score) and in terms of knee stability with double bundle ACL reconstruction using the anteromedial portal technique as well as in a comparison study looking at bone-patellar tendon-bone and hamstring grafts[51,56]. 3D-computed tomography was used to assess tunnel position in these two cases. Studies have also documented worse clinical outcomes and poorer IKDC scores with nonanatomical positions[57-59]. Anatomical femoral tunnel positions may be associated with earlier return to sports on previous Tegner score level and better functional outcomes at 12 mo follow-up[60].

TRANSTIBIAL *VS* ANTEROMEDIAL PORTAL TECHNIQUES FOR THE FEMORAL TUNNEL

There is still debate as to whether this changes the clinical outcomes for the patient. No difference in functional outcome was demonstrated by two large cohort studies[61,62]. Moreover with the transtibial technique, there were significantly higher odds of the knee requiring repeat ipsilateral knee surgery[61]. The latter finding is also supported by, a Danish Knee Ligament Reconstruction Registry study (RR = 2.04, 95%CI: 1.39-2.91)[63]. However, some benefits of AMP have been documented such as increased stability with a higher Lysholm score, better lateral movement functional tests at 3 and 6 mo, significantly lower recovery time from surgery to walking without crutches, return to

normal life, return to jogging and significantly higher activity level at 3-5 and 6-10 year follow-up[52,64,65]. Seo *et al*[66] (2013) compared the "outside in" technique, to the transtibial technique for single bundle ACL reconstruction. They found with this technique, a more anatomical femoral tunnel placement was achieved with better knee joint rotational stability on pivot shift test and subjectively on the IKDC questionnaire items for instability. There was however no difference on the Lysholm score, range of movement measurements, Lachman tests or Tegner activity scale[66].

High (1 o'clock/11 o'clock) vs low (2 o'clock/10 o'clock) femoral tunnel position

The low tunnel has been shown to have similar or significantly better intraoperative internal rotational stability at 0 and 30 degrees of knee flexion compared to high position[53-55]. However, the functional benefit of this has been supported by one study and refuted by others[53-55]. There was no significant difference between the groups in stability tests or functional scores at final follow-up.

TIBIAL TUNNEL POSITION

Few studies in the literature which focus primarily on the clinical outcomes of the tibial tunnel position in ACL reconstruction. Anterior placement of the tibial tunnel inside the footprint has shown better anterior knee stability, pivot shift and side to side stability tests and knee flexion but no difference in loss of knee extension or graft failure at minimum 2 year follow-up[67,68]. The intermeniscal ligament and Parsons knob should be used as the landmarks for the tibial tunnel for ACL reconstruction. Maximum favourable results were achieved through 35%-46% anteroposterior placement of the tibial tunnel[69]. However that too anterior (anterior 25% of the tibial plateau) placement of the tibial tunnel results in poor clinical outcomes[69]. However, the effect of tibial tunnel position on the clinical outcome (measured by IKDC score) is not established[59,69]. Overall, the literature suggests that more anatomical placement of both the tibial and femoral tunnels confers better stability to the knee and some benefit in terms of functional outcomes. To achieve this for femoral tunnel, the anteromedial portal or outside-in techniques have been suggested to be better.

In conclusion, our understanding of ACL injuries and their reconstruction continues to evolve. The importance of tunnel placement in the success of ACL reconstruction is well established. Definite clinical and functional data is lacking to establish the superiority of the single or double bundle reconstruction technique. While there is a trend towards the use of anteromedial portals for femoral tunnel, their clinical superiority over trans tibial tunnels is yet to be established. Any change in clinical practice of anatomical bundles, tunnel position or placement for ACL reconstruction must follow long-term clinical study results to establish definite advantages of newer techniques or bio-mechanical theories.

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P- Reviewer: Boffano P **S- Editor**: Ji FF
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DOI: 10.5312/wjo.v6.i2.263

World J Orthop 2015 March 18; 6(2): 263-268
ISSN 2218-5836 (online)

MINIREVIEWS

Frozen shoulder: A systematic review of therapeutic options

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Author contributions: All authors contributed equally to this work.
Conflict-of-interest: There are no conflicts of interests for any authors.

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Telephone: +44-13-92411611
Received: May 28, 2014
Peer-review started: June 18, 2014
First decision: August 14, 2014
Revised: September 14, 2014
Accepted: October 1, 2014
Article in press: October 10, 2014
Published online: March 18, 2015

Abstract

Frozen shoulder is a common disease which causes significant morbidity. Despite over a hundred years of treating this condition the definition, diagnosis, pathology and most efficacious treatments are still largely unclear. This systematic review of current treatments for frozen shoulder reviews the evidence base behind physiotherapy, both oral and intra articular steroid, hydrodilatation, manipulation under anaesthesia and arthroscopic capsular release. Key areas in which future research could be directed are identified, in particular with regard to the increasing role of arthroscopic capsular release as a treatment.

Key words: Frozen shoulder; Adhesive capsulitis; Bursitis; Shoulder; Arthroscopic capsular release; Arthrographic distension; Physiotherapy; Steroid; Hydrodilatation

Core tip: Frozen shoulder is a common disease which causes significant morbidity. Despite over a hundred years of treating this condition the definition, diagnosis, pathology and most efficacious treatments are still largely unclear. This systematic review of current treatments for frozen shoulder reviews the evidence base behind physiotherapy, both oral and intra articular steroid, hydrodilatation, manipulation under anaesthesia and arthroscopic capsular release. Key areas in which future research could be directed are identified, in particular with regard to the increasing role of arthroscopic capsular release as a treatment.

Uppal HS, Evans JP, Smith C. Frozen shoulder: A systematic review of therapeutic options. *World J Orthop* 2015; 6(2): 263-268 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/263.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.263

INTRODUCTION

The first recorded description of a frozen shoulder was reported by Duplay[1] in 1872 in his description of a "periarthritis scapulohumeral", though the term frozen shoulder was first used in 1934 by Codman[2], who described the common features of a slow onset of pain felt near the insertion of the deltoid muscle, inability to sleep on the affected side, and restriction in both active and passive elevation and external rotation, yet with a normal radiological appearance. Many patients present with a painful restriction of shoulder motion due to pain inhibition or due to weakness from rotator cuff tears or neurological deficits which appear to form a separate clinical entity

from patients with no underlying cause for their symptoms. Patients with secondary frozen shoulder with a clearly identifiable painful primary shoulder pathology often have a poorer prognosis[3] and often pose the greatest diagnostic challenges, largely due to the heterogenous nature of the primary pathology. Patients with primary idiopathic frozen shoulder, *i.e.*, patients with a painful global restriction of shoulder movement with no other identifiable shoulder pathology form the basis of this review article.

Frozen shoulder is thought to have an incidence of 3%-5% in the general population and up to 20% in those with diabetes[4]. Its peak incidence in between the ages of 40 and 60 and is rare outside these age groups and in manual workers[3] and is slightly more common in women. In terms of consultations to general practice it is thought that the cumulative incidence of consultations is 2.4/1000/year (95%CI: 1.9-2.9)[5]. Bilateral contemporaneous frozen shoulder occurs in 14% of patients whilst up to 20% of patients will develop some form of similar symptoms in the other shoulder[6]. Diabetes is the most common associated disease with frozen shoulder and a patient with diabetes has a lifetime risk of 10%-20% of developing this condition[7,8]. Patients with frozen shoulder have a higher risk of having some form of prediabetic condition with an abnormal fasting glucose or impaired glucose tolerance test[8].

Frozen shoulder starts with a painful phase which leads to stiffness which suggests that there is an initial inflammatory response which evolves into a fibrotic reaction. There is some evidence of this occurring histologically[9] and there are some similarities to the fibrous contractures in Dupuytren's disease[10]. Current models indicate that initial active fibroblastic proliferation in the capsule of the shoulder joint is later accompanied by some transformation of fibroblasts to myofibroblasts[9,10]. This thus causes an inflammatory contracture of the shoulder reducing the capsular volume and ultimately restricting glenohumeral movements. The initiating factors that cause this pathoanatomy are poorly understood[3]. Current approaches consider the key role of matrix metalloproteinases in the construction of the extracellular matrix and in the various cytokines that control collagen deposition. That drugs such as Marimastat (a synthetic matrix metalloproteinase inhibitor) can induce conditions very similar to primary frozen shoulder and Dupuytren's disease[11] is evidence that there may be a common aberrant molecular pathway in these disorders.

The biomechanics of frozen shoulder indicate that the primary pathology can be correlated to contractures of individual structures in the capsule. Gerber demonstrated[12] with capsulorrhaphy in cadaveric experiments that restriction of the anterosuperior capsule (including the rotator interval, superior glenohumeral ligament and coracohumeral ligament) produces restriction of external rotation in the adducted shoulder whilst anteroinferior capsular restriction produces restriction of external rotation in the abducted shoulder. Posterior capsular restriction reduces internal rotation of the shoulder and may be present in more severe forms of frozen shoulder[12].

This disorder is thus one of the most common musculoskeletal problems seen in orthopaedics[4]. However, despite the ubiquity of this condition and the advances in shoulder surgery over the last fourteen decades there are still many unknowns in deciding what the best treatment options are for this condition[6].

OPERATIVE INTERVENTIONS

Arthroscopic capsular release

Initial recommendations suggested that arthroscopy has no place in the treatment of frozen shoulder[13]. However in the present day arthroscopic capsular release has become increasingly commonplace[3,4,14]. The technique requires general anaesthesia and an examination under anaesthesia to document the preoperative range of motion. Standard posterior and anterior portals are made, a diagnostic arthroscopy is performed to confirm the diagnosis and a synovectomy of the rotator interval is performed. The capsular release starts with excision of the rotator interval to the under surface of the conjoint tendon, the release is extended inferiorly posterior to the tendon of subscapularis down to the five o'clock position. Some surgeons advocate release of the superior edge of subscapularis[15], though this is highly controversial. The superior release is then extended to reach the long head of biceps and is continued to release the coracohumeral ligament in the plane between the superior glenoid and supraspinatus. If internal rotation of the shoulder is significantly restricted then the camera portal can be reversed to facilitate a posterior capsular release. Some surgeons complete the inferior release with a gentle manipulation but some surgeons advocate a full 360 degree capsulectomy under direct vision whilst accepting the higher risk of iatrogenic injury the axillary nerve[14]. A randomised study by Chen *et al*[16] demonstrated that not performing any form of inferior release, such as a manipulation at the end of surgery, results in poorer functional outcome and range of motion at three months post intervention, though these differences are not maintained at longer follow up points.

A systematic review was conducted using the following search strategy '{"joint capsule release" (MeSH Terms) OR ["joint"(All Fields) AND "capsule" (All Fields) AND "release"(All Fields)] OR "joint capsule release"(All Fields) OR ["capsular"(All Fields) AND "release"(All Fields)] OR "capsular release"(All Fields)} AND {"bursitis"(MeSH Terms) OR "bursitis"(All Fields) OR ["frozen"(All Fields) AND "shoulder"(All Fields)] OR "frozen shoulder"(All Fields)}' in PubMed on May 11th 2014. Embase and cochrane databases were also searched with the same search strategy and the references of selected journals were scanned to try to

Table 1 Reviewed studies investigating arthroscopic capsular release as a treatment for primary frozen shoulder

Ref.	Year	Patients	Outcome measure(s)	Outcome score pre intervention (standard deviation or range)	Outcome score post intervention (standard deviation or range)	Complications
Smith *et al*[6]	2014	136	OSS, VAS	19.2 (7.4)	38.1 (8.6)	One portal site superficial infection - treated oral antibiotics
Jerosch *et al*[17]	2012	91	Constant	42 (19-58)	85 (36-100)	One shoulder infection - debridement required
Le Lievre *et al*[18]	2012	43	Likert		All 43 pain free on Likert score at 5-12 yr from surgery	Nil
Waszczykowski *et al*[19]	2010	16	Modified constant score (0-75), ASES	19.3	65.9	Nil
Cinar *et al*[20]	2010	26	Constant, UCLA	30.4 (6.2)	82 (18.2)	Nil
Baums *et al*[21]	2006	30	ASES, VAS, SF36	35 (10-70)	91 (62-96)	One case of delayed healing of portal site (no infection), one haematoma
Klinger *et al*[22]	2001	36	Constant	29 (14-51)	66 (35-91)	Nil
Ogilvie-Harris *et al*[23]	1997	17	ASES	2 patients mild pain, 6 in moderate pain, 8 in severe pain	11 pain free, 4 in mild pain, 1 in moderate pain, 1 in severe pain	Nil
Segmüller *et al*[24]	1995	24	Modified constant score	10/20	18/20	Nil

OSS: Oxford shoulder score; ASES: American shoulder and elbow score; VAS: Visual analogue pain score; UCLA: UCLA shoulder score; SF36: Short form 36.

find more studies.

Inclusion criteria

Clinical studies investigating arthroscopic capsular release to treat primary idiopathic frozen shoulder; studies in English.

Exclusion criteria

Review articles; studies investigating arthroscopic capsular release in conjunction with another surgical procedure; studies with less than fifteen participants; Double publication of data.

Studies on patients with secondary frozen shoulder: 76 Studies were identified; 18 articles were shortlisted for further review following application of eligibility criteria on published abstracts.

Closer examination of these studies revealed: 2 studies included data that had been published twice; 4 studies were not available in English; 2 studies reported results on arthroscopic capsular release and subacromial decompression; One study investigating a mixture of primary and secondary frozen shoulder with no separation of data analysis.

Nine studies[6,17-24] were eligible for review and the results of the data abstraction are compiled in Table 1. This review includes the treatment of 419 patients with primary frozen shoulder. All studies demonstrated a rapid statistically significant increase in postoperative shoulder function following capsular release. Five studies used the Constant-Murley score as the primary outcome measure. The Constant-Murley score is a commonly used measure of shoulder function which unfortunately has very little formal validation[25]. Other outcome measures used with more validation include the oxford shoulder score in Smith *et al*[6], Likert score in Le Lievre *et al*[18] and American shoulder and elbow score in Waszczykowski *et al*[19] and Baums *et al*[21]. None of the studies included any comparative control groups which forms the largest weakness in the current evidence base behind arthroscopic capsular release. Overall, the evidence reviewed demonstrates that arthroscopic capsular release appears to be a safe and effective treatment that can provide a rapid improvement in patient reported shoulder function.

Manipulation under anaesthesia

In this technique a general anaesthetic is administered and the shoulder joint capsule is gently stretched by moving the humerus into flexion, abduction and finally (optionally) by moving the adducted humerus into external rotation. Great care must be taken to minimise the lever arm used and to maximise the surface area of the arm to which pressure is applied. The largest risk in this procedure is of iatrogenic damage to the upper limb including, humeral fracture, glenohumeral dislocation, rotator cuff tears, glenoid fractures, brachial plexus injuries, labral tears and haematomas[14]. It has been demonstrated in post manipulation arthroscopy[26] that the typical appearances are of haemarthrosis and capsular tearing but other lesions often seen include iatrogenic superior labral anterior posterior tears, partial subscapularis ruptures and rupture of the anterior labrum. Manipulation under anaesthesia has been shown to be an efficacious treatment[27]. However, the results of manipulation when compared to hydrodilation[28] and steroid injection[29] are equivocal at best.

Non-operative treatments

Hydrodilation (arthrographic distension): This

treatment involves the injection of local anaesthetic into the capsule at a pressure high enough to distend and stretch the joint capsule. This procedure first described by Andren *et al*[30] does not need to be performed in the operating theatre but is often associated with poor tolerance due to the painful nature of the distension[4]. Buchbinder *et al*[31]'s systematic cochrane review of hydrodilation searched MEDLINE, EMBASE, CINAHL and CENTRAL databases from 1966 till November 2006 for studies investigating hydrodilation type procedures in the treatment of frozen shouder. These searches were repeated from November 2006 till May 2014 and a total of 7 extra studies were identified two of which were randomised comparative studies[28].

Buchbinder *et al*[32]'s randomised controlled study of 46 patients compared hydrodilatation to placebo and demonstrated a statistically and clinically significant improvement in functional outcome scores (shoulder pain and disability index) to 6 wk following intervention but this was not maintained at follow up points beyond this.

Three studies compared hydrodilation with steroid to intra articular steroid injection alone[33-35]. Gam *et al*[33]'s and Corbeil *et al*[34]'s studies had weaknesses in study construction especially with regard to randomisation systems, elimination of systematic bias and in sample size calculation. Tveitå *et al*[35]'s study on the other hand is a well constructed study which scores highly against the Consort criteria[36]. Gam *et al*[33], Corbeil *et al*[34] and Tveitå *et al*[35] all failed to demonstrate any statistically significant differences in functional outcome compared to steroid injection at any outcome point. Gam *et al*[33] did report an increase in the range of shoulder motion of the hydrodilation group as compared to the steroid group. However, given that range of motion is an unvalidated and poor measure of shoulder function it is difficult to make generalisable recommendations on this evidence. Khan *et al*[37] compared hydrodilation and physiotherapy to physiotherapy alone in 36 patients in this quasi randomised and underpowered study. Khan *et al*[37] demonstrated statistically significant improvements in range of motion at eight weeks but no differences in visual analogue pain scores.

Jacobs *et al*[38] reported results of a three way randomised study comparing a mixture of low volume local anaesthetic and air, intra articular steroid and local anaesthetic with air and steroid. Though this study claims to be investigating arthrographic distension, the low volumes used (3 mL of air in distension group) mean that the study design does not pass the test of face validity. Given that all comparative studies use twenty to forty millilitres of saline, which is many orders of magnitude less compressible than air, it seems very unlikely than any patients capsule was distended in any meaningful way in this study.

Quraishi *et al*[28] reported results of small randomised study comparing hydrodilation to manipulation under anaesthesia. Though no differences were found in Constant score at any point up to six months following intervention both groups made a clinically significant improvement following intervention.

The major side effect of hydrodilation appears to be of pain during the procedure[32,33,35] though Gam also reported one instance of stroke which was not thought to be related to the intervention.

This systematic review of hydrodilatation demonstrates that this technique appears to efficacious but there is no good evidence to suggest any superiority to other treatments. High quality randomised studies comparing hydrodilatation to other common treatments, such as arthroscopic capsular release, are needed.

Physiotherapy

Most patients are initially prescribed a course of physiotherapy prior to referral to a surgeon. The aim behind most regimens is to prevent further reduction in range of motion and eventually to increase the range of motion in the affected shoulder. Passive mobilisation and capsular stretching are two of the most commonly used techniques. Despite the near universal use of physiotherapy as a first line treatment for frozen shoulder there is very little high quality evidence to support its use. Cochrane reviews have demonstrated that the current literature base shows that physiotherapy alone has little to no benefit as compared to control groups[39]. There are a number of adjuncts that are often used with physiotherapy including extracorporeal shockwave therapy, electromagnetic stimulation, acupuncture and the use of lasers, none of which have been subjected to investigation with randomised controlled studies[3].

Steroid injection

Steroid injection is an another almost ubiquitous intervention in frozen shoulder. Multiple cochrane reviews have noted the eventual location of a blind glenohumeral or subacromial injection is highly variable[31,40]. The most recent cochrane review collates the information from 26 very heterogenous studies[40] and concludes that there is at best a small short term benefit to steroid injection alone for frozen shoulder but that the evidence base is poor. The difficulty in extracting the effect of steroid from that of physiotherapy, an intervention with which it is often combined in studies has long been noted[41].

Oral steroid

This treatment is rarely prescribed by surgeons, however to date, five trials have been conducted investigating oral steroid therapy, comparing steroid to placebo[32,42], no treatment[43], intra articular injection[44] and in conjunction with manipulation under anaesthesia[45]. These trials were reviewed in a systematic cochrane review in 2006[46] and showed that there is a mild short term (under 6 wk) benefit to oral steroid therapy but

that this is not maintained in the longer term. This small short term benefit must be offset against the well known side effects and risks of oral steroid therapy.

CONCLUSION

Frozen shoulder is a common disease which causes significant morbidity. Despite over a hundred years of treating this condition the definition, diagnosis, pathology and most efficacious treatments are still largely unclear. This review of the recent evidence base highlights key areas for future research in particular with regard to the increasing role of arthroscopic capsular release as a treatment. High quality adequately powered randomised controlled trials comparing the most common interventions to a sham procedure would be the ideal way to improve the current evidence base. However these are difficult studies to construct and recruit for. Frozen shoulder can be such an intensely painful condition that in severe cases one could consider that an option of no treatment as part of a control group could be considered to be unethical. Given these real world problems in construction of clinical trials the optimum area to concentrate further research is in comparing treatments like arthroscopic capsular release to hydrodilatation with an adequately powered high quality randomised controlled trial.

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P- Reviewer: Daglar B, Lin JJ, Swanik C, Zheng N **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

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DOI: 10.5312/wjo.v6.i2.269

World J Orthop 2015 March 18; 6(2): 269-277
ISSN 2218-5836 (online)

Use of demineralized bone matrix in the extremities

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Author contributions: Drosos GI and Touzopoulos P contributed to conception and design of the study; Drosos GI, Touzopoulos P and Ververidis A contributed to acquisition, analysis and interpretation of data; Drosos GI, Touzopoulos P and Tilkeridis K contributed to drafting the article; Drosos GI, Ververidis A, Kazakos K and Tilkeridis K contributed to revising the article; all the authors read and approved the final manuscript.

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Received: April 29, 2014
Peer-review started: April 30, 2014
First decision: June 27, 2014
Revised: July 7, 2014
Accepted: October 14, 2014
Article in press: October 16, 2014
Published online: March 18, 2015

Abstract

Autologous bone graft is considered as the gold standard for all indications for bone grafting procedures but the limited availability and complications in donor site resulted in seeking other options like allografts and bone graft substitutes. Demineralized bone matrix (DBM) is an allograft product with no quantity limitation. It is an osteoconductive material with osteoinductive capabilities, which vary among different products, depending on donor characteristics and differences in processing of the bone. The purpose of the present review is to provide a critical review of the existing literature concerning the use of DBM products in various procedures in the extremities. Clinical studies describing the use of DBM alone or in combination with other grafting material are available for only a few commercial products. The Level of Evidence of these studies and the resulting Grades of Recommendation are very low. In conclusion, further clinical studies of higher quality are required in order to improve the Recommendation Grades for or against the use of DBM products in bone grafting procedures.

Key words: Bone; Grafting; Allograft; Demineralized bone matrix; Non-union

Core tip: Demineralized bone matrix (DBM) is an allograft product that was found to be safe as an option of bone grafting. As far as its effectiveness is concerned, and according to the existing literature: (1) there is a good evidence for its use in bone cysts combined with autologous marrow aspirate; (2) in fracture nonunion and filling the defects after tumor surgery DBM used alone or combined with other grafting material are supported by a lower quality studies; and (3) there is insufficient evidence to make a treatment recommendation for DBM use in fracture treatment of other applications. Furthermore, according to the existing literature there are results of clinical use of only a few DBM products and thus the recommendation concerning the DBM use should probably also be referred to these specific products and not to any DBM product.

Drosos GI, Touzopoulos P, Ververidis A, Tilkeridis K, Kazakos K. Use of demineralized bone matrix in the extremities. *World J Orthop* 2015; 6(2): 269-277 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/269.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.269

INTRODUCTION

In recent years, the requirements for bone grafting have increased, due to the increasing number of procedures, in orthopaedic, oral and maxillofacial surgery[1]. Autologous bone is considered the ideal graft for any indication providing the best osteogenic, osteoinductive and osteoconductive potential of all grafts, with no immunological rejection[2-5]. Allograft materials and graft substitutes have been developed to avoid limitations of autologous graft, like limited availability and donor site morbidity[6-12].

Demineralized bone matrix (DBM) is an osteoconductive and osteoinductive allograft product, but no osteogenic capacity because of its processing[13-18]. The osteoinductive capacity of DBM can be affected by storage, demineralization process, washing procedure, sterilization method and vary from donor to donor resulting in differences between and within products[19-25]. DBM has no immunological rejection as the antigenic surface structure of the bone is destroyed during demineralization by acid[26], but, on the other hand, it is known that a host immune response can be induced by allogeneic bone[27-30], despite its processing Nevertheless, to the best of our knowledge, there are no studies concerning the possible immunogenicity and its influence on the bone formation for the different DBM products.

Since DBM was found to be effective and safe as an option of bone grafting, it has been used to induce bone formation in various procedures.

The aim of this study is to present a critical review of the existing literature concerning the use of DBM products, alone or as a composite graft, in various procedures requiring bone grafting in the extremities.

The key words "demineralized bone matrix", and "DBM", were used for a MEDLINE search and results were restricted to clinical trials in the English language. Clinical studies of use of DBM in spinal fusion were excluded.

Clinical studies were evaluated using the levels of evidence rating for clinical studies[31] and grades of recommendation are based on this evaluation[32] as follows: (1) Grade-A recommendations: Consistent level-Ⅰ studies; (2) Grade-B recommendations: Consistent level-Ⅱ or Ⅲ studies; (3) Grade-C recommendations: Level-Ⅳ or Ⅴ evidence, or conflicting evidence; and (4) Grade-Ⅰ recommendations: Insufficient evidence to make a treatment recommendation. Twenty one clinical studies were selected for this review. These studies were analysed and described by category of use (Table 1).

USE OF DBM IN FRACTURES

One level Ⅱ[33] and two level Ⅲ[34,35] comparative studies concerning the use of DBM in long bone fractures have been published. In the level Ⅱ study the DBM combined with bone marrow aspirate was used in diaphyseal long bone fractures. In the first level Ⅲ study the DBM combined with allograft cancellous chips was used in patients with periarticular fractures when in the second the DBM with calcium sulfate and vancomycin was used in displaced intra-articular calcaneal fractures.

Lindsey *et al*[33], in a prospective randomized pilot study, compared the results in patients with diaphyseal long bone fractures treated with either DBM Grafton® (Osteotech, Eatontown, NJ, United States) combined with aspirated bone marrow or autologous iliac crest bone graft alone. In 12 mo follow up, 90% of the patients who received DBM and aspirated bone marrow achieved full bone formation *vs* 75% of the autologous graft group. Additionally, finally healing rate was 100% in DBM group and 63% in the autograft group. Results suggest that the use of DBM with aspirated bone marrow is comparable with the use of autologous graft, in treatment of long bone fractures.

In a retrospective study, Cheung *et al*[34], compared Grafton® (Osteotech, Eatontown, NJ, United States) with Orthoblast (Gensci, Irvine, CA, United States) in the treatment of periarticular fractures in 28 patients. In both groups allograft cancellous chips were used in combination with the DBM. Bone union was achieved with no complications in 100% with Grafton® and in 69% in Orthoblast. Authors suggest the combination of allograft cancellous chips with Grafton® could be an alternative to autologous grafting for these fractures.

Bibbo *et al*[35] studied retrospectively bone healing and complications in 44 patients with displaced intra-articular calcaneal fractures with bone defect treated with open reduction and internal fixation. DBM with calcium sulfate (AlloMatrix™, Wright Medical, Arlington, TN) and vancomycin used in 33 patients and no grafting in 11 patients. The mean union time in the combined graft group was of 8.2 wk and of 10.2 wk in the control group. There were wound problems in 5 of 33 patients in DBM group (two minor and three serious wound problems), but in mean follow up time of 22 mo, no evidence of osteomyelitis were demonstrated.

USE OF DBM IN NON-UNIONS

One level Ⅲ and three level Ⅳ studies concerning the use of DBM in non-unions were found. The level Ⅲ study is a comparative study between DBM and autologous iliac crest bone graft in humeral delayed and non-unions[36]. The level Ⅳ studies report the results[37,38] and the complications[38] of the DBM use in bone non-unions.

Table 1 Clinical studies of demineralized bone matrix use in extremities

Ref.	Design	Diagnosis/procedures	Type of graft	Main outcomes	Level of evidence
Clinical studies of DBM used in fractures					
Lindsey *et al*[33]	Prospective, randomized pilot study	Patients treated for long bone fractures	DBM (Grafton®) + bone marrow $n = 10$ Iliac crest autograft $n = 8$	Full bone formation in 90% with DBM + marrow and 75% with autograft at 12/12 Totally 100% healed with DBM + marrow and 63% heal with autograft	II
Cheung *et al*[34]	Retrospective comparative study	Periarticular fractures ($n = 28$)	Allograft conductive cancellous chips + DBM Grafton® ($n = 13$) Allograft conductive cancellous chips + DBM Orthoblast ($n = 15$)	Healing on the first graft attempt without complications DBM Grafton®: 69% DBM Orthoblast: 100%	III
Bibbo *et al*[35]	Retrospective comparative study	Patients treated for displaced intra-articular calcaneal fractures	DBM + $CaSO_4$ + vancomycin $n = 33$ Control group $n = 11$	Union in 8.2 wk with graft, while 10.4 wk in control group $P < 0.05$ Wound problems in 15% in graft group	III
Clinical studies of DBM used in nonunions					
Hierholzer *et al*[36]	Retrospective consecutive cohort study	Patients with an aseptic, atrophic delayed union or nonunion of a humeral shaft fracture were treated with ORIF and graft	Autologous iliac crest bone graft $n = 45$ DBM (Grafton®) $n = 33$	Union in 100% with autologous graft *vs* 97% in DBM group Union in 4.5 mo with autologous graft *vs* 4.2 mo in DBM group 44% of the autologous graft group had donor site morbidity	III
Wilkins *et al*[37]	Prospective clinical study	Patients with stiff nonunions of long bones ($n = 66$)	Percutaneous use of a mixture of autologous bone marrow and allograft DBM (AlloMatrix)	61 of 69 patients with stiff nonunion went on to union in an average of 8.1 mo; 7 more healed after a second procedure	IV
Wilkins *et al*[39]	Retrospective clinical study	Patients undergoing surgical intervention for removal of benign tumors ($n = 41$) or treatement of nonunions in multiple bone types ($n = 35$)	AlloMatrix Injectable Putty	38 of 41 patients with benign tumors healed within an average of 4.8 mo, and 30 of 35 patients with nonunion went on to union in an average of 3.5 mo	IV
Ziran *et al*[38]	Consecutive patients	Patients required bone grafting for atrophic/avascular nonunions	AlloMatrix + morselized cancellous allograft chips (1:1 ratio) $n = 41$	51% developed postoperative drainage, 34% developed deep infection, 32% required surgical intervention	IV
Clinical studies of DBM used in bone cysts					
Park *et al*[40]	Retrospective comparative study	Calcaneal unicameral cysts were treated with graft	Lyophilized irradiated CAB + bone marrow $n = 13$ DBM + bone marrow $n = 10$	Complete healing in 9/13 in CAB group *vs* 5/9 in DBM group Healed with defect in 4/13 in CAB group and 3/9 in DBM group No infections or pathologic fractures during 48/12 follow up	III
Di Bella *et al*[41]	Retrospective comparative study	184 patients treated for unicameral bone cysts with cortical erosion	Multiple injection of corticosteroid Single injection of DBM + bone marrow concentrate	38% healed with steroids at 48/12 and 71% healed with DBM + BMC at 20/12 Failure rate after 1 steroid injection was 63% *vs* 24% with DBM + BMC	III
Rougraff *et al*[42]	Consecutive patients	Active unicameral bone cyst ($n = 23$)	Trephination and percutaneous injection of a mixture of demineralized bone matrix (Grafton) and autologous bone marrow	Healing on the first graft attempt: 78%	IV
Kanellopoulos *et al*[43]	Consecutive patients	Active unicameral bone cyst ($n = 19$)	Combination of percutaneous reaming, injection of a mixture of allogenic DBM (AlloMatrix) and autologous bone marrow	Healing on the first graft attempt: 89.5%	IV
Hass *et al*[44]	Retrospective case series	Treatment of juvenile bone cysts at all sites with DBM	Juvenile bone cysts packed with DBM ($n = 9$)	Totally osteodense images after an average of 8 mo, with no other significant changes in 2 yr follow-up	IV

Sung *et al*[45]	Retrospective comparative study	Patients, younger than 20, treated for humeral and femoral unicameral bone cysts	Corticosteroid injection $n = 94$, curretage + bone graft $n = 39$, Steroids + DBM + bone marrow aspirate $n = 34$	Failure rate was 84% with steroids, 64% with curretage and 50% with SDB $P < 0.001$. Retreatment in 76% with steroids, 63% with curretage and 71% with SDB	III
Clinical studies of DBM used in tumor surgery					
Kim *et al*[46]	Retrospective comparative study	Bony defects after tumor surgery of various bone tumors	ICS $n = 28$ DBM $n = 28$	ICS and DBM success rate = 85.7% (24/28) and 88.9% (24/27) $P < 0.05$ Average healing time for ICS and DBM was 17.3 wk and 14.9 wk $P < 0.05$	III
Wilkins *et al*[39]	Retrospective clinical study	Patients undergoing surgical intervention for removal of benign tumors ($n = 41$) or treatment of nonunions in multiple bone types ($n = 35$)	AlloMatrix injectable putty	38 of 41 patients with benign tumors healed within an average of 4.8 mo, and 30 of 35 patients with nonunion went on to union in an average of 3.5 mo	IV
Clinical studies of DBM used in various long bone applications					
Dallari *et al*[47]	Prospective, randomized control trial	High tibial osteotomy for genu varus	DBSint® (Mg-hydroxyapatite + DBM) $n = 9$ SINTlife® $n = 13$ Lyophilised bone chips $n = 9$	6/52 DBSint® showed higher osseointegration rate than lyophilized bone chips ($P < 0.01$) 52/52 DBSint® was demonstrated as effective and safe as SINTlife® and bone chips	II
Hatzokos *et al*[48]	Retrospective comparative study	Patients were managed with bone transport for the treatment of a tibial bone defect, with 3 types of docking procedures ($n = 43$)	Group A: closed compression Group B: autologous iliac graft Group C: BMC + DBM	Healing time was significantly longer in the compression group as compared with the BMC + DBM $P < 0.05$, no significant difference among the groups in terms of complication rates	III
Wilkins *et al*[49]	Prospective clinical study	Patients requiring bone grafting procedures ($n = 50$)	Combination product of bioassayed DBM (AlloGro®) and calcium sulfate pellets	Healing rate of 98% within an average period of 11.8 wk	IV
Clinical studies of DBM used in osteonecrosis of femoral head					
Feng *et al*[50]	Retrospective comparative study	Treatment of large osteonecrotic lesions of the femoral head with graft	OsteoSet®2 DBM + free vasculated fibular graft $n = 2$, Free vasculated fibular graft + autologous cancellous bone $n = 24$	Improvement in the mean Harris hip score was noted in both groups $P < 0.001$, no significant differences in Harris hip score and clinical outcomes between groups	III
Clinical studies of DBM used in acetabular revision					
Etienne *et al*[51]	Retrospective clinical study	Acetabular revision surgery ($n = 20$)	Acetabular reconstruction using a mixture of DBM (ALLOMATRIX™ C Bone Putty) and cancellous allograft chips	Successful graft incorporation in 18 of 20 patients (90%)	IV
Clinical studies of DBM used in fusion					
Thordarson *et al*[52]	Retrospective Comparative Study	Complex ankle or hindfoot fusion with commercially available DBM formulations that did or did not contain crushed cancellous allograft bone ($n = 63$)	Grafton® + allograft cancellous bone chips $n = 37$ Orthoblast + allograft cancellous bone chips $n = 26$	Clinical and radiological fusion In DBM Grafton: 86% In DBM Orthoblast: 92%	III

DBM: Demineralized bone matrix; CAB: Chip allogenic bone; ICS: Injectable calcium sulfate; SDB: Steroids and demineralized bone matrix and bone marrow aspirate; BMC: Bone marrow concentrate.

Hierholzer *et al*[36], reported the results after open reduction, internal fixation and bone grafting in ninety-eight patient with non-union or delayed union of humeral shaft fractures. No significant difference was found between Grafton® DBM and autologous iliac crest bone graft. The union rate in Grafton® group was 97% with a mean healing time of 4.2 mo while in the autologous graft group the union rate was 100% with a mean healing time of 4.5 mo. However, in the autologous grafting group donor site morbidity was 44%.

Wilkins *et al*[37] treated 66 patients with non-unions of long bone fractures by percutaneous application of DBM (AlloMatrix™) and autologous bone marrow. Union rate was 88% at an average of 8.1 mo after surgery. Authors suggested that this method of treating nonunions is as successful as iliac crest autologous bone grafting,

with additional benefits of reduced cost, decreased morbidity of donor site and shorter hospital stay.

In a retrospective clinical study, Wilkins *et al*[39] used AlloMatrix™ putty in 35 patients with non-union in various bones and in 41 patients after surgical treatment of benign tumors. Union rate for the non-union group was 85.7% in a mean time of 3.5 mo while the heling rate in the tumor group was 92.7% in an average of 4.8 mo.

In the other hand, Ziran *et al*[38], in a series of 41 consecutive patients, who required bone grafting for atrophic/avascular nonunions, presented the complications associated with the use of a specific graft (AlloMatrix™). Patients were monitored for healing and adverse effects, (local or systemic reactions, wound problems, infection). Of the 41 patients, 13 had drainage which required surgical intervention, and 14 patients developed deep infection of the surgical area, of whom 11 patients required surgical treatment. Authors suggest that the use of that type of graft resulted in an unaccepted rate of complications, compared to the complication rate of the use of allograft in literature.

USE OF DBM IN BONE CYSTS

Over the last years DMB becomes more and more popular for the treatment of bone cysts. Several studies present good results of the use of DBM in bone cysts, proving high healing and low complication rate. There are two level Ⅲ[40,41] and two level Ⅳ[42,43] studies, which present the use of DBM and autologous bone marrow in treatment of active unicameral bone cysts, one level Ⅳ[44] study with the use of DBM in juvenile bone cysts and one level Ⅲ[45] study with use of DBM combined with autologous bone marrow and steroids in bone cysts.

Park *et al*[40] compared retrospectively the efficacy of percutaneous local injection of lyophilized chips of allogeneic bone and autogenous bone marrow, *vs* demineralized bone powder (Injecta bone TR, Modumedi Ltd., Daegu, Republic of Korea) and autogenous bone marrow, in 23 calcaneal unicameral cysts. Patients were followed up for an average of four years. Complete healing was achieved in 9 out of 13 cysts treated with chip allogeneic bone and in 5 out of 10 cysts treated with demineralized bone powder. Four of the first group and three of the DBM group healed with a defect, while the other two of the DBM group, classified as persistent cysts. During follow up there was no sign of infection or pathologic fractures.

Di Bella *et al*[41], in a retrospective comparative study of 184 patients with unicameral bone cysts and cortical erosion, compared the outcomes of multiple injections of costricosteroids *vs* single injection of DBM (Musculoskeletal Tissue Bank of the Rizzoli Orthopaedic Institute) and bone marrow concentrate. Minimum follow up of both groups was 12 mo. After first injection, authors observed a healing rate of 21% in the steroids group *vs* 58% in the DBM and bone marrow concentrate group. Multiple injections of steroids followed in the steroid group. Finally 38% healed with corticosteroids when 71% healed with DBM and bone marrow mixture. There was no difference of fracture rates between the two groups. Authors concluded that treating unicameral bone cysts with a single injection of a mixture of DBM and bone marrow concentrate appears to provide high healing rate, and better outcomes when compared with percutaneous corticosteroid injections.

Rougraff *et al*[42] applied percutaneously autologous bone marrow combined with DBM (Grafton®) in 23 patients with bone cysts. The healing rate was 78% in a mean time of 50 mo, while in 5 patients a second procedure was required. No pathologic fracture was reported.

In another series of 19 children, Kanellopoulos *et al*[43], used a combination of percutaneous reaming and an injection of a mixture of DBM (AlloMatrix™) and autologous bone marrow, in the treatment of active unicameral bone cysts. During a mean follow up time of 28 mo, authors reported a healing rate after the first graft attempt, up to 89.5%, while two patients required second surgical intervention. Authors reported no pathologic fracture or other complication.

Hass *et al*[44], treated 9 children with bone cysts (juvenile cysts) with Grafton® packing after curettage of the cyst. Complete healing was achieved in all patients, with totally osteodense radiographic images after an average time of 8 mo. There was only one significant complication in a child, who sustained a pathologic distal tibial fracture five months post-operatively. There were no other significant changes in two years follow up.

In a retrospective comparative study of 167, younger than 20 years old, patients, Sung *et al*[45], presented the failure rates of three surgical managements of humeral and femoral unicameral bone cysts. One therapeutic strategy was the use of corticosteroid injection in 94 patients, the second was curettage of the cyst and use of bone graft in 39 patients and the third was a combination of injection of steroids, DBM (Grafton® gel) and bone marrow aspirate in 34 patients. Mean follow up was 7.3 years and outcomes included treatment failure, defined clinically as pathologic fracture or need for retreatment, and complications. After one treatment, 84% of cysts treated with steroids had failed while, 64% of the curettage group failed and only 50% of the third group with the steroids, DBM and bone marrow mix didn't healed. For unicameral bone cysts requiring retreatment, 76% retreated with steroids had failed *vs* 63% with curettage and 71% with mix composite. Authors concluded that the use of steroids with DBM and bone marrow aspirate is a reasonable first surgical treatment of unicameral bone cysts in young patients.

USE OF DBM IN TUMOR SURGERY

There are at least two studies[39,46], presenting the use of DBM in defects due to surgical intervention of bone tumors. One level Ⅳ study presents the use of an injectable type of graft, which is DBM and calcium sulfate, in bone tumor surgery. The other level Ⅲ study investigates the use of DBM in defects after removal various bone tumors.

Recently, Kim *et al*[46] investigated, retrospectively, the efficacy of injectable calcium sulfate and DBM in bone defects after tumor surgery of various bone tumors. 56 patients, who were surgically treated for bone tumors, randomly allocated in two groups. 28 patients treated with injectable calcium sulfate, while the other 28 with DBM graft (Orthoblast Ⅱ, Integra OrthoBiologics Inc., Irvine, CA, United States). Radiologic and clinical outcomes compared between groups. One case with early pathologic fracture in DBM groups has been excluded from the study, so the reference value of this group was 27 patients. Results showed successful healing in 24 out of 28 patients, in an average of 17.3 wk with injectable calcium sulfate *vs* 24 out of 27 patients, in an average of 14.9 wk with DBM graft. Authors concluded that both grafts appear to be comparable and effective in the treatment of bone defects following tumor surgery.

Wilkins *et al*[39] analysed retrospectively a series of 41 patients with benign tumors treated with removal of the lesion and use of AlloMatrix™ Injectable Putty for grafting. In the same study, 35 patients with nonunions in multiple bone types, treated with the same graft, as mentioned above. Bone healing was observed at an average of 4.8 mo in 38 out of 41 patients in the tumor group. Complications developed in 12 patients, in both groups, including infection in two patients, continued sterile wound drainage in five patients, refracture in two cases, hardware failure in one case, one postoperative neuroma formation, and one case of decreased range of joint motion. A recurrence of the tumor occurred in three patients. In this study, AlloMatrix™ Injectable Putty used as bone void filler in bone defects after tumor surgery. Authors believed that the use of DBM shows results equal to those reported with autograft.

DBM IN VARIOUS LONG BONE APPLICATIONS

In a prospective randomized control trial, Dallari *et al*[47] investigated the bone healing ability of DBSint®, which is a biomimetic composite, obtained by mixing SINTlife® (Fin-Ceramica SpA, Faenza, Italy) and human DBM, produced in authors Institute Bone Bank (Rizzoli Orthopaedic Institute, Bologna, Italy), *vs* a Mg-hydroxyapatite graft (SINTlife®) and lyophilized bone chips, in high tibial osteotomies for genu varus. Nine patients randomly received DBSint®, 13 patients SINTlife®, and nine patients received allograft lyophilized bone chips, as a control group. Radiological, clinical and histomorphological outcomes were evaluated. At six-weeks follow-up, DBSint® showed a higher osseointegration rate in comparison with lyophilised bone chips. while, at the same time, histomorphometry of computed tomography guided bone biopsies showed that a good osteogenetic potential was demonstrated with DBSint®, as well as with SINTlife® and the control group. At final follow-up of 1 year, all patients had relief from knee pain and improvement of walking ability. The Knee Society Functional Score was significantly different between groups, but all recorded values were in normal range. The study concluded that DBSint® was demonstrated as effective and safe as SINTlife® and lyophilized bone chips, within the limits of the study.

Hatzokos *et al*[48], evaluated the use of different grafts in the docking site in patients who managed with bone transport for treatment of a tibial defect. All 43 patients were divided into three groups according to the "docking site procedure" used. In group A, closed compression was applied, in group B surgical debridement of the docking site followed by the application of autologous iliac bone graft, and in group C, debridement followed by the application of bone marrow concentrate and DBM (Grafton Putty DBM OST Development SA, Clermont-Ferrand, France). Docking site consolidation was assessed both radiographically and clinically. Healing time was significantly longer in the first group treated only with closed compression, compared with DBM group, while there was no difference between the grafting groups. There was no significant difference in complication rates between the different groups. Authors concluded that the application of DBM and autologous bone marrow concentrate is equivalent to autologous bone graft in management of docking site during distraction osteogenesis, proving that it is an effective and safe treatment option.

In a prospective clinical study, Wilkins *et al*[49] reported that a mixture of calcium sulphate pellets and DBM (AlloGro®). In this level Ⅳ study, 50 patients underwent bone grafting for a variety of diagnosis including benign bone lesions (n = 35), non-union of long bones (n = 11), osteomyelitis (n = 3), and one patient for acute fracture. Results showed high efficacy of grafting, since 49 out of 50 patients healed in an average of 11.8 wk. The complication rate was very low, with a re-infection in one patient, and a recurrence of a bone cyst in another patient. According to the authors this mixture of calcium sulphate pellets and AlloGro® DBM was safe with no graft-related complications and effective for bone regeneration.

USE OF DBM IN OSTEONECROSIS OF FEMORAL HEAD

In a level Ⅲ study, Feng *et al*[50] studied the safety and efficacy of a type of DBM (OsteoSet®) in treatment

of patients with large osteonecrotic lesions of the femoral head. In a retrospective study the authors compared 24 patients that underwent free vascularized fibular grafting and OsteoSet® with 24 patients who underwent fibular grafting and autologous cancellous bone grafting. There was no significant difference in clinical outcomes, Harris Hip Score or complication rates between the two groups. The authors concluded that in patients with femoral head osteonecrosis treated with free vasculated fibular grafting, harvesting autologous bone can be avoided using the equally effective OsteoSet® DBM.

USE OF DBM IN ACETABULAR REVISION

Etienne *et al*[51] in a level Ⅳ retrospective study reported the results after bone grafting for bone loss in acetabulum revision surgery in 20 patients. The authors used allograft cancellous bone mixed with DBM (Allomatrix™). Successful graft incorporation was found in 90% of the patients in a mean follow-up of 27 mo.

USE OF DBM IN FUSION

There is one level Ⅲ study, of Thordarson *et al*[52], comparing two different DBM products used in 63 patients with ankle or foot fusions. In 37 patients Grafton® putty was used, and in the rest 26 patients Orthoblast used to enhance fusion. All patients followed-up, clinically and radiographically to fusion or non-union time, with a minimum follow-up of 1 year. The Grafton group succeeded a fusion rate of 86%, while the Orthoblast group healing rate reached 92%. Authors concluded there was no significant difference between union rates of those two grafts.

CONCLUSION

Although there is an able number of studies in the literature, examining the use of DBM products either alone or in combination with other grafting materials, in several applications in extremity operations, there is little information concerning the true efficacy of most of these products.

There are very few studies that examine the true efficacy of specific DBM products alone as a graft. In the other hand there are a lot of studies, which examined the use of DBM in combination with osteogenic grafts such as bone marrow, with osteoconductive bone-void filler such as calcium sulphate, and other allografts like cancellous chips.

It is also obvious that from a big variety of available DBM in the market, there are clinical studies available for only a few commercial products. Although information from clinical data is limited, pre-clinical studies have shown that there are differences between the different products concerning their osteoconductive and osteoinductive characteristics. Therefore, our recommendations should probably also be referred to the specific products as well as to the levels of the available studies.

INDICATIONS AND RECOMMENDATIONS

Use of DBM in fractures

According to the existing literature there is insufficient evidence to make a treatment recommendation (grade-Ⅰ recommendations).

There is only (1) one Level Ⅱ[33] comparative study where the DBM combined with bone marrow aspirate was used in diaphyseal long bone fractures; (2) one Level Ⅲ study[34] where the DBM combined with allograft cancellous chips was used in patients with periarticular fractures; and (3) one Level Ⅲ[35] study where the DBM with calcium sulfate and vancomycin was used in displaced intra-articular calcaneal fractures.

Use of DBM in nonunions

Four studies (one Level Ⅲ[36] and three Level Ⅳ studies[37-39]) concerning the use of DBM in non-unions were found (grade-C recommendations).

Although there is a comparative study between DBM and autologous iliac crest bone graft in humeral delayed and non-unions[36] (level Ⅲ study) this is the only comparative study.

Use of DBM in bone cysts

There are four studies (two Level Ⅲ[40,41] and two Level Ⅳ[42,43] studies), presenting the use of DBM and autologous bone marrow in treatment of active unicameral bone cysts, one level Ⅲ[45] study with use of DBM combined with autologous bone marrow and steroids and one level Ⅳ[44] study with the use of DBM alone.

Therefore it is suggested that the use of DBM and autologous bone marrow in treatment of active unicameral bone cyst is a good option (grade-B recommendations).

Use of DBM in tumor surgery

There is only one retrospective comparative (Level Ⅲ) study[46] between injectable calcium sulfate and DBM and one level Ⅳ study presenting the results of an injectable DBM (grade-C recommendations).

DBM in various applications

There is insufficient evidence to make a treatment recommendation (grade-Ⅰ recommendations) as there is only one available study for the following procedures: (1) High tibial osteotomy for genu varus[47] (level Ⅱ study); (2) Docking site procedure in bone transport for the treatment of a tibial bone defect (level Ⅲ study)[48]; (3) Various bone grafting procedures (level Ⅳ study)[49]; (4) Treatment of large osteonecrotic lesions of the femoral head with graft (level Ⅲ study)[50]; (5) Acetabular revision surgery (level Ⅳ study)[51]; and (6)

Complex ankle or hindfoot fusion (level Ⅲ study)[52].

In conclusion, further clinical studies of higher level of Evidence are required in order to improve the Recommendation Grades for or against the use of DBM products (alone or combined with other grafting material) in bone grafting procedures.

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DOI: 10.5312/wjo.v6.i2.278

World J Orthop 2015 March 18; 6(2): 278-283
ISSN 2218-5836 (online)

Is non-biological treatment of rheumatoid arthritis as good as biologics?

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Received: February 12, 2014
Peer-review started: February 13, 2014
First decision: March 26, 2014
Revised: April 10, 2014
Accepted: September 6, 2014
Article in press: September 10, 2014
Published online: March 18, 2015

Abstract

The management of rheumatoid arthritis (RA) in the past three decades has undergone a paradigm shift from symptomatic relief to a "treat-to-target" approach. This has been possible through use of various conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) which target disease pathogenesis at a molecular level. Cost and infection risk preclude regular use of biologics in resource-constrained settings. In the recent years, evidence has emerged that combination therapy with conventional DMARDs is not inferior to biologics in the management of RA and is a feasible cost-effective option.

Key words: Rheumatoid arthritis; Disease modifying drugs; Biologics; Methotrexate; Sulfasalazine; Leflunomide; Cyclosporine; Hydroxychloroquine; Tumor necrosis factor; Remission; Radiologic outcome

Core tip: In developing world cost of treatment remains a major concern. Recent evidences are emerging that support the equal efficacy of conventional disease modifying anti-rheumatic drugs (DMARDs) as compared to biological DMARDs. In this review we have presented evidences supporting conventional DMARDs in management of rheumatoid arthritis.

Parida JR, Misra DP, Wakhlu A, Agarwal V. Is non-biological treatment of rheumatoid arthritis as good as biologics? *World J Orthop* 2015; 6(2): 278-283 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/278.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.278

INTRODUCTION

The management of rheumatoid arthritis (RA) has witnessed sweeping changes in the past three decades. The emergence of disease modifying anti-rheumatic drugs (DMARDs), has resulted in slowing or halting the progression of RA, including radiographic progression and has resulted in better quality of life and clinical outcomes. In early 1980s, standard of care was oral or intramuscular gold or d-penicillamine, and methotrexate (MTX) had not yet seen the light of day

as a DMARD. Over the next one-and-a-half decades, MTX emerged as a safe, cheap and most compliant drug with convenience of once weekly dosing. Soon it became the first line DMARD for RA. Subsequent studies reported those combination therapy of multiple DMARDs are more effective in achieving treatment targets owing to their synergistic action with a favorable efficacy/toxicity profile. Till late 1980s DMARD therapy was based on "No harm" due to drugs principle, therefore, aggressive strategies targeting remission were hardly realized.

With the advances in the understanding of the pathogenesis of RA, tumor necrosis factor-α (TNF-α) emerged as a major cytokine causing damage to the joint. Development of anti-TNF-α monoclonal antibodies and its efficacy in management of RA revolutionized the management in early 1980s. These drugs, called as biologics, were highly effective with more rapid onset of action than conventional DMARDs and achieving remission in quite a large proportion of patients. Subsequently, newer biologics with different therapeutics targets were found to be effective in RA and led to the broadening of the treatment armamentarium. However, the superior efficacy of biologics was accompanied with risk of serious infections and malignancy. Moreover, prohibitive cost of biologics made it inaccessible to the majority of patients in the developing countries. This compelled researchers to evaluate the efficacy/safety profile of combination DMARDs and to adopt aggressive strategies such as "treat to target" using both combination DMARDs and biologics in head-on trials over last decade.

Keeping these in view, recent years have seen many clinical trials comparing the relative efficacy of triple drug therapy with conventional DMARDS (cDMARDs) and biologic DMARDs (bDMARDs).

MEASURING DISEASE ACTIVITY

It is important to know how to measure disease activity in RA as most clinical trials employ these as outcome measures. This can be measured by a number of indices including the disease activity score (DAS), DAS28, simplified disease activity index, clinical disease activity index, rheumatoid arthritis disease activity index, patient activity scale and routine assessment patient index data. Each assesses a various combination of factors including number of tender joints, number of swollen joints, acute phase reactants [erythrocyte sedimentation rate, C-reactive protein (CRP)], patient global assessment and physician global assessment. Each of these has varying definitions of remission, low disease activity, moderate disease activity and high disease activity. A good degree of correlation exists between the various measures. Recently, the ACR and EULAR have jointly defined "remission" in RA clinical trials as no more than one tender or swollen joint, CRP less than 1 mg/dL and patient global assessment $\leqslant$ 1 (on a scale of 0-10). Such stringent criteria lend credence to the fact that as low a disease activity as possible should be the aim of treating RA[1,2].

"TREAT-TO-TARGET" APPROACH

Before the era of biologics, remission in majority of RA was not achievable due to fear of toxicity and restricted the use of combination of cDMARDs.

The concept of "treat to target" where treatment target is a state of remission or low disease activity emerged from the TICORA trial[3]. In this trial, patients with RA of duration less than 5 years were randomized to receive either routine care or intensive care (monthly visits with target DAS $\leqslant$ 2.4 achieved by protocolised sequential cDMARD therapy). Both Groups had significant improvement in DAS. However the Group treated more intensively to reach a low disease activity had a significantly larger proportion of patients achieving an ACR70 response (71%) as compared to the Group receiving routine care (18%) and retardation of radiographic progression. Such a high ACR70 response has never been achieved even in trials with biologics. Intensive treatment was not associated with increased risk of adverse effects, and was cost-effective. The CAMERA trial[4] demonstrated that in early RA, intensive treatment approach with MTX (with cyclosporine if needed) resulted in remission in 50% patients (median duration 11 mo in 2 years) as compared to 37% (median duration 9 mo in 2 years) with conventional approach. At 2 years, the intensive treatment Group had an ACR 50 response of 58% compared to 45% in the conventional treatment Group. This again proves that an intensive treatment approach in patients using conventional DMARDs is effective in greater than half the patients in achieving remission. This data emphasized that outcome of RA depends on treating to target and not on the drugs used to achieve this. All patients are different in their treatment response to different drugs, so there is no unifying treatment algorithm which suits all.

Delving into the available evidence pool, the treatment of RA can be discussed separately for DMARD naïve patients and for patients who have failed these DMARDs.

TREATMENT OF EARLY, DRUG-NAÏVE RA

With the change in criteria for diagnosis of RA in 2010 it has become possible to diagnose much early and initiate DMARDs therapy to an optimum dose to target lowest disease activity or remission. As reported in the CAMERA trial[4], TICORA trial[3], FIN RACo[5,6], COBRA study[7], combination cDMARDs in various combinations not only achieve low disease activity or remission in quite a significant proportion of patients but also resulted in clinical and radiological outcomes in the long term. TICORA[3] trial resulted in ACR70 response in greater than 70% patients with a combination of conventional DMARDs alone. The FIN RACO[5] study showed that in early RA, combination therapy was

Table 1 RCTs comparing outcomes in rheumatoid arthritis

Trial	Arms	No. of patients	Mean/median disease duration at presentation	Outcome assessment at	Outcome		
					Clinical	Functional (change in HAQ)	Radiological
TICORA[3]	Intensive	55	Approximately 20 mo	18 mo	EGR 82% *vs* 45% ER 64% *vs* 16% ACR70 71% *vs* 18%	NA	Median change TSS 4.5 *vs* 8.5
	Conventional	55					
CAMERA[4]	Intensive	151	< 1 yr	1 yr	Remission for 3 mo 35% *vs* 14% ACR50 58% *vs* 43%	NS	NS
	Conventional	148		2 yr	Remission for 3 mo 50% *vs* 37% ACR50 43% *vs* 45%		
FINRACO[5]	SSZ + MTX + HCQ	87	Approximately 8 mo	2 yr	ACR remission 37% *vs* 18%	NS	Increase Larsen score 4 *vs* 12
	SSZ	91			ACR50 71% *vs* 58%		
NEO-RACO[20]	SSZ + MTX + HCQ + IFX	50	4 mo	5 yr	Remission-ACR: 60% *vs* 61%	NA	Change in SHS NS
	SSZ + MTX + HCQ + Placebo	49			DAS28: 84% *vs* 89%		
BEST[8]	Seq Monotherapy	126	2 wk	1 yr	LDA 53%; 64%; 71%; 74%	0.7; 0.7; 0.9; 0.8	Change in SHS 2; 2.5; 1; 0.5
	Step up	121					
	MTX + SSZ + Pred	133					
	MTX + IFX	128		2 yr	LDA 75%; 81%; 78%; 82%	0.7; 0.8; 0.9; 0.9	Change in SHS 2; 2; 1; 1
TEAR[10]	Immediate ETAN	244	Approximately 4 mo	2 yr	ACR20 45%-50% in all	NS	Change in TSS 0.5; 1.9; 0.7; 1.4
	Immediate triple	132			ACR50 35%-40% in all		
	Step-up ETAN	255			ACR70 10%-20% in all		
	Step-up triple	124					

NS: Not significant; NA: Not available; SHS: Modified sharp score; MTX: Methotrexate; SSZ: Sulfasalazine; HCQ: Hydroxychloroquine; IFX: Infliximab; ETAN: Etanercept; Pred: Prednisolone; LDA: Low disease activity; EGR: EULAR good response; ER: EULAR remission; TSS: Total sharp score; DAS: Disease activity score.

more effective than monotherapy in achieving ACR remission (14% *vs* 3%) and DAS28 remission (51% *vs* 16%). In COBRA[7] trial, initial intensive combination of MTX with sulfasalazine (SSZ) and prednisolone *vs* SSZ monotherapy alone not only resulted in significant clinical improvement at 28 and 56 wk but also resulted in better radiologic outcome even at 5 years.

BeSt trial[8,9] is a landmark open label trial which included 4 treatment arms (Table 1). Group 1 (sequential monotherapy) treated with initial MTX followed by SSZ followed by leflunomide, *etc*. Group 2 (step up combination therapy) treated with initial MTX but subsequently stepped up to combination therapy with MTX + SSZ + hydroxychloroquine (HCQ) + prednisolone. Group 3 (initial combination therapy) started with combination therapy from beginning (MTX + SSZ + HCQ + prednisolone) whereas. Group 4 (Initial biologic therapy) started with infliximab with MTX. At 1 year, low disease activity (DAS44 < 2.4) was attained in more than half the patients (53%, 64%, 71% and 74% in Groups 1, 2, 3 and 4 respectively) with about a third of the patients in remission in all the Groups. Of interest to answering the question posed earlier is a comparison of the results in Groups 3 and 4. At 1 and 2 years, both Groups 3 and 4 achieved similar DAS and HAQ scores at similar rates (both improved quicker than Groups 1 and 2) and had similar radiographic progression. Radiographic progression was numerically greatest in Group 1 and for Groups 1 and 2 taken together compared to combination Groups, although it did not reach statistical significance. This suggested that combination therapy with non-biologic DMARDs has similar efficacy to biologics in treatment naïve RA.

Treatment of early aggressive rheumatoid (TEAR)[10] trial further sought to explore whether triple therapy with MTX-SSZ-HCQ could be similar to MTX-etanercept (ETAN) (Table 1). This large trial involved 755 patients with poor prognostic factors (RF or anti CCP positive

Table 2 PREMIER study - outcome at 2 years follow-up[13]

	Ada + MTX	Ada	MTX
ACR20	69%	49%	56%
ACR50	59%	37%	43%
ACR70	47%	28%	28%

Ada: Adalimumab; MTX: Methotrexate.

with erosive disease). The study had four arms: (1) Initial MTX + ETAN; (2) Initial triple therapy (MTX + SSZ + HCQ); (3) Initial MTX for 24 wk followed by step up addition of ETAN for 78 wk if disease activity was not controlled; and (4) Initial MTX for 24 wk followed by step up triple therapy for 78 wk if disease activity was not controlled. The results showed similar outcomes at 1 and 2 years for all the Groups, with a small but significant advantage of the ETAN Groups *vs* the triple therapy Groups with respect to radiographic progression (change in total Sharp score-ΔTSS - 0.51/year). This again showed that combination DMARD therapy is not inferior to biologics in management of early RA.

Biologics have also been tried in DMARD-naïve RA, however head to head trials with combination cDMARDs are not available. The IMAGE[11] trial showed that use of rituximab in early RA with background MTX use resulted in ACR20, ACR50 and ACR70 responses of 77%-80%, 59%-65% and 42%-47% as compared to placebo (64%, 42%, 25% response rates respectively). Tocilizumab in drug-naïve RA (AMBITION trial)[12] had ACR 20, ACR50 and ACR70 response rates of 68%, 45% and 27% respectively. The PREMIER trial[13] (Table 2) showed that MTX monotherapy was comparable to adalimumab monotherapy. A trial of ETAN (25 mg twice weekly) in early RA compared to MTX monotherapy showed comparable ACR20 (50% *vs* 60%), ACR50 (about 40% in both) and ACR70 (about 20% in both) responses at 1 year[14]. In the ASPIRE trial[15], on a background of MTX, infliximab compared to placebo resulted in better ACR20 (62%-66% *vs* 53%), ACR50 (45%-50% *vs* 32%) and ACR70 responses (32%-37% *vs* 21%). It must be noted that most of these trials had a background MTX, so how much of a benefit was attributable to the biologic agent alone is a matter of debate.

The next question that arises is: Which one is preferable as initial combination therapy? Whether to go for triple therapy "MTX + SSZ + HCQ" or to add bDMARDs. To this regard multiple trials have been conducted and as discussed above, all concluded that if treated to a target, both options yielded similar result.

MANAGEMENT OF RA FAILING INITIAL METHOTREXATE MONOTHERAPY

If initial treatment with MTX monotherapy fails, then what is the best treatment option? Should we go directly to biologics or try combinations of cDMARDs? A closer look at the 3rd and 4th arms of the TEAR trial shows that 72% patients on MTX monotherapy had to be stepped up in a blinded fashion with addition of either SSZ + HCQ or ETAN due to persisting disease activity (DAS > 3.2). At 12 wk following stepping up as well as at the completion of the trial period (102 wk), both Groups had similar disease activity outcomes, quality of life and radiographic progression[10].

A Swedish study attempted to look at whether addition of infliximab was a better option to adding SSZ + HCQ in patients with inability to achieve low disease activity with MTX alone. The initial 1 year randomized trial showed similar outcomes with both approaches at 6 mo, but significantly better outcomes for the infliximab Group at 1 year (EULAR good response was attained in 26% triple therapy Group and 39% infliximab + MTX Group at 1 year). However at 18 and 24 mo of follow up this significance of difference was lost. This led the investigators to conclude that for those patients who fail initial MTX monotherapy, add-on therapy with conventional DMARDs serves as an appropriate treatment option. Of note, the triple therapy Group had a significantly higher radiographic progression of disease compared to the infliximab Group[16,17].

A recently published trial with a randomized double-blind design further compared addition of SSZ + HCQ verses addition of ETAN in failure of MTX monotherapy (RACAT Trial). At 24 wk, the patients having inadequate response were switched over to the other Group. Both Groups showed similar reductions in DAS 28 at 24 and 48 wk, with no significant differences in radiographic progression or quality of life. There was no significant difference in response after switching between the two Groups. This led the investigators to conclude that triple therapy with conventional DMARDs was non-inferior to ETAN + MTX in patients with RA having active disease inspite of MTX monotherapy[18,19].

Another recent study, the NEO-RACo trial[20] showed that at 5 years, treatment with combination cDMARDs (MTX, SSZ, hydroxychloroquine and low dose prednisolone) with or without infliximab during the first 6 mo had similar ACR remission rates (60% *vs* 61%) and DAS 28 remission rates (84% *vs* 89%) and radiologic outcomes. This again suggests that combination of cDMARDs is as effective as use of bDMARDs even on long term follow up.

SAFETY PROFILE

Although no form of therapy is absolutely safe, experience with conventional DMARDs is long-term over decades and side effect profile is well known. MTX and SSZ usage entails a risk of cytopenias and liver toxicity but if monitored properly does not pose a real threat. HCQ is a relatively safe drug and only need yearly

eye check up to look for retinal toxicity which is rarely encountered.

Biologic agents in general carry a definite increased infection risk, as they act by perturbing crucial pathways in anti-microbial defense like interleukin-6 and TNF-α. This is of greater importance in developing countries. Of note reactivation of tuberculosis is a definite threat in developing countries and there is still controversy regarding proper screening methods for this in literature. Most studies regarding anti TNF-α are from the North American and Scandinavian regions, where prevalence of TB is low[21,22]. Extrapolating the same data to developing countries where tuberculosis is rampant needs caution. Moreover, case reports of unusual infections like leprosy with use of anti TNF-α in developed countries, where these infections were unheard of previously, rang the warning bell[23]. RA has increased risk of lymphomas; furthermore, anti-TNF-α agent therapy also has been associated with risk of lymphoma and solid tumors[24]. Risk of demyelinating diseases as multiple sclerosis and flare of autoimmunity are also concerns with anti-TNF-α agents[21,22]. Although data regarding these are not very robust at present, we have to remember most of the biologic trials have been short term and exact risk of malignancy needs long-term follow up. Tocilizumab is associated with transaminitis, dyslipidemia and neutropenia which require monitoring for patients on follow-up[12]. Postmarketing surveillance had revealed Rituximab carries a small risk of fatal progressive multifocal leucoencephalopathy[25].

We feel worldwide experience with biologics is more limited than with cDMARDs, and they need to be used over few decades for estimating exact risk of malignancy and other long-term side effects. There is industry pressure to embrace biologics early and use it more liberally and multiple guidelines are being formulated supporting these. But in absence of a clearcut efficacy benefit and a definite risk of infection and malignancy, we have to be careful while using these and exercise more caution atleast in developing countries where cost both of biologics and any complication arising out of its use is significant.

CONCLUSION

Although biologics have revolutionized the field of RA treatment, their overwhelming costs, risk of serious infections and limited availability result in their inaccessibility to a majority of the population in resource constrained healthcare settings. Triple therapy, whether used initially or as rescue therapy in patients with MTX failure, has similar efficacy to combination of anti-TNF-α agents with MTX, and this has been demonstrated across various populations. There is paucity of data comparing biologics other than anti-TNF-α agents with conventional DMARDs, and this remains to be addressed in future clinical trials.

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P- Reviewer: Saviola G **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Orthopedics

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DOI: 10.5312/wjo.v6.i2.284

World J Orthop 2015 March 18; 6(2): 284-289
ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Retrospective Study

Total knee arthroplasty: Effect of obesity and other patients' characteristics on operative duration and outcome

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Received: May 6, 2014
Peer-review started: May 7, 2014
First decision: May 23, 2014
Revised: September 22, 2014
Accepted: October 14, 2014
Article in press: October 16, 2014
Published online: March 18, 2015

Abstract

AIM: To examine the effects of patients' characteristics mainly obesity on operative duration and other outcome measures of knee arthroplasty.

METHODS: This is a retrospective chart review of 204 patients who had knee arthroplasty within the past five years (2007-2011) at King Abdulaziz Medical City in Riyadh, Kingdom of Saudi Arabia. The data collection form was developed utilizing the literature review to gather all the needed variables. Data were gathered from admission notes, nursing notes, operative reports and discharge summaries.

RESULTS: A feasible sample of 204 patients were included in the study. Of those patients, 155 (76%) were females. The mean age was 70.1 years for males (SD ± 9.4) and 62.7 years (SD ± 8) for females. Regarding the type of total knee replacement (TKR), 163 (79.9%) patients had unilateral TKR and 41 (20.1%) had bilateral TKR. Nine patients (4.4%) had a normal body mass index (BMI) (18.5 to < 25). Overweight patients (BMI 25 to < 30) represented 18.1%. Obesity class Ⅰ (BMI 30 to < 35) and obesity class Ⅱ (BMI from 35 to < 40) were present in 23% and 29.9% of the patients, respectively. Morbid obesity (BMI greater than 40) was present in 24.5%. The mean duration of surgery was 126.3 min (SD ± 30.8) for unilateral TKR and 216.6 min (SD ± 55.4) for bilateral TKR.The mean length of stay in the hospital was 12 d (SD ± 4.9). The complications that patients had after the operation included 2 patients (1%) who developed deep venous thrombosis, 2 patients (1%) developed surgical wound infections and none had pulmonary embolism. Patients' characteristics (including age, gender, BMI and co-morbidities) did not have an effect on the operative duration of knee replacement nor the length of hospital stay.

CONCLUSION: Our study shows that obesity and other patients' characteristics do not have effect on the operative duration nor the length of hospital stay following TKR.

Key words: Knee; Replacement; Arthroplasty; Implantation; Surgery; Orthopedics; Total knee arthroplasty; Total knee replacements

Core tip: Studying the effects of obesity and other patient's characteristics on the outcome and operative duration of knee arthroplasty (KA) is of great value for both patients and physicians. Studies regarding this subject have shown conflicting results, and the importance of these factors on the decision to perform KA is debatable among surgeons. In our study, we demonstrated that higher body mass index values were not associated with longer duration of surgery. We also found that patients' characteristics did not seem to be an important determinant of length of stay.

Al Turki AS, Al Dakhil Y, Al Turki A, Ferwana MS. Total knee arthroplasty: Effect of obesity and other patients' characteristics on operative duration and outcome. *World J Orthop* 2015; 6(2): 284-289 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/284.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.284

INTRODUCTION

Knee replacement (KR) is one of the most commonly performed orthopedic procedures in the United States and United Kingdom. Over 600000 KRs are carried out annually in the United States. The articular surfaces that form the knee joint are covered with cartilage that functions like a shock absorber. When this cartilaginous coverage is lost or damaged, patients experience varying degrees of pain and functional impairment.

Osteoarthritis and rheumatoid arthritis are the underlying reasons of the majority of total knee arthroplasties[1-4]. KR is considered a safe and cost-effective procedure that improves patients' quality of life, physical function and alleviates pain[5]. Complications of KR, although rare and preventable, include thromboembolism, infection and prosthesis failure[6].

Many studies have reported how patients' characteristics such as age, gender and obesity influenced the outcome and prognosis of knee arthroplasty[7,8]. Nonetheless, the importance of these factors on the decision to perform knee arthroplasty is debatable among surgeons[9]. This may reflect the lack of available data. A systematic review of sixty-four studies concluded that future studies are needed to sort out the question of how patients' characteristics affect the outcome of knee arthroplasty[8]. With regard to the operative duration and its association with the obesity, we found relatively little literature addressing this issue. These studies have shown conflicting results, for example, a study of 172 KRs in United Kingdom found that higher body mass index (BMI) was associated with increased tourniquet time[10]. However, another study conducted in Spain on 100 patients found no association between the BMI and tourniquet time[11].

The length of hospital stay (LOHS) following KR is significantly affected by patients' characteristics. A recent study in the United States reviewed the preoperative data of 383 patients and found the mean LOHS to be 4.35 d and that increased age and lower BMI prolonged the hospital stay[12,13]. Furthermore, obese patients had higher revision rates in a study of 326 total KRs (TKR) conducted in London[13]. Yet, another study showed that the risk of prosthesis failure was not influenced by the patient's BMI[13].

Only a few studies were conducted in the Kingdom of Saudi Arabia concerning KR[14-17]. One study in Jeddah concluded that TKR improves quality of life and the observed complications compared well with the literature[15]. Another study surveyed patients' attitude toward TKR[17]. However, no national or regional studies have evaluated the effect of patient's characteristics on the outcome of the procedure.

The purpose of this study was to examine the effects of some patients' characteristics (age, gender, obesity and co morbidities) on certain outcome measures (operative duration, revision rate, length of hospital stay and post operative complications) of KR. Main focus was on the association between the patients' BMI and operative duration of KR.

MATERIALS AND METHODS

The Medical records of a feasible sample of all the patients (204) who underwent TKR (both unilateral and bilateral) within the past five years (2007-2011) at King Abdulaziz Medical City in Riyadh, Kingdom of Saudi Arabia were reviewed. Most of those patients were National Guard Health Affiars employees (military and non-military) or their families. Almost all of them were Saudis and some live in Riyadh (the capital of Saudi Arabia), while others came from suburban areas. Data were gathered from admission notes, nursing notes, operative reports and discharge summaries.

The data collection form was developed utilizing the literature review to gather all the needed variables. It contains two main sections, the first is about the patients' characteristics (*e.g.*, age, gender, BMI, co-morbidities…, *etc.*), while the second is regarding the surgery itself (*e.g.*, date, duration and complications).

Patients' confidentiality was maintained throughout the study, patients' names were not used. Instead patients' record numbers were documented for the purpose of validation. Access to the data was restricted to the investigators. Patients' consent was not required for this type of study. The study was approved by King Abdullah International Medical Research Center Institutional Review Board.

SPSS V20 was used. Data were entered into the

Table 1 Patient's characteristics

Variable		Frequency (*n*)	%
Gender	Males	49	24
	Females	155	76
Type of TKR	Unilateral	163	79.9
	Bilateral	41	20.1
Co-morbidities	Hypertension	126	61.8
	Diabetes	84	41.2
	Dyslipidemia	67	32.8
BMI	Normal BMI (BMI value 18.5 to < 25)	9	4.4
	Overweight (BMI value 25 to < 30)	37	18.1
	Obesity class 1 (BMI value 30 to < 35)	47	23
	Obesity class 2 (BMI value 35 to < 40)	61	29.9
	Morbid obesity (BMI value > 40)	50	24.5
Post Operative Complications	DVT	2	1
	PE	0	0
	Infection	2	1

TKR: Total knee replacement; BMI: Body mass index; DVT: Deep venous thrombosis; PE: Pulmonary embolism.

program from the completed forms. Univariate analysis (frequencies) and bivariate analysis were calculated. *P* value of $\leqslant$ 0.05 was considered significant. Different statistical tests were used including ANOVA and *t*-tests.

RESULTS

A total of 204 patients who underwent KR surgery were included in the study. Of those, 155 (76%) were females. Females' mean age was 62.7 years (SD ± 8) while males' mean age was 70.1 (SD ± 9.4) years.

Only 9 patients (4.4%) had a normal BMI (18.5-25). Overweight patients (BMI 25-30) represented 18.1%. Obesity class 1 (BMI 30-35) and obesity class 2 (BMI from 35 to 40) were present in 23% and 29.9% of the patients, respectively. Morbid obesity (BMI greater than 40) was present in 24.5% of the patients (Table 1).

Hypertension was present in 126 (61.8%) patients, diabetes was present in 84 (41.2%) patients, and dyslipidemia was present in 67 patients (32.8%). Osteoarthritis was the main cause of TKR (99.5%) of patients. One hundred and sixty-three (79.9%) patients had unilateral TKR while the rest had bilateral TKR. The mean duration of surgery was 126.3 min (SD ± 30.8) for unilateral TKR and 216.6 min (SD ± 55.4) for bilateral TKR. The mean length of stay in the hospital was 12 d (SD ± 4.9).

Two patients (1%) developed deep venous thrombosis, 2 patients (1%) had surgical wound infection and none had pulmonary embolism (Table 1).

t-test was used to assess the association between patients' gender and the mean operative duration. *P* values for unilateral and bilateral TKR are non significant (*P* = 0.69 for unilateral, 0.51 for bilateral). There is no difference between males and females with regard to the operative duration in either groups of TKR.

ANOVA test was used to assess the association between the BMI of patients and the operative duration. *P* = 0.28 for unilateral and *P* = 0.66 for bilateral TKR which means that there is no association between the BMI and operative duration in either groups.

There is no association between the presence of diabetes milletus, hypertension or dyslipidemia with the operative duration in both groups (Table 2).

Table 3 shows no difference between males and females with regard to the LOHS in either groups (*P* = 0.37 for unilateral, 0.79 for bilateral), also there is no association between the BMI and length of hospital stay in either groups (*P* = 0.27 for unilateral, 0.32 for bilateral).

DISCUSSION

Studying the effects of obesity (as measured by the BMI) and other patient's characteristics on the outcome and operative duration of KR is of great value for both patients and physicians.

In our study we found that the BMI is not associated with the operative duration of KR. In other words, we demonstrated that higher BMI values were not associated with longer duration of surgery in both unilateral and bilateral TKR. Thus, we believe that the BMI should not be considered an indicator for prolonged operative time when performing KR. This information is important because it will allow surgeons to appropriately utilize the operating room time and resources. Our finding is supported by the results of a study conducted in Spain on 100 patients who found that the BMI doesn't affect the operative duration[11]. However, a United Kingdom study that included 172 patients showed that higher BMI was associated with increased operative time[10]. Recently, two studies in New York, United States, found that obesity was related to longer duration of unilateral KR[18,19].

Our results showed that certain patients' characteristics (namely: age, gender and co-morbidities) did not have an effect on the operative duration of KR. To the best of our knowledge there are no studies that looked at the association between age, gender and co-morbidities and operative duration of KR.

The mean length of stay following TKR in our study was 12 d compared to 7.6 d in a study done in United Kingdom on over 500 patients[3]. This might be explained by including pre-operative admission days in our study when calculating the length of stay. This study revealed that patients' characteristics did not seem to be an important determinant of length of stay. A retrospective study in United States supports this as they found that age, gender, living arrangement and co-morbidities did not contribute significantly to

Table 2 Association of patient's characteristics and duration of surgery

Duration of surgery *vs*		Unilateral TKR					Bilateral TKR				
		n	%	Mean duration	SD	*P* value	*n*	%	Mean duration	SD	*P* value
Gender	Males	35	21.5	124.5	29.2	0.69	14	34.1	224.7	50.2	0.51
	Females	128	78.5	126.9	31.4		27	65.9	212.4	58.3	
BMI	Normal BMI (BMI value 18.5 to < 25)	5	3.1	115.8	44.6	0.28	4	9.8	239	51.2	0.66
	Overweight (BMI value 25 to < 30)	27	16.6	117.1	24		10	24.4	215.3	66.3	
	Obesity class 1 (BMI value 30 to < 35)	40	24.5	125.9	37.3		7	17.1	228.4	33.5	
	Obesity class 2 (BMI value 35 to < 40)	48	29.4	127	29.5		13	31.7	198.8	64.3	
	Morbid obesity (BMI value > 40)	43	26.4	133	27.4		7	17.1	226.8	42.5	
DM	Yes	63	38.7	124.7	30.8	0.59	21	51.2	215.2	56.4	0.87
	No	100	61.3	127.4	33.8		20	48.8	218.1	55.7	
HTN	Yes	99	60.7	126.3	29	1	27	65.9	223.8	50.3	0.25
	No	64	39.3	126.3	33.8		14	34.1	202.7	63.7	
DLP	Yes	52	31.9	126.7	25.8	0.92	15	36.6	227.1	42.2	0.36
	No	111	68.1	126.2	33.1		26	63.4	210.5	61.7	

TKR: Total knee replacement; BMI: Body mass index; DM; Diabetes mellitus; HTN: Hypertension; DLP: Dyslipidemia.

Table 3 Association of patients' characteristics and length of hospital stay

Length of hospital stay *vs*		Unilateral TKR					Bilateral TKR				
		n	%	Mean	SD	*P* value	*n*	%	Mean	SD	*P* value
Gender	Males	35	21.5	12.6	6.3	0.37	14	34.1	14.6	4.1	0.79
	Females	128	78.5	10.9	3.7		27	65.9	15	6.1	
BMI	Normal BMI (BMI value 18.5 to < 25)	5	3.1	10.8	2.5	0.27	4	9.8	12	2.2	0.32
	Overweight (BMI value 25 to < 30)	27	16.6	10.7	3.6		10	24.4	14.7	6.9	
	Obesity class 1 (BMI value 30 to < 35)	40	24.5	12.6	6.8		7	17.1	16.6	5.6	
	Obesity class 2 (BMI value 35 to < 40)	48	29.4	10.7	3.3		13	31.7	13.5	4.1	
	Morbid obesity (BMI value > 40)	43	26.4	10.9	3.3		7	17.1	17.9	6.1	

TKR: Total knee replacement; BMI: Body mass index.

LOHS[13]. But one recently published study in United Kingdom found that age > 80 and higher BMI were significant predictors for prolonged hospital stay following TKR[3].

The effects of patients' characteristics on the post-operative complications and KR revision rate could not be assessed because the numbers were too small to do appropriate statistical analysis.

Our study showed that osteoarthritis is the leading cause for TKR. One large community house-held study in Saudi Arabia showed the prevalence of knee osteoarthritis among adult Saudi inhabitants (those aged older than 16) was 13%, of which 30% between the ages 45-55 years. This was doubled by the age of 65 year[20]. In another study, 90% of patients with knee osteoarthritis were overweight and obese[21].

There is a strong association between obesity and osteoarthritis, which is more in females than males (OR for males is 2.0 and for females is 3.0)[22].

Obesity prevalence is increasing in all areas of the Kingdom of Saudi Arabia[23]. This will probably lead to increasing numbers of KRs because obesity is a well-known risk factor for osteoarthritis[24].

Strengths of our research include examining the outcome of both unilateral and bilateral KRs. Our research question is the first to be studied in Saudi Arabia.

There are several limitations to our study. First, the inter-surgeons differences and surgeons' expertise were not accounted for when calculating the operative duration of KR. Second, we looked at the total operative time which is not very accurate because other factors like anesthesia timing might affect it. Also, the type of the implant (prosthesis) was not considered. This is a retrospective chart review study and has the limitations common to those types of study designs mainly documentation bias. Another weakness is the small sample size.

To conclude, KR is a safe and cost-effective procedure that alleviates pain and improves function. The relationship between patients' demographics and the outcome of TKR is still not clear. Our study shows that patient's characteristics particularly obesity do not increase the operative time and do not prolong the hospital stay following TKR.

Total knee arthroplasty (TKA) is a safe procedure that alleviates pain and improves function. Patient's characteristics particularly obesity do not increase the operative time and do not prolong the hospital stay following TKA.

We believe that when scheduling patients for KR, patient's characteristics should not be viewed as accurate measures of operative difficulty and operative duration. However, this information should be addressed with caution as the literature review revealed contradicting results. Therefore, we recommend that larger and controlled studies should be done to better assess this topic especially in Saudi Arabia.

COMMENTS

Background

More than half million knee arthroplasties are done annually in United States, mainly due to osteoarthritis, which improves the quality of their lives. Patients with Osteoarthritis are usually old, obese with high percentage of comorbidities. There is controversies among studies of the effect of such patient's characteristics on the outcome of the surgery.

Research frontiers

There is controversy among studies of the effect of age, obesity and other patients' characteristics on the outcome of total knee arthroplasty (TKA). The result shows no effect.

Innovations and breakthroughs

There is debate among surgeons of the influence of patients' characteristics on the outcome of TKA. A systematic review of sixty-four studies concluded that further studies are needed to sort out this conflict. This study shows that there is no association between age, gender, obesity and comorbidities on TKA outcome.

Applications

This study shows that there is no effect of patients characteristics on the outcome of TKA, surgeons don't need to select their patients based on their characteristics to perform TKA or to predict a worse outcome.

Terminology

Total knee replacement, also referred to as TKA, is a surgical procedure where damaged surfaces of a knee joint are removed and replaced with artificial joint or prosthesis (http://ehealthmd.com/content/what-knee-replacement#ixzz39bBCZ6ak).

Peer-review

The objective of this study was to examine the effects of patient's characteristics on operative duration following knee arthroplasty. This is an interesting study.

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P- Reviewer: Bruyere O, Drosos GI, Fenichel I **S- Editor**: Ji FF
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DOI: 10.5312/wjo.v6.i2.290

World J Orthop 2015 March 18; 6(2): 290-297
ISSN 2218-5836 (online)

Computerised tomography *vs* magnetic resonance imaging for modeling of patient-specific instrumentation in total knee arthroplasty

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Telephone: +44-1582-491166
Received: February 27, 2014
Peer-review started: February 27, 2014
First decision: April 28, 2014
Revised: August 15, 2014
Accepted: September 4, 2014
Article in press: September 10, 2014
Published online: March 18, 2015

Abstract

AIM: To summarise and compare currently available evidence regarding accuracy of pre-operative imaging, which is one of the key choices for surgeons contemplating patient-specific instrumentation (PSI) surgery.

METHODS: The MEDLINE and EMBASE medical literature databases were searched, from January 1990 to December 2013, to identify relevant studies. The data from several clinical studies was assimilated to allow appreciation and comparison of the accuracy of each modality. The overall accuracy of each modality was calculated as proportion of outliers > 3% in the coronal plane of both computerised tomography (CT) or magnetic resonance imaging (MRI).

RESULTS: Seven clinical studies matched our inclusion criteria for comparison and were included in our study for statistical analysis. Three of these reported series using MRI and four with CT. Overall percentage of outliers > 3% in patients with CT-based PSI systems was 12.5% *vs* 16.9% for MRI-based systems. These results were not statistically significant.

CONCLUSION: Although many studies have been undertaken to determine the ideal pre-operative imaging modality, conclusions remain speculative in the absence of long term data. Ultimately, information regarding accuracy of CT and MRI will be the main determining factor. Increased accuracy of pre-operative imaging could result in longer-term savings, and reduced accumulated dose of radiation by eliminating the need for post-operative imaging and revision surgery.

Key words: Patient-specific instrumentation; Arthroplasty; Alignment; Accuracy; Cost-effectiveness

Core tip: At present there is not enough published data to convincingly conclude in favour of computerised tomography (CT) or magnetic resonance imaging for

accuracy of pre-operative imaging in patient-specific instrumentation. We recommend CT as a more favourable option at present due to reduced scanning times, increased availability, and relatively cheaper cost.

Stirling P, Valsalan Mannambeth R, Soler A, Batta V, Malhotra RK, Kalairajah Y. Computerised tomography *vs* magnetic resonance imaging for modeling of patient-specific instrumentation in total knee arthroplasty. *World J Orthop* 2015; 6(2): 290-297 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/290.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.290

INTRODUCTION

Patient-specific instrumentation (PSI) was developed to simultaneously optimize patient outcomes and surgical efficiency in total knee arthroplasty (TKA), and PSI evolved with the aims to improve component placement accuracy. Improving accuracy of placement of the tibial component can reduce the incidence of malalignment and rotation, errors which are associated with patient dissatisfaction after arthroplasty[1] - reported in up to 19% of cases[2] - and are believed to reduce implant survival[3,4]. The current technique combines pre-operative imaging using computerised tomography (CT) or magnetic resonance imaging (MRI) and full-length radiograph in combination with rapid-prototyping technology to create bespoke guides or jigs which direct cutting tools during bony resection. Pre-operative computer-assisted planning allows determination of resection margins, implant size and position, the overall aim being to improve component alignment and operative efficiency[5,6] whilst avoiding violation of the intramedullary canal. Pre-operative imaging and planned guides are approved by the surgeon, thus shifting the navigational aspects of the procedure to the pre-operative stage, which may improve operative efficiency[6].

Proponents of the technique argue that PSI can improve component alignment accuracy, post-operative functional outcome[7], whilst reducing intraoperative blood loss, operative time, number of surgical steps[7], and time between cases, ultimately resulting in cost savings associated with reduced inventory and sterilization costs. Evidence in this area is still however conflicting. Many studies report good alignment achieved with PSI[8-11] in both coronal and frontal planes, yet separate studies have demonstrated no significant difference in component alignment using PSI[12-14], with some even reporting an increase in outlier incidence[7,15]. In addition, there are conflicting reports of the proposed reduction in operative time and technicality: whilst some studies report a significant reduction in operating time[7,16], others report increased intra-operative changes to implant size[17] due to mismatching of the specific prosthesis and the pre-operative plan[18].

Many current opinions regarding PSI remain speculative in the absence of medium and long-term data. Proposed benefits regarding patient functional outcomes, complication rates, alignment, and cost-effectiveness are summarized comprehensively in review articles authored by Ast *et al*[6], Nam *et al* [19], and Lachiewicz *el al*[20].

The use of pre-operative CT *vs* MRI varies depending on the PSI system used, and is a source of major ongoing debate. CT is relatively inexpensive and imaging times are short. It is therefore financially appealing. However, exposure to radiation is a concern and there have been recent reports of increase in cancer attributed to unnecessary CTs[21,22]. MRI, on the other hand, does not use ionising radiation and is deemed a safer and more appealing imaging modality. Some pre-operative MRI imaging for PSI also requires a whole leg plain film and so may not wholly be without additional radiation exposure. Moreover, most CT-based PSI systems utilise focused scans of the hip, knee, and ankle to reduce unnecessary exposure: the equivalent dose has been calculated at 5 mSv, comparable to a yearly background radiation dose, or roughly 70 chest X-rays[23].

Although MRI avoids radiation exposure, the cost and time of the investigation is greater than for CT. For PSI, there is no need to report the scans once performed as the image data is sent directly to the company, and the only cost of imaging is in performing the scan itself. In our trust, the cost of pre-operative imaging using MRI is almost double that of CT (£171 *vs* £97). Importantly, the comparatively longer length of time for an MRI scan may result in movement artefacts worsening the quality of MRI images.

Ultimately, information regarding accuracy of CT and MRI will be the main determining factor. This review article summarises and compares currently available evidence regarding accuracy of pre-operative imaging, which is one of the key choices for surgeons contemplating PSI surgery.

MATERIALS AND METHODS

The MEDLINE and EMBASE medical literature databases were searched, from January 1990 to December 2013, to identify relevant studies. The Keywords used were (1) Patient Specific templates in total knee replacement (TKR); (2) Patient specific instrumentation in TKR; and (3) Customised Patient Jigs in TKR. Studies were eligible for review if they met the following criteria: (1) the language was English and one of the following; (2) had a comparison between conventional TKR and PSI; (3) comparison between CT and MRI for PSI; and (4) reported cadaveric or clinical analysis of accuracy of component placement using PSI. Due to scarcity of clinical studies available, studies were stratified for inclusion, with animal studies considered lowest in the hierarchy, followed by human cadaveric studies, and finally, human clinical studies.

Table 1 Articles directly comparing computerised tomography and magnetic resonance imaging

Ref.	Article type	Sample size	Comparison of accuracy	Dimensional accuracy
Ensini *et al*[25]	Prospective randomized trial	25 CT PSI and 25 MRI PSI	Intra-operative navigation system and post-operative radiographic alignment	Comparable outcome
Cenni *et al*[9]	Prospective randomised trial	23 CT and 21 MRI PSI	Post-operative radiograph	Comparable outcome
Fritschy *et al*[26]	Prospective controlled trial	10 PSI patient, 10 standard TKAs (control)	Intra-operative navigation and post-operative long standing X-ray	Comparable outcome
Van den Broeck *et al*[27]	Human cadaveric study	9 cadaveric tibia	Comparison with bone dimensions using optical white-light scanner	Comparable outcome
White *et al*[28]	Animal study	10 ovine knees	Direct comparison with bone dimensions	CT > MRI
Rathnayaka *et al*[29]	Animal study	5 ovine limbs	Direct comparison with bone dimensions	Comparable outcome

TKA: Total knee arthroplasty; PSI: Patient-specific instrumentation; CT: Computerised tomography; MRI: Magnetic resonance imaging.

As most studies available focus on validation of a single technique rather than a direct comparison, the data from several clinical studies was assimilated to allow appreciation and comparison of the accuracy of each modality. The overall accuracy of each modality was calculated as proportion of outliers > 3% in the coronal plane of both CT and MRI. A test for assumption of homogeneity between studies was conducted using Cochrane Q statistics and ratio of heterogeneity to total variance was calculated (I^2 statistic). A random-effects method was performed with single stage proportion meta-analysis using R-software. The metaprop command available in meta library was applied with Freeman-Tukey Double arcsine transformation to calculate overall proportion and DeSimonian-Laird method for estimation of variance between studies[24].

RESULTS

Only six studies were identified which directly compared CT and MRI. These studies are summarised in Table 1.

Aside from the study by Ensini *et al*[25] and Cenni *et al*[9], all studies focus on 3D reproduction of bone models, rather than surgical outcomes. White *et al*[28] undertook an animal study in 2008, comparing CT and MRI based 3D reproductions using PSI systems and compared the reproduced bone dimensions with the actual bony anatomy of 10 ovine knees. They found that bony dimensions of the MRI-based models were significantly less accurate than those created by CT, reporting an average accuracy of 0.61 mm ± 0.41 mm for CT, and 2.15 mm ± 2.44 mm with MRI. This study also found increased bony landmark resolution in CT-based systems compared with MRI. This contradicts previous theories that CT may be less accurate due to its reduced ability to delineate articular cartilage from bone[30]. Rathnayaka *et al*[29] repeated the study in 2012 using five ovine femora but found comparable outcomes with both imaging modalities. The cadaveric study undertaken by Van den Broeck *et al*[27] and presented at the European Society of Biomechanics in 2013 corroborated these results, using clinical scanning protocols and human tibia, and finding comparable accuracy of 0.42 mm ± 0.38 mm for MRI and 0.53 mm ± 0.38 mm for CT[27]. Fritschy *et al*[26] prospectively compared accuracy of CT and MRI in ten patients undergoing computer-navigated TKA, concluding that either technique may be used effectively for PSI synthesis.

There were only two clinical studies which directly compared post-operative alignment in two separate patient groups randomised to CT or MRI. Ensini *et al*[25] undertook a prospective, randomized study comparing 25 patients randomized to TKA with MRI-based PSI, with 25 patients randomized to TKA with CT. Outcomes measured were intra-operative accuracy and resection thickness, and post-operative axis alignment as defined by post-operative plain radiograph. The authors found acceptable alignment and intra- and post-operative measurements with both systems in the coronal, sagittal and frontal planes. Importantly, the authors reported a higher incidence of mechanical axis outliers of 37% in the pre-operative CT group, compared with 18% in the MRI group. This result however did not reach statistical significance. Cenni *et al*[9] report a similar study with 23 patients randomised to pre-operative CT and 21 to MRI. Similar mean post-operative mechanical axes were found in both groups (-0.9 ± 2.3 for CT, 0.7 ± 2.4 for MRI) with three outliers in each group.

Seven clinical studies matched our inclusion criteria (3) for comparison and were included in our study for statistical analysis. Three of these reported series using MRI and four with CT. The data from these studies is summarised in Table 2.

All studies reported alignment in the coronal plane. Several studies reported alignment and percentage of outliers with reference to the sagittal plane, and rotational alignment. As a result we were only able to compare percentage of outliers in the coronal plane between studies.

Table 2 shows consistent outlier percentage in all studies investigating accuracy of pre-operative CT. The largest study was reported by Koch *et al*[31] reporting outlier incidence of 12.4% in a cohort of 301 patients. Accuracy of component placement was found to be

Table 2 Data assimilation of current patient-specific instrumentation literature

Ref.	Comparison	Type of study	System used	Imaging used	No. of patients	% outliers > 3%
Boonen *et al*[8]	PSI with disposable guides *vs* conventional intramedullary guides	Case control	Signature	MRI	40	29
Barrett *et al*[12]	PSI *vs* conventional - absolute mechanical axis measure	Prospective cohort study	Trumatch	CT	66	19
Bugbee *et al*[33]	PSI *vs* conventional	Retrospective cohort	Trumatch	CT	25	4
Chareancholvanich *et al*[13]	PSI *vs* conventional instrumentation	RCT	Zimmer	MRI	80	2.5
Koch *et al*[31]	PSI *vs* computer-navigated		My knee	CT	301	12.4
Chen *et al*[15]	PSI *vs* conventional TKA	Randomised control study	Zimmer PSI	MRI	30	31
Roh *et al*[32]	PSI *vs* conventional	RCT	Signature	CT	50	12

TKA: Total knee arthroplasty; PSI: Patient-specific instrumentation; CT: Computerised tomography; MRI: Magnetic resonance imaging; RCT: Randomised controlled trial.

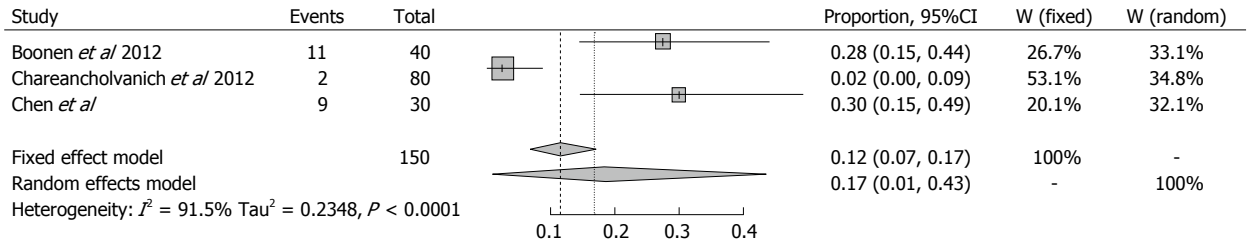

Figure 1 Forest plot for outlier incidence using magnetic resonance imaging.

equal to computer-navigated surgery. Comparable outcomes were reported by Roh *et al*[32] in their randomised controlled trial of 50 patients treated with PSI and 50 with conventional TKA, reporting outlier incidence of 12%. Barrett *et al*[12] reported a slightly higher outlier incidence of 19% from their study of 66 patients using the CT-based Trumatch system. Bugbee *et al*[33] reported the most accurate results in a retrospective cohort study with 25 patients treated with conventional TKA and 25 with the CT-based Trumatch PSI system, with an outlier incidence of 4%. These result show little variation and all studies report comparable accuracy between CT-based PSI and computer-navigated or conventional instrumentation.

For the four studies using CT, I^2 was 30.1% (0%; 74.6%) and this was not significant (P = 0.2317). To maintain the similarity with MRI a random-effects method was applied. The overall proportion of outlier > 3% was 0.1249 (95%CI: 0.0827-0.1737). Therefore we conclude that percentage of outliers > 3% is 12.50% and with 95% confidence at least 9.27% and at most 17.4% for the cohort using pre-operative CT.

Three studies were identified which investigate post-operative outcomes with MRI-based PSI. Although Chareancholvanich *et al*[13] reported excellent post-operative alignment and an outlier incidence of 2.5% in their randomised controlled trial of 80 patients, results from the studies by Boonen *et al*[8], and Chen *et al*[15] reported much higher outlier incidence of 29% and 31% respectively. It is worth noting that the highest incidence of outliers in the MRI-based systems occurred in the sagittal plane with 24% for both femoral and tibial component as reported by Chen *et al*[15] , and 41% and 36% for sagittal femoral and tibial respectively as reported by Boonen *et al*[8].

For the three studies evaluating MRI, I^2 was 91.5% (95%CI: 0.782-0.967) suggesting a high degree of variance between the studies (Q statistic, P < 0.0001). Sensitivity analysis revealed that the study reported by Chareancholvanich *et al*[13] dramatically influenced on the heterogeneity of the analysis. The overall proportion of outliers > 3% was 0.1696 (95%CI: 0.0117-0.4349). Therefore the percentage of outliers > 3% was 16.96% and with 95% confidence at least 1.2% and at most 44% for the cohort using pre-operative MRI. This suggests a higher level of variability between studies, and that overall outlier percentage may in fact be higher than the 16.96% reported.

It was not possible to directly compare the two cohorts, however due to the overlapping confidence intervals, it can be concluded that the difference in outlier incidence appears to be slightly lower using pre-operative CT. No statistically significant conclusions can be drawn from this analysis, however. These results are presented in Figures 1 and 2.

DISCUSSION

Increasing costs in healthcare together with financial restraints are forcing further rationalisation of available resources. There is a year-on-year increase in the

Table 3 Currently available patient-specific instrumentation platforms (data adapted from Ast *et al*[61])

Manufacturer	Product	Imaging	Type of guide	Launched
Biomet	Signature-vanguard	CT or MRI	Pinning	MRI-2007 CT-2010
DePuy	Trumatch	CT	Cutting	2009
Smith and nephew	Visionaire	MRI	Pinning	2008
Wright medical	Prophecy	CT or MRI	Pinning	2009
Zimmer	PSI	MRI	Pinning	2009
Conformis	Conformis iTotal	CT	Cutting	2011
Medacta	My knee	CT	Cutting	2009

PSI: Patient-specific instrumentation; CT: Computerised tomography; MRI: Magnetic resonance imaging.

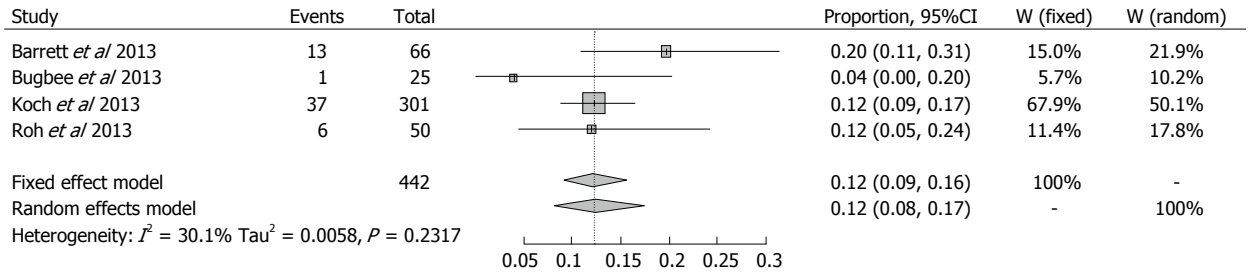

Figure 2 Forest plot for outlier incidence using computerised tomography.

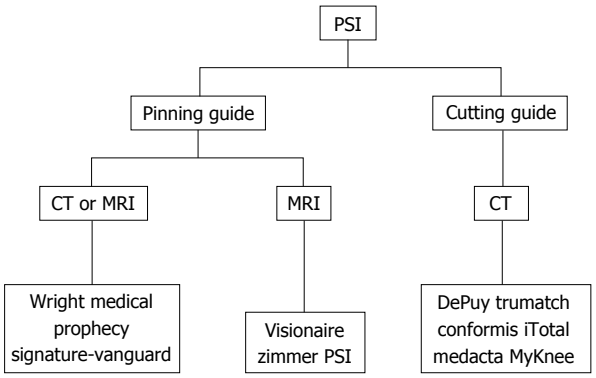

Figure 3 Summary of currently available patient-specific instrumentation systems. PSI: Patient-specific instrumentation; CT: Computerised tomography; MRI: Magnetic resonance imaging.

number of primary knee arthroplasties and all national joint registries are reporting increasing numbers of revision arthroplasties[34,35]. A great percentage of these revisions are due to mechanical failure as a result of malalignment[36,37]. The cost of revision TKR is high and depending on the bone loss, implant required, and hospital stay, it can exceed many times over the cost of primary TKR[38-40].

If through a primary procedure we can accurately reproduce a patient's mechanical and anatomical alignment, then we may reduce the burden of revision surgery. PSI was introduced to improve implant positioning. Component positioning with traditional instrumentation uses coronal plane alignment with reference to the femoral head and ankle joint[41], or anterior or posterior referencing in the sagittal plane. Rotational alignment of the femoral component is also a point of debate as it may affect patella tracking.

Despite the rapid evolution and growing body of evidence around PSI in recent years, Joint Registry Data shows that conventional arthroplasty using standard instrumentation remains in more widespread use[42]. Current commercial systems differ from each other in three key ways. Firstly, pre-operative imaging modality, whether CT or MRI, is always required to collate the 3-dimensional data required for creation of the patient-specific guide. Secondly, two types of PSI are currently in use: pinning guides and cutting guides. The third and final difference is the method of alignment used, whether mechanical axis or pre-arthritic knee anatomy matching. All currently available systems favour mechanical axis alignment.

Table 3 and Figure 3 summarise the different pre-operative imaging modalities and types of guide employed for currently available PSI systems.

Choice of pre-operative imaging modality will be affected by availability and cost, but will ultimately be determined by accuracy. Comparison of the accuracy of 3D modeling of knee anatomy using CT and MRI was first reported by Smith *et al*[43] in 1989, who found equally high quality of reconstruction using the two techniques. Subsequent development of PSI means that the emphasis has shifted to accuracy of the reciprocal guides created. Due to the subsequent rapid-prototyping stages of manufacturing, there will result a small degree of acceptable variation between the final models and the native anatomy[23]. This

inherent variation may be a source of incremental error between imaging modalities. We were not able to account for this and thus it is a potential limitation to this study.

The non-clinical cadaveric and animal studies summarised in Table 1 show similar accuracies for both modalities. Due to the heterogeneous nature of these studies, it is impossible to perform statistical analysis on this subset of data. Hypothetically, CT would be expected as a more accurate imaging modality, due to improved imaging of osteophytes over MRI as landmarks for PSI guides. The small-sample comparison studies in Table 1 did not demonstrate this. The two direct clinical comparison undertaken by Cenni *et al*[9] and Ensini *et al*[25] also demonstrated comparable results both in terms of proportion of outliers and in post-operative alignment.

Assimilation of currently available clinical reports showed good post-operative mechanical alignment using CT-based PSI systems. Outlier incidence, although high at 19% in the study by Barrett *et al*[12] was not found to be significantly higher than conventional or computer-assisted TKA in any of the studies.

Examination of studies using MRI-based PSI systems revealed a range of post-operative results. Chareancholvanich *et al*[13] found a low outlier incidence of 2.5% with MRI-based systems. This study only performed post-operative imaging in the coronal plane, which may partially explain their lower incidence of outliers. Comparison of all studies evaluating MRI showed comparable outlier percentage, but a wider range of outlier percentages when compared to CT.

In our study we were only able to directly compare outlier incidence with CT and MRI in the coronal plane. We were unable to analyse component alignment in the sagittal or rotational axes and this is a further limitation of our study. We found the overall percentage of outliers > 3% in patients with CT-based PSI systems to be 12.5% in the current literature. For MRI-based PSI, outlier percentage was higher at 16.9%. Therefore outlier incidence appears to be slightly lower using pre-operative CT. There is also lower variability between studies in the CT group, however no statistically significant conclusions can be drawn from this analysis.

Current evidence shows comparable accuracy with both imaging modalities. Increased accuracy of pre-operative imaging could result in longer-term savings, and reduced accumulated dose of radiation by eliminating the need for post-operative imaging or revision surgery. Concern regarding radiation exposure with CT, and increased cost of MRI could both be accepted if one modality had been proven superior to the other. The lack of convincing evidence towards one imaging modality creates difficulty for the clinician. Our review has been unable to demonstrate a significant difference in accuracy between the two systems, primarily due to a lack of published evidence. As such, imaging selection will depend on surgeon preference, PSI system used, and local facilities available to the surgeon. At present there is no difference in waiting times for manufacture of the PSI components from MRI or CT-based models once the images are acquired. It is important to note that many district general hospitals will have more than one CT scanner, but usually only one MRI scanner, and these must be shared with other elective specialties as well as emergency work. This will be of logistical concern to the surgeon and may increase waiting times to PSI arthroplasty.

At present there is not enough published data to convincingly conclude in favour of CT or MRI for accuracy of pre-operative imaging in PSI. Large-number randomised controlled trials would be required to determine the ideal modality. Given the developing nature of PSI, this seems unlikely in the near future. It is our conclusion, therefore, that CT would be a more favourable option at present due to reduced scanning times, increased availability, and relatively cheaper cost.

COMMENTS

Background

Patient-specific instrumentation (PSI) was developed to improve the accuracy of component placement in total knee arthroplasty (TKA). The technique utilizes pre-operative imaging using computed tomography (CT) or magnetic resonance imaging (MRI) to create bespoke cutting or pinning guides for bony resection customized to the patients' own anatomy.

Research frontiers

The benefits and drawbacks of CT *vs* MRI for use in PSI is a source of ongoing debate. CT is widely available, relatively inexpensive, and imaging times are short when compared with MRI, yet MRI avoids radiation exposure and so is deemed a safer method of imaging. Although many studies have been undertaken to determine the ideal pre-operative imaging modality, conclusions remain speculative in the absence of long term data.

Innovations and breakthroughs

Ultimately, information regarding accuracy of CT and MRI will be the main determining factor. Increased accuracy of pre-operative imaging could result in longer-term savings, and reduced accumulated dose of radiation by eliminating the need for post-operative imaging and revision surgery.

Applications

This could improve patient satisfaction following TKA, and reduce the rate of implant failure and revision arthroplasty.

Terminology

PSI: Patient-specific instrumentation; TKA: Total knee arthroplasty; CT: Computed tomography; MRI: Magnetic resonance imaging.

Peer-review

Well researched and presented paper on a very relevant topic. Adds to the current knowledge. The statistics are well presented.

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P- Reviewer: Kamat YD **S- Editor**: Song XX
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DOI: 10.5312/wjo.v6.i2.298

World J Orthop 2015 March 18; 6(2): 298-310
ISSN 2218-5836 (online)

Bone mass in axial spondyloarthritis: A literature review

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Received: January 29, 2014
Peer-review started: February 8, 2014
First decision: April 4, 2014
Revised: August 15, 2014
Accepted: September 4, 2014
Article in press: September 10, 2014
Published online: March 18, 2015

Abstract

AIM: To review the published literature reporting bone loss in patients with axial spondyloarthritis (SpA) particularly those studies using dual X-ray absorptiometry (DXA) methods.

METHODS: This literature review examines the reported bone mass in patients with ax-SpA, particularly those using the DXA methods. The MEDLINE, Web of Science and Scopus databases were searched for relevant articles published between September 1992 and November 2013. Some of used search terms were ankylosing spondylitis (AS), SpA, spondyloarthropathy, bone loss, bone mass, osteopenia, bone mineral density, osteoporosis (OP), densitometry. Studies in which bone loss was investigated by using DXA in patients with SpA were eligible. Each article was reviewed and the key elements were noted.

RESULTS: There were 286 hits on MEDLINE, 200 on Web of Science and 476 on Scopus. After applying inclusion and exclusion criteria, we identified 55 articles in our systematic search. The sample size of the studies varied from 14 to 332 patients with SpA. The reported age range varied from 25 to 56 years in the reviewed studies. The symptom duration of patients with axSpA varied from 1.6 to 49 years. There were more males than females in these studies. Most of the recruited females were premenopausal women. Reported HLA-B27 positivity changed between 19% to 95%. The prevalence of OP and osteopenia in patients with SpA varied from 3%-47% to 5%-88%, respectively, in the included studies. In particular, the prevalence of OP and osteopenia ranged from 2.0%-47.0% and 5.0%-78.3%, respectively, in patients with AS. There are conflicting results regarding the relationship among disease activity, acute phase response and bone mass. Some studies suggest good correlation of bone mass with disease activity and acute phase reactants.

CONCLUSION: Bone loss may be determined in patients with axSpA at the lumbar spine or proximal femur even in the early phase of the disease and may be associated with inflammation (bone marrow edema) at the vertebral colon.

Key words: Bone mineral density; Dual X-ray absorptiometry; Osteoporosis; Spondyloarthritis; Ankylosing spondylitis

Core tip: Osteoporosis is a well-known problem in patients with ankylosing spondylitis and other forms of spondyloarthritis. It may begin even in the early stages of the disease and inevitably causes vertebral fractures.

Bone loss can be prevented with tumor necrosis factor blocking therapy by reducing inflammation at skeletal sites. Dual X-ray absorptiometry (DXA) is the preferred method to assess bone mass in the early stages of the disease or in patients without aberrant ossification of the spine. In advanced cases DXA measurements with lateral spinal projections or quantitative computed tomography may be referred.

Kilic E, Ozgocmen S. Bone mass in axial spondyloarthritis: A literature review. *World J Orthop* 2015; 6(2): 298-310 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/298.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.298

INTRODUCTION

Spondyloarthritis (SpA) is a chronic inflammatory disease characterized by predominant involvement of the spine and/or sacroiliac joints. It consists of ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated type[1]. Axial (SpA) comprises a heterogeneous group of diseases which predominantly involve the axial skeleton and have many overlapping clinical features. The axial SpA spectrum ranges from non-radiographic axial SpA (nr-axSpA) at one end to AS at the other. Nr-axSpA comprises SpA patients without definite sacroiliitis on pelvic X-ray[2]. The most important clinical and laboratory features of this group are inflammatory back pain, enthesitis, dactylitis, extra-articular manifestations (acute anterior uveitis, psoriasis and inflammatory bowel disease) and association with HLA-B27.

Low bone mass [osteopenia or osteoporosis (OP)] and osteoporotic vertebral fractures are well known complications of SpA, especially in AS[3]. The pathogenesis and onset of OP in SpA is not clear. The prevalence of low bone mineral density (BMD) has been reported to be as high as 47% at the hip and lumbar spine even in patients with early SpA[4]. Patients with SpA may have increased risk of bone loss as a result of high disease activity, pro-inflammatory cytokines, mechanical factors (*i.e.*, rigidity of the spine, vertebral deformities) and decrease in physical activity or mineralization defects due to subclinical gut involvement[5,6].

Several techniques have been used to measure bone mineral density in SpA including quantitative ultrasound (QUS), quantitative computed tomography (QCT), high-resolution peripheral QCT (HRpQCT), single-photon absorptiometry, dual photon absorptiometry, dual-energy X-ray absorptiometry (DXA), and morphometric X-ray absorptiometry[7-11]. Among these techniques DXA can be considered as an accurate, repeatable and quantitative method to assess BMD at the spine and hip[12]. Several studies have indicated that DXA may be a misleading method to assess BMD in advanced AS. New bone formation and aberrant hyperostosis inevitably cause a pseudo increase in bone density. However the most appropriate and valid method to assess BMD in patients with advanced AS is still unclear. A systematic evaluation of DXA methods used to assess BMD in SpA is strongly needed. Therefore this comprehensive review will examine the published literature assessing bone density in patients with axial SpA particularly those studies using DXA as the measurement method.

MATERIALS AND METHODS

The MEDLINE, Web of Science and Scopus databases were searched for relevant articles published between September 1992 and November 2013. The following search terms (synonyms and combinations) were used: "ankylosing spondylitis" OR "spondyloarthritis" OR "spondyloarthropathy" AND "bone loss" OR "bone mass" OR "osteopenia" OR "bmd" OR "bone mineral density" OR "osteoporosis" OR "fracture" AND "mri" OR "ct" OR "resonance" OR "computed tomography" OR "densitometry" OR "dxa" OR "dexa". The references of the reviewed articles were manually scanned for other relevant studies. Studies in which bone loss was investigated by using DXA in patients with SpA were eligible. The selection criteria consisted of original articles involving humans and published in English. Articles were excluded if they were case reports, review articles or meta-analyses and did not measure bone density by using DXA. Each article was reviewed and the key elements are summarized in Tables 1-3.

RESULTS

Figure 1 shows the flow chart and the selection process. There were 286 hits on MEDLINE, 200 on Web of Science and 476 on Scopus. Using the above-mentioned inclusion and exclusion criteria, we identified 55 articles (Cross sectional studies: 41, follow-up studies: 6 and interventional studies: 8) in our systematic search.

Population of the studies

Fifty five articles are summarized in Tables 1-3. The sample size of the studies varied from 14 to 332 patients with SpA including AS, ReA, PsA, undifferentiated SpA and nr-axSpA. The reported age range varied from 25 to 56 years in the reviewed studies. The reported symptom duration of patients with axSpA ranged between 1.6 to 49 years. As expected, there were more males than females in these studies. Most of the recruited females were premenopausal women. Reported HLA-B27 positivity changed between 19% to 95% and vertebral fractures were reported with a prevalence of up to 39% in the reviewed studies. The prevalence of OP and osteopenia in patients with SpA varied from 3%-47%

Table 1 Summary of the cross sectional studies

Ref.	Sample size (M/F)	Mean age (yr)	Menopausal status pre:post	Disease duration (yr)	DXA machine	Dexa site (coefficient variation %, if available)	Outcome	Conclusion
Devogelaer *et al*[19]	AS: 70 (60/10)	39	10:0	15.4	Novo	SPA: non dominant radius DXA: L2-4 QCT: 10 patients LS	DXA values at LS was decreased in the male VF: 2.9%	In patients with severe AS, DXA demonstrates normal values due to new bone formation
Donnelly *et al*[42]	SpA: 87 (62/25) AS: 82.5% PsA: 8%	M: 43.5 F: 44.8	NM	M: 16.3 F: 16.6	Hologic	L1-4 (0.7), FN (1.5), whole body	AS: in early disease LS-BMD decreased, in advanced AS increased Lumbar Spine density lower in M than F VF 10.3%	DXA is doubtful to truly reflect the state of demineralization in the spine and more emphasis should be placed on measures on FN-BMD
Mullaji *et al*[43]	AS: 33 (27/6): Mild: 22 (16/6) Adv: 11 (11/0)	32.3	0:6	M: Mild: 8.7 Adv: 11.7 F: Mild: 6.8	Norland	Whole body	LS BMD lower in mild and higher in advanced AS than C In Adv. AS, LS BMD higher than mild AS and C HLA-B27: 100% LS, FN and leg BMD decreased in mild AS compared with C in men	The relation between BMD and severity of disease in the axial skeleton may help to explain the etiology and pathogenesis of the spinal deformities and complications of this disabling condition
Singh *et al*[44]	AS: 14 (14/0)	50	NA	NM	Hologic	AP L1-4, non dominant hip	FT BMD lower than LS Osteopenia at FN: 64%, LS: 36%	Femoral measurements of BMD are superior to lumbar measurements in the detection of osteopenia in patients with AS
Acebes *et al*[51]	AS: 18 (16/2)	44.7	NM	10.3	Hologic	L2-4, FN	M: OP 0% osteopenia: 53.8% F: OP and Osteopenia 0% HLA-B27: 100%	Osteopenia in AS occurs as a result of high resorption of bone with normal formation
Meirelles *et al*[50]	AS: 30 (27/3)	37	3:0	17	Hologic	L1-4, PF	LS openia: 23% OP: 27% FT: openia: 55% OP: 31% AS has lower BMD at LS and proximal femur than C	Bone mass loss in AS is better evaluated in the proximal femur, because of almost free of artifacts
Juanola *et al*[52]	AS: 18 (0/18)	36.7	18:0	15.1	Hologic	L2-4 (0.5), FN (1)	HLA-B27: 94.4% OP: 5.6%, Osteopenia: 11.1% VF: 5.6%	Slight reduction in BMD in premenopausal women with early AS, but the difference was not statistically significant
Mitra *et al*[3]	AS: 66 (66/0)	37.8	NA	9.9	Hologic	L1-4 (1.4), FN (2.9)	In patients with AS, BMD and T scores were reduced in both LS and FN VF: 16.7% in AS, 2.6% in C	AS patients with mild disease had higher risk of VF compared with the normal population and this increased with the duration of disease
Borman *et al*[53]	AS: 32 (32/0)	39.1	NA	14.8	Hologic	Lat L1-4 (2.7)	L1-4 T score and BMD similar among AS and C BMD was similar among active and inactive AS VF: 31.2% Osteopenia: 34.3% in AS, 21.8% in C OP: 34.3% in AS, 6.2% in C	The incidence of osteoporosis is high in AS and patients with active disease are have risk for developing osteoporosis
Dos Santos *et al*[54]	AS: 39 (39/0)	37.6	NA	8.4	Hologic	Whole body	HLA-B27 79.5% AS had bone loss at spine compared with control group 46% of patients with AS had Z score < –1.5 SD	AS is associated with bone loss, mainly concerning the lumbar spine, in patients whose disease is biologically most active
Toussirot *et al*[13]	AS: 71 (49/22)	39.1	22:0	10.6	Lunar	L2-4 (1), left FN (1.5)	HLA-B27: 84.5 AS: Lumbar osteopenia: 32.4%, OP: 14.1% higher than C Femur: osteopenia: 22.5%, OP: 14.1% higher than C Good correlation between lumbar, femur, total BMD with QUS	AS has decreased lumbar, hip and total body BMD but soft tissue composition was not involved in disease process

Grisar *et al*[55]	AS: 30 (22/8) PsA: 23 (17/6) ReA: 10 (5/5)	AS: 44.2 PsA: 45.2 ReA: 47.8	NM	AS: 9.2 PsA: 10.4 ReA: 1.3	Hologic	LS and non dominant hip	AS; OP 47%	
Speden *et al*[7]	AS: 66 (0/66)	43.4	50:16	21.1	Hologic	PA L1-4 (1), non-dominant hip (1.8) and Whole body (0.82)	Hip and whole body BMD reduced in AS Femoral neck OP: 6%, osteopenia: 52% in AS and higher than control Lumbar OP: 8%, osteopenia: 18% in AS	Women with AS have lower hip BMD without correlation with disease duration suggesting that low BMD is an early feature of disease
Capaci *et al*[56]	AS: 73 (49/24)	37.3	NM	11.8	Hologic	L1-4, FT	L BMD similar in mild and advanced AS, F BMD lower in advanced AS In advanced AS osteopenia or OP higher in the total hip than mild AS VF: 5.5% LS Osteopenia or OP: 68.4%-54.3% PF osteopenia or OP: 51.9-91.7 (mild-advanced)	Syndesmophytes and ligament calcification may mask bone loss in LS therefore hip BMD more convenient to asses OP in AS
Jansen *et al*[14]	AS: 50 (35/15)	52	NM	21	Hologic or Lunar	AP LS, FN	HLA-B27: 88% VF LS: 6% LS openia: 54% OP: 15% FN openia: 72% OP: 20% and 70% of them correctly diagnosed with QUS	The performance of QUS is similar to DEXA in finding patients with osteoporosis-associated fractures Both osteoporosis and fractures are common sequel in AS
Obermayer-Pietsch *et al*[16]	AS: 104 (71/33)	41	33:0	15	Hologic or Lunar	LS (2.2-0.9), PF (2-1.6) QCT (1)	HLA-B27: 19%-93% OP: 25% In male AS patients FokI genotypes were independent predictors of low BMD	Vitamin D receptor gene may be involved in BMD differences, bone metabolism and inflammatory processes in ankylosing spondylitis
Baek *et al*[47]	AS: 76 (76/0) mild AS: 59.2% severe AS: 40.8%	28.1	NA	9.4	Lunar	L2-4, PF	BMD and T score at FN and FT lower in severe AS than mild AS but not at LS Osteopenia: 48% in mild AS (more frequently at LS than proximal Femur) and 31% in severe AS	Osteopenia is frequently observed in both severe and mild AS with little mobility limitation Both BMD in severe disease are lower than in mild disease at the FT but not in the lumbar spine, probably due in part to progressing paravertebral calcification during the course of AS
Gilgil *et al*[48]	AS: 20 (20/0)	25-63	NA	16.7	Norland	PA L2-4 (1), lat L3 (2.7), left FN (1.2)	PA L2-4 BMD similar between groups but lateral L3 and FN BMD reduced in AS No VF Syndesmophytes: 60% PA LS OP: 20% in AS, 15% in C	Lateral L3 DXA is superior to PA DXA in detecting a decrease in BMD in patients with AS
Karberg *et al*[20]	AS: 103 (66/37) Ⅰ: < 5 yr (n:27) Ⅱ: 5-10 yr (48) Ⅲ: > 10 yr (28)	Ⅰ: 34.2 Ⅱ: 38.1 Ⅲ: 49.1	NM	Ⅰ: 2.5 Ⅱ: 7.0 Ⅲ: 19.7	Hologic	L1-4, FN, radius	HLA-B27: 92.2% Disease duration < 5 yr OP: 11%, 15% (hip, spine) > 10 yr OP: 29%, 4% (hip, spine) DEXA: OP: 24%, 14% and osteopenia: 52%, 31% (hip, spine) DEQCT OP: 11% and openia: 44% (L) pQCT OP: 1% openia: 16% (radius)	Patients with AS already have reduced BMD at the lumbar spine and the femoral neck early in the disease process. In later stage, OP ratio at hip increased but at LS did not increase
Lange *et al*[8]	AS: 84 (53/31) Ⅰ: (10/17) Ⅱ: (12/10) Ⅲ: (12/3) Ⅳ: (19/1)	Ⅰ: 32 Ⅱ: 47 Ⅲ: 45 Ⅳ: 56	NM	Ⅰ: 9 Ⅱ: 20 Ⅲ: 21 Ⅳ: 32	Lunar	LS (0.9-1), total hip (1.6)	A high decrease in axial bone density could be verified in both initial and advanced stages of the disease (SE-QCT is better) DXA: osteopenia in 5% and OP in 9.2% SE-QCT: osteopenia in 11.8% and osteoporosis in 30.3% HLA-B27: 81.5%-95% VF: 10.7%	In stages of advanced ankylosis in the vertebral region, priority should be given to SE-QCT to detect bone loss, due to the selective measurement of trabecular and cortical bone

Incel *et al*[45]	AS: 53 (46/7)	39.5	7:0	10.6	Lunar	L2-4, FN	AS patients have lower BMD in LS and FN in both inactive and especially active patients. Osteopenia is 78.3% in early AS Osteopenia or OP is 63.3% in advanced AS	Severe disease and concomitant urolithiasis may increase bone loss and fracture risk especially at the femur neck
Jun *et al*[28]	AS: 68 (68/0)	30.7	NA	7.2	Hologic	PA L2-4, left Prox Femur	BMD of LS and FN significantly lower than C VF correlated with BMD femur. VF: 16.2%	Measurement of femur BMD may provide useful information to predict the risk of vertebral fractures in patients with AS
Kim *et al*[24]	AS: 60 (51/9)	31.2	NM	5.5	Hologic	AP L1-4 (1), right FN (1.2)	HLA-B27 83% OP: LS 19%, FN 33% Osteopenia: LS 37%, FN 41% The patients with AS presented reduced BMD and T score at spine	About 74% of AS patients have reduced BMD The imbalance between RANKL and OPG might be involved in the pathogenesis and clinical courses of osteoporosis in AS
Sarikaya *et al*[57]	AS: 26 (21/5)	44.3	5:0	NM	Hologic	Non dominant hip (1), forearm (1)	Hip BMD values are lower in AS whereas radius BMD values are similar between 2 group Hip Osteopenia or OP: 76.9%	OP at hip region may be due to localized effects of inflammatory activity or immobility rather than a systemic effect
Altindag *et al*[58]	AS: 62 (36/26)	33.4	NM	5.7	Hologic	AP L2-4, left FN	Lumbar and femoral neck BMD scores are significantly lower in AS OP: 32% osteopenia: 17.7%	Lumbar BMD scores negatively correlated with the length of disease duration in AS patients
Stupphann *et al*[15]	AS: 21 (10/11)	51	NM	25.4	Lunar	L1-4, total hip	TH: Osteopenia or OP 45% by DXA LS: Osteopenia or OP 48% by QCT QCT and DXA at proximal femur show a significant correlation but not at LS	Activated CD4+ and CD8+ T cells contribute to the production of RANKL in the inflammatory bone-resorption
Ghozlani *et al*[23]	AS: 80 (67/13)	38.9	13:0	10.8	Lunar	AP L1-4, proximal F	OP: 25% VF: 18.8% OP is common in patients with AS and seems to be related to disease activity	Measuring BMD in early disease should include DXA in the spine and hip. In advanced disease, BMD evaluation should rely on hip DXA
Mermerci Başkan *et al*[25]	AS: 100 (75/25)	39.9	25:0	10.5	Hologic	AP L1-4 and Lat L2-3, FN	Thoracic VF: 16% Lumbar VF: 3% OP: 32% Acute phase reactant levels of the AS patients with OP are higher than the patients without OP	Vitamin D deficiency in AS may indirectly lead to osteoporosis by causing an increase in the inflammatory activity
Arends *et al*[22]	AS: 128 (93/35)	41		14	Hologic	AP L1-4, PF	BMD of the lumbar spine, measured by DXA, may be overestimated due to osteoproliferation in patients with advanced AS HLA-B27: 84% VF: 39% Osteopenia or OP: 57%	Bone turnover, inflammation, and low vitamin D levels are important in the pathophysiology of AS-related osteoporosis
Korczowska *et al*[59]	AS: 66 (66/0)	AS: 51.6	NA	17.4	DTX-200 or ECLIPSE	Forearm and hip	Forearm: Osteopenia: 54% and OP: 14% Hip: Osteopenia: 51% and OP: 5%	Accelerated loss of bone tissue is observed in patients with AS
Vasdev *et al*[29]	AS: 80 (80/0) C: 160 (160/0)	32.9		8.1	Hologic	LS (1), hip (1)	In active and inactive patients, BMD is similar OP: 28.8% at LS and 11.5% at FN VF: 1.25% HLA-B27: 86%	OP is a significant complication in AS even in early disease, and more prevalent in the spine compared to femur Spinal BMD is the most sensitive site for defining OP in AS
van der Weijden *et al*[4]	SpA: 130 (86/44) AS: 72% uSpA: 12% PsA: 8%; ReA: 4%	38	42:2	6.3	Lunar	L2-4, left PF	Osteopenia: 38%, OP: 9% HLA-B27: 74% No differences between group for distribution of the osteopenia and OP at hip or LS BMD	A high frequency of low BMD is found in patients with early SpA and it is associated with male gender and decreased functional capacity

Grazio *et al*[26]	AS: 80 (46/34)	52.3	NM	21.8	Hologic	L2-4, left PF	HLA-B27 86% at LS: OP: 25% and osteopenia: 20% at FN OP: 22.5 and osteopenia: 47.4% More patients with osteopenia at the lumbar spine had lower BASDAI score	Hip BMD seems to be more associated with disease activity and functional ability than BMD at the lumbar spine
Klingberg *et al*[27]	AS: 204 (117/87)	50	42:45	24	Hologic	AP L1-4 (0.4), lateral L2-4 (0.6), left hip, non-dominant radius	HLA-B27: 87% ⩾ 50 yr osteopenia: 43.6 and OP: 20.8% < 50 yr low BMD 4.9% BMD at lateral LS was lower than AP and revealed more OP	OP and osteopenia is common in AS and associated with high disease burden. Lateral and volumetric lumbar DXA are more sensitive than AP DXA in detecting OP
Klingberg *et al*[60]	204 (117/87)	50	42:45	24	Hologic	AP L1-4, Lat L2-4, non dominant PF and forearm	BMD was significantly lower in the patients with VF HLA-B27: 87% VF: 11.8%	BMD in the femoral neck, total hip, and estimated vertebral BMD show the strongest association with VF
Taylan *et al*[61]	AS: 55 (48/7)	AS: 36		10	Hologic	PA L2-4, Left femur	BMD at proximal femur is lower but at lumbar spine was similar HLA-B27: 64.9%	
van der Weijden *et al*[62]	SpA: 113 (75/38) AS: 71%	37	38:0	5.7	Lunar	L2-4, left PF	In patients with VF, BMD at LS is lower than patients without VF HLA-B27: 75% VF: 15%	The VFs are associated with low BMD of the lumbar spine and with axial PsA
Akgöl *et al*[30]	nr-axSpA: 46 (32/14)	31.4	14:0	< 3	Hologic	LS (1), PF (3)	Patients with nr-axSpA have significant bone loss at the lumbar spine compared with patients with mLBP Comparison of BMD in the nr-axSpA subgroups reveal that patients with inflammation had lower BMD at the LS and PF HLA-B27: 60.8%; no VF	Inflammation on MRI is closely associated with low bone mass in patients who are in the very early stage of the disease
Briot *et al*[21]	SpA: 332 (174/158)	33.8	151:7	1.6	Hologic or Lunar	L1-4, FN, FT	Low BMD associated with presence of inflammatory lesions on MRI, ESR or CRP HLA-B27 62.1% Low BMD: 13% (M: 88%)	Patients with early SpA had 13.0% low BMD and the main risk factor associated with low BMD was inflammation on MRI
Klingberg *et al*[9]	AS: 69 (69/0)	49	NA	23	Hologic	AP L1-4, lat L2-4, non dominant forearm and hip HRpQCT: radius (0.3-3.9) and tibia (0.1-1.6) QCT: L1-4	The AS patients have lower vBMD in peripheral bone Syndesmophytes are significantly associated with decreasing trabecular vBMD in lumbar spine Estimated lumbar vBMD by DXA correlate with trabecular vBMD measured by QCT HLA-B27 94%	Male patients with AS have axial osteopenia. New bone formation cause false normal BMD at LS by DXA
Ulu *et al*[46]	AS: 86 (69/17)	AS: 34.5	NM	11.7	Hologic	PA L1-4, lat L2-4, femur	HLA-B27: 66.3% Syndesmophytes: 37.2% VF: 28% PA spine BMD similar with C Lateral spine, hip BMD lower in AS PA BMD higher in late stage AS than early stage FN, FT BMD lat spine BMD similar in two stage	Bone loss increase in AS The BMD measurement at the lateral lumbar spine reflects bone loss and fracture risk better than PA spine and femoral measurements

BMD: Bone mineral density; C: Control; DEQCT: Dual-energy quantitative computed tomography; DXA: Dual energy X-ray absorptiometry; F: Female; FN: Femur neck; FT: Femur total; HRpQCT: High-resolution peripheral quantitative computed tomography; M: Male; mLBP: Mechanic low back pain; NA: Not applicable; NM: Not mentioned; OP: Osteoporosis; PA: Posteroanterior; PF: Proximal femur; pQCT: Peripheral quantitative computed tomography; SE-QCT: Single energy quantitative computed tomography; vBMD: Volumetric BMD; VF: Vertebra fracture; LS: Lumbar spine.

Table 2 Summary of the follow-up studies

Ref.	Sample size (M/F)	Mean age (yr)	Menopausal status (pre:post)	Disease duration (yr)	Dexa machine	Dexa site (coefficient variation %)	Follow-up (mo)	Outcome	Conclusion
Lee *et al*[17]	AS: 14 (14/0) 7 early AS 7 advanced AS	33.3 54.6	NA	5.4 27	Hologic	LS (1), FN (1)	15	Baseline LS BMD measured by QCT decrease in both early (also by DXA) and advanced diseases and do not change significantly over 15 mo HLA-B27 92.9%	AP LS DXA in late AS is less useful than QCT in determining the degree of osteopenia in late AS
Gratacós *et al*[6]	AS: 34 (27/7) Active 14 (12/2) Inactive 20 (15/5)	Active: 33 Inactive: 31	7:0	7.5 5.3	Lunar	LS (0.8), FN (2.3)	19	At the end of the follow-up period, patients with active AS show a significant reduction in bone mass in the LS (5%) and FN (3%)	Loss of bone mass only in patients with persistent active AS suggests that inflammatory activity plays a major role in the pathophysiology of the early bone loss
Maillefert *et al*[32]	AS: 54 (35/19)	37.3	16:3	12.4	Hologic	PA L2-4 (2.8), left FN (4)	24	After 2 yr, BMD did not change at the LS and decreased at the FN The change in BMD at FN was related to persistent systemic inflammation HLA-B27 88.9% VF: 3.7% after 24 mo	Persistent inflammation may be an etiologic factor of bone loss in AS
Kaya *et al*[31]	AS: 55 (42/13) Active: 22 Inactive: 33	35.8	13:0	11.1	Lunar	AP L2-4 (2.1), PF (2.3)	24	Active AS have lower BMD at PF than inactive ones but LS BMD was similar 0.9% decrease in BMD at FN and increase at LS after follow-up, this change not different in active and inactive AS Active AS OP: PF: 22.7%, LS: 27.3% Osteopenia: PF: 40.9%, LS: 31.8 inactive AS OP; PF: 3%, LS: 21,2% Osteopenia; PF 45.5%, LS: 33.3%	PF measurements seem to be less affected from disease-related new bone formation
Haugeberg *et al*[33]	SpA: 30 (15/15)	31.1	15:0	6	Lunar	AP L2-4 (2.3), both hip (2.8) and hand (1.1)	12	No significant reduction in BMD at hip, spine and hand is seen after 12 mo follow-up Bone loss at PF is found to be associated with raised baseline CRP levels, baseline BMO of the SIJs on MRI HLA-B27 56.7	Bone loss in patients with SpA is a result of systemic inflammation and starts early in the disease process
Korkosz *et al*[18]	AS: 19 (19/0)	45.6	NA	16.5	Lunar	L2-4 (1.6-2.2), left hip QCT: L1-5	120	During the follow-up VF: 15.8% In spine, trabecular BMC decrease by QCT whereas BMD increase by DXA	In AS patients, spinal trabecular bone density evaluated by QCT decrease over 10-yr follow-up and it is not related to baseline radiological severity of spinal involvement

AP: Anteroposterior; AS: Ankylosing spondylitis; BMC: Bone mineral content; BMD: Bone mineral density; BMO: Bone marrow edema; DXA: Dual energy X-ray absorptiometry; F: Female; FN: Femur neck; HLA: Human leukocyte antigen; LS: Lumbar spine; M: Male; MRI: Magnetic resonance imaging; NA: Not applicable; NM: Not mentioned; OP: Osteoporosis; PA: Posteroanterior; PF: Proximal femur; QCT: Quantitative computed tomography; SIJs: Sacroiliac joints; VF: Vertebra fracture.

Table 3 Summary of the interventional studies

Ref.	Sample size (M/F)	Mean age	Menopausal status pre:post	Disease duration (yr)	Dexa machine	Dexa site (coefficient variation %)	Follow-up duration	Outcome	Conclusion
Allali *et al*[39]	SpA: 29 (23/6)	35	6:1	13	Hologic	AP L2-4, left PF	6	A significant increase in BMD at the LS, total hip and trochanter is observed in patients with SpA treated with anti-TNF	Benefit of anti-TNFα therapy on BMD in patients with SpA may be through an uncoupling effect on bone cells
Briot *et al*[37]	SpA: 19 (17/2)	40	NM	16.5	Hologic	L2-4, left FT	12	After 1 yr of treatment BMD increase at the spine and femur total	Treatment with anti-TNFα in SpA is associated with an increase of BMD, which results from a decrease of bone resorption
Biriot *et al*[41]	SpA: 106 (80/26) AS: 87.8% PsA: 6.6%	38	NM	16.5	Hologic	L2-4, left PF	24	At 1 and 2 yr of treatment, there is a significant gain in BMD at both lumbar spine and PF HLA-B27: 89% Baseline: OP: 28%, osteopenia: 23%	This 2-yr prospective study show a significant increase in BMD, in patients with SpA receiving anti-TNFα treatment
Visvanathan *et al*[40]	AS: 279 (225/54)	40.3	NM	11.9	NM	L1-4, PF	24	BMD at the spine and hip increase after anti-TNF therapy compared with placebo HLA-B27: 86.7%	Infliximab have positive effect on BMD over 2 yr
Kang *et al*[34]	AS: 90 (72/18)	29.9 (onset age)	18:0	8.2	Lunar	AP L1-4, right PF	36	The most increase in BMD is observed at the spine and hip in the group treated with concurrent bisphosphonate and anti-TNF HLA-B27: 97% OP: 36.7%	BMD increases more with the combination treatment (bisphosphonate and anti-TNF) and gain of bone mass is associated with the decrease in inflammation
Arends *et al*[35]	AS: 111 (78/33)	42.2	NM	16	Hologic	AP L1-4, PF	36	LS and hip BMD significiantly increase compared to baseline after anti-TNFα theraphy HLA-B27: 81% LS OP: 9%, openia: 34% TF OP: 2%, openia: 37%	Three years of anti-TNF therapy results increase in bone formation in accordance with the continuous improvement in lumbar spinal BMD
Dischereit *et al*[38]	RA: 18 (3/15) AS: 16 (9/7)	RA: 62 AS: 48	NM	-	Lunar	AP L2-4 (1.5), FN (2)	24	At baseline in AS, osteopenia: 50% and OP: 6.3% A stable peripheral BMD, significant increases in axial BMD, could be observed after 24 mo of anti-TNFα therapy compared with baseline	Anti-TNF therapy has favorable effects over osteoprotective pathways in patients with AS and RA
Kang *et al*[36]	AS: 63 (52/11)	36.8	11:2	8.6	Prodigy	L1-4, right PF	24	BMD at LS and FT of patients receiving anti-TNF increase regularly over 2 yr TNF blocking therapy and the increase in SASSS are independently associated with increased BMD at lumbar spine HLA-B27: 87%	TNF inhibitors appear to be associated with increased SASSS scores and improvements in BMD

BMD: Bone mineral density; F: Female; M: Male; FN: Femur neck; FT: Femur total; NM: Not mentioned; PF: Proximal femur; TNF: Tumor necrosing factor; SpA: Spondyloarthritis; AS: Ankylosing spondylitis; SASSS: Stoke Ankylosing spondylitis spine score; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; TF: Total femur; OP: Osteoporosis; HLA: Human leukocyte antigen; LS: Lumbar spine.

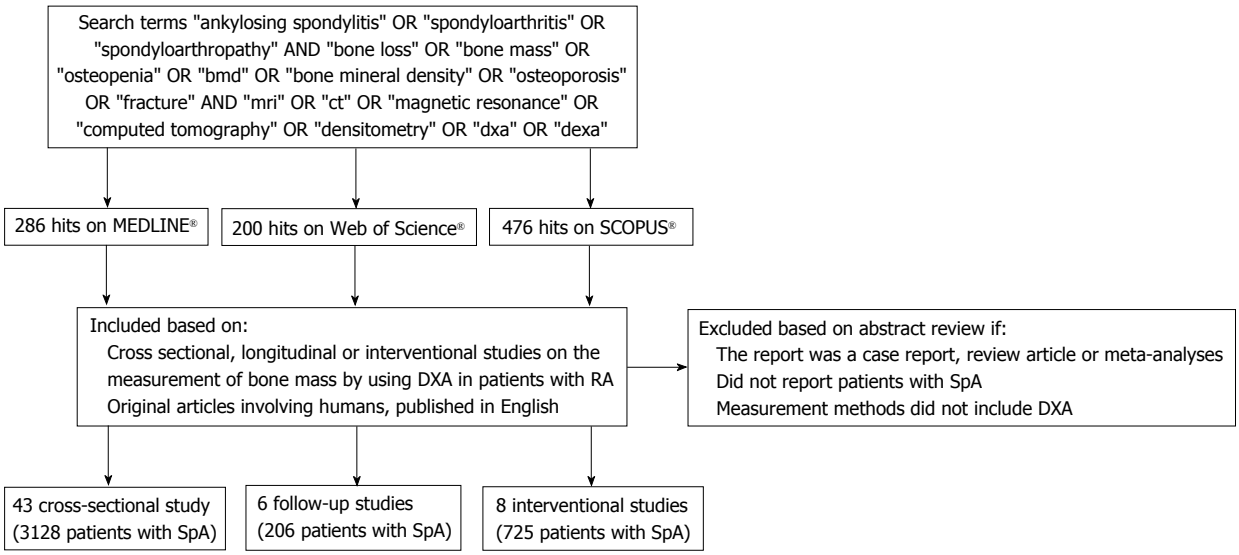

Figure 1 Flow chart. SpA: Spondyloarthritis; DXA: Dual X-ray absorptiometry.

to 5%-88%, respectively, in the included studies. In particular, the prevalence of OP and osteopenia ranged from 2.0%-47.0% and 5.0%-78.3%, respectively, in patients with AS.

Techniques used to detect BMD

We included studies which used DXA as the technique of BMD assessment in patients with axSpA. Eleven of the 55 studies were comparative studies in which DXA techniques were compared with QUS[7,13,14], single energy QCT[8], QCT[9,15-19], dual-energy QCT[20], peripheral QCT[20] and HRpQCT[9].

Regarding the comparative studies, one study demonstrated that QUS correlated with DXA[13] but this result was not confirmed in any other study[7]. On the other hand, Jansen *et al*[14] demonstrated similar performance with QUS compared to DXA in detecting OP-associated fracture risk.

Numerous QCT studies demonstrated higher prevalence of OP compared to those studies which used DXA as the assessment tool[8,9,18], whereas only one study revealed no difference between QCT and DXA[20]. Two studies revealed a good correlation between QCT and DXA[9,15], however lumbar spine DXA was shown to be less useful than QCT to detect the degree of osteopenia in late stage AS[15,17].

The change in bone formation and resorption markers including bone alkaline phosphatase (bALP), osteocalcin (OC), C-terminal cross-linking telopeptide of type I collagen (CTX), and deoxypyridinoline is presented in Table 4. There are conflicting results regarding the levels of bone formation and resorption markers in patients with AS and other forms of SpA.

Relationship between BMD, disease activity and acute phase reactants

There are conflicting results regarding the relationship between disease activity, acute phase response markers and bone mass. Some studies suggested a good correlation between bone mass with disease activity[16,21-26] and acute phase reactants[4,16,21,23-28], whereas others[7,13,20,29] did not report a significant relationship.

A recent study revealed the close association between bone mineral density and magnetic resonance (MR) defined acute inflammatory changes in the lumbar spine[30]. The results of this study, as well as the results obtained in patients with early inflammatory back pain, clearly defined the inflammation induced bone loss in patients with axial SpA[21,30].

Changes in bone mass and longitudinal studies

Patients with active disease (BASDAI > 4) had significantly lower proximal femur BMD compared to patients with inactive disease, whereas spinal BMD was similar in the study by Kaya *et al*[31]. After 24-mo of follow-up lumbar spinal BMD increased in both groups; however hip BMD decreased in the inactive group[31]. On the other hand, Gratacós *et al*[6] reported that BMD at the lumbar spine and at the femoral neck decreased in patients with active disease but no change was observed in patients with inactive disease after 19 mo of follow-up. There are conflicting results in follow-up studies. For examples, Maillefert *et al*[32] reported unchanged lumbar BMD but decreased femoral neck after 12 mo of follow-up, whereas Haugeberg *et al*[33] failed to demonstrate significant reduction in hip, spine or hand BMD.

C-reactive proteine (CRP) levels have been suggested as an independent predictor of BMD change in patients with AS[6]. Additionally, femoral neck BMD has been found to be associated with persistent systemic inflammation which was defined by elevated erythrocyte sedimentation rate (ESR)[32]. On the

Table 4 Variation of the bone formation and resorption markers

Ref.	Bone formation markers		Bone resorption markers	
	bALP	OC	CTX	DPD
Borman *et al*[53]		Increased		
Grisar *et al*[55]	Increased	Increased	Increased	Increased
Speden *et al*[7]	Decreased	Decreased		Increased
Sarikaya *et al*[57]		Decreased		Increased
Lee *et al*[17]		Normal		Normal
Altindag *et al*[58]	Increased	Decreased	Increased	
Mermerci Başkan *et al*[25]	Normal			
Acebes *et al*[51]			Normal	Increased

bALP: Bone alkaline phosphatase; OC: Osteocalcin; CTX: C-terminal cross-linking telopeptide of type Ⅰ collagen; DPD: Deoxypyridinoline.

other hand, another study failed to show significant interactions among spinal or hip BMD measurements and age, body mass index, disease duration, lumbar Schober, BASDAI, ESR or CRP[31].

Although bath ankylosing spondylitis functional index had a significant negative effect on hip BMD[31]. An 8 year follow-up study revealed that hip bone loss was associated with raised baseline CRP levels, MR defined bone marrow edema of the SIJs and the presence of radiographic sacroiliitis[33].

Change in bone mass after anti-tumor necrosis factor therapy

In all interventional studies BMD at the lumbar spine[34-41] increased in patients treated with anti-tumor necrosis factor (TNF) therapy. Additionally, hip BMD also increased[34-37,39-41] except for one study in which hip BMD remained unchanged[38].

Baseline bALP, OC and CTX levels significantly correlated with the increase in spinal BMD at weeks 24 and 102 after anti-TNF therapy[40]. Changes in acute phase reactants as well as disease activity scores have been demonstrated to correlate with the changes in BMD measurements[36,39,41]. Spinal BMD changes were shown to be associated with changes in ESR and newly formed syndesmophytes under anti-TNF therapy[36].

DISCUSSION

OP is a well-known problem in patients with AS which begins in the early stages of the disease and inevitably causes vertebral fractures[42-44]. The reported prevalence of OP in AS varies from 3% to 47% according to the measurement techniques and patient selection criteria used. Osteopenia has been reported in up to 88% of patients with SpA. An increased prevalence of spinal bone loss may occur even in early and mild forms of SpA[8,42-46].

Systemic inflammation may play a critical role in the pathogenesis of OP in patients with systemic inflammatory disorders including SpA. This notion is supported with data from studies revealing reduced spinal BMD in patients with early or mild disease without advanced structural damage at the spine[20,21,30,43,47]. In advanced cases, spinal ossifications may mislead normal or artificially increased BMD at the lumbar spine. In such cases DXA measurements of the spine with lateral projections have been suggested to improve sensitivity[27,48]. On the other hand, the precision of DXA measurements on the lateral spine is reasonably lower than on the AP spine or proximal femur[27,48].

As an alternative method QCT, which selectively measures trabecular and cortical bone density, can be used to determine spinal BMD in cases with advanced structural changes[8,9,19,20].

Dual-energy X-ray absorptiometry is known as the reference method to measure BMD. It is an accurate, reproducible, and non-invasive method with good short or long-term precision. Multiple skeletal sites can be safely and precisely assessed by DXA[49]. Direct radiography is still a valid method for assessing structural damage in patients with axial SpA; however it gives little information about bone density since demineralization needs to reach 50% in order to confirm a reliable bone loss on radiographs. Higher incidence of bone loss at the hip compared to the lumbar spine has been suggested in various studies conducted in patients with AS[7,14,15,20,24,44,46-48,50].

There are inconclusive results regarding the association between DXA measurements with clinical and laboratory findings. Bone mineral density at the lumbar spine and hip has been shown to correlate with BASDAI[16,24-26], ESR[16,24-26,28] and CRP[16,24-26,28]. However conflicting results have also been reported[7,13,20,29].

The follow-up studies included in this review revealed that BMD measurements at the proximal hip usually decreased but lumbar spinal measurements increased or were unchanged after a reasonable follow-up.

Regarding the interventional studies, we identified 8 studies which assessed the influence of TNF blocking therapy on BMD in patients with SpA. In 7 out of 8 studies, BMD at the lumbar spine and proximal hip increased after treatment with anti-TNF drugs[34-37,39-41]. The positive effects of these potent anti-inflammatory treatments (TNF blockers) on BMD indirectly support the role of systemic or local inflammation in bone metabolism.

In patients with SpA, bone loss starts in the early stages of the disease and can be prevented with TNF blocking treatments that have been shown to reduce inflammation at the skeletal sites. DXA is the most suitable technique to determine bone mass at both the lumbar spine and proximal femur in early or non-advanced cases. However it may cause misleading results particularly at the AP lumbar spine due to the aberrant ossification or degenerative changes. Despite its limitations, DXA measurements with lateral spinal projections or QCT may be a solution to

this problem in patients with advanced disease.

COMMENTS

Background

Spondyloarthritis (SpA) is a chronic inflammatory disease characterized by predominant involvement of the spine and/or sacroiliac joints. Low bone mass [osteopenia or osteoporosis (OP)] and osteoporotic vertebral fractures are well known complications of SpA, especially in ankylosing spondylitis (AS). The pathogenesis and onset of OP in SpA is not clear.

Research frontiers

Low bone mass and osteoporotic vertebral fractures are common complications of SpA, especially in AS. The prevalence of low BMD has been reported to be as high as 47% at the hip and lumbar spine even in patients with early SpA. Patients with SpA may have increased risk of bone loss as a result of high disease activity, pro-inflammatory cytokines and decrease in physical activity or mineralization defects due to subclinical gut involvement.

Innovations and breakthroughs

This review includes studies, which used dual X-ray absorptiometry (DXA) as the technique of BMD assessment in patients with axSpA. In twenty percent of studies, DXA techniques were compared with quantitative ultrasound or different type of quantitative computed tomography. Among these techniques DXA can be considered as an accurate, repeatable and quantitative method to assess BMD at the spine and hip but new bone formation and aberrant hyperostosis inevitably cause a pseudo increase in bone density.

Applications

The most appropriate and valid method to assess BMD in patients with advanced AS is still unclear. A systematic evaluation of DXA or alternative methods used to assess BMD in SpA is strongly needed.

Peer-review

Overall the paper is well written and the subject is certainly of interest.

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DOI: 10.5312/wjo.v6.i2.311

World J Orthop 2015 March 18; 6(2): 311-315
ISSN 2218-5836 (online)

Impact of osteoporosis in dental implants: A systematic review

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Supported by Sao Paulo Research Foundation, FAPESP, No. 2008/06972-6; The National Council for Scientific and Technological Development, CNPq Nos. 579157/2008-3, 302768/2009-2 and 473282/2007-0; Pesq-Doc scholarship to Dr. Shibli from University of Guaruhos and Scholarship to Dr. Giro from University of Guarulhos.

Conflict-of-interest: The authors declare that there are no conflicts of interest related to this study.

Data sharing: No additional data are available.

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Received: May 29, 2014
Peer-review started: May 29, 2014
First decision: July 18, 2014
Revised: December 3, 2014
Accepted: Janurary 9, 2015
Article in press: Janurary 12, 2015
Published online: March 18, 2015

Abstract

AIM: To assess the failure and bone-to-implant contact rate of dental implants placed on osteoporotic subjects.

METHODS: Extensive examination strategies were created to classify studies for this systematic review. MEDLINE (*via* PubMed) and EMBASE database were examined for studies in English up to and including May 2014. The examination presented a combination of the MeSH words described as follow: "osteoporosis" or "osteopenia" or "estrogen deficiency" AND "implant" or "dental implant" or "osseointegration". Assessment of clinical and/or histological peri-implant conditions in osteoporosis subjects treated with titanium dental implants. The examination included a combination of the MeSH terms described as follow: "osteoporosis" or "osteopenia" or "estrogen deficiency" AND "implant" or "dental implant" or "osseointegration".

RESULTS: Of 943 potentially eligible articles, 12 were included in the study. A total of 133 subjects with osteoporosis, 73 subjects diagnosed with osteopenia and 708 healthy subjects were assessed in this systematic review. In these subjects were installed 367, 205, 2981 dental implants in osteoporotic, osteopenic and healthy subjects, respectively. The failure rate of dental implant was 10.9% in osteoporotic subjects, 8.29% in osteopenic and 11.43% in healthy ones. Bone-to-implant contact obtained from retrieved implants ranged between 49.96% to 47.84%, for osteoporosis and non-osteoporotic subjects.

CONCLUSION: Osteoporotic subjects presented higher rates of implant loss, however, there is a lower evidence to strengthen or refute the hypothesis that osteoporosis may have detrimental effects on bone healing. Consequently, final conclusions regarding the effect of osteoporosis in dental implant therapy cannot be made at this time. There are no randomized clinical trial accessible for evaluation and the retrospective

nature of the evaluated studies shall be taken in account when interpreting this study.

Key words: Dental implants; Osteoporosis; Failures; Osteopenia; Osseointegration

Core tip: This systematic review focused on failure rates and percentage of osseointegration of dental implants in healthy and osteoporotic subjects. Definitive conclusions regarding the impact of osteoporosis on dental implant therapy cannot be made at this time. Clinically, it could be suggested that osteoporotic subjects can receive dental implant therapy.

Giro G, Chambrone L, Goldstein A, Rodrigues JA, Zenóbio E, Feres M, Figueiredo LC, Cassoni A, Shibli JA. Impact of osteoporosis in dental implants: A systematic review. *World J Orthop* 2015; 6(2): 311-315 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/311.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.311

INTRODUCTION

Osteoporosis is defined as a generalized skeletal disease noted by decreased bone mass and degradation of the microarchitecture of the bone tissue caused by increase of the marrow spaces, resulting in fragility of the bone tissue with subsequent greater risk of fractures[1]. According to the World Health Organization, osteoporosis is defined as a generalized disease of the skeleton characterized by a decrease of 25% of bone mass; meanwhile osteopenia is a term that characterize the physiological bone mineral density decrease of 10% to 25% from the normal condition as a precursor to osteoporosis[1]. Although it is defined by several factors, as calcium and vitamin D deficiency, sedentary and genetic factors, the post menopausal estrogen deficiency is the major known etiology, since estrogen regulates bone remodeling and the cessation of estrogen production induces a bone remodeling imbalance with bone resorption exceeding bone formation, leading to bone fragility and increasing risk of fracture[2]. Previous animal studies[3-13] using an ovariectomy model of osteoporosis induction with implants inserted in rats have shown that estrogen deficiency results in lower bone turnover rate, bone-to-implant contact, bone/implant interface biomechanical competence, and bone density on cancellous bone. Therefore, it has being reported as a systemic alteration possibly related as risk factor to osseointegration process and some authors suggested that the predictability of dental implant success may be seriously impaired when patients present osteoporosis or osteopenia[14]. Despite these evidences, from a clinical perspective, the literature findings on the topic are sparse and contradictory. Thus, the present systematic review aimed to evaluate the clinical and histological findings on subjects with osteoporosis that received dental implants and its relationship to dental implant failures.

The following focus questions were raised: (1) "Can osteoporosis be considered a risk factor for dental implant failures?"; and (2) "Does osteoporosis influence bone-to-implant contact rate?"

MATERIALS AND METHODS

This review was followed PRISMA[15], the Cochrane Collaboration[16], and Check Review[17].

Evaluated studies and search criteria

This study considered eligible for inclusion case reports, case series, randomized clinical trial (RCT) and clinical trial studies reporting outcomes from subjects with osteoporosis submitted to oral rehabilitation using dental implants. Studies without follow-up, animal studies and reviews were excluded from this study.

Outcome measure

Assessment of clinical and/or histological peri-implant conditions in osteoporosis subjects treated with titanium dental implants.

Examination focus

Systematic examination was performed to evaluate studies for this systematic review. MEDLINE (*via* PubMed) and EMBASE database was exanimated for papers published in English up to and including May 2014. The search strategy included a combination of the MeSH terms described as follow: "osteoporosis" or "osteopenia" or "estrogen deficiency" AND "implant" or "dental implant" or "osseointegration".

Cochrane Central Register of Controlled Trials, ClinicalTrials.gov were also examined using the same target. The electronic database of 4 dental implant journals considered important to this review (*i.e.*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *The International Journal of Oral and Maxillofacial Implants*, and *Journal of Oral and Maxillofacial Surgery*) were also hand examined.

Assessment of validity and data extraction

Six independent examiners (GG, JAR, EZ, AC, AG, LCF) assessed study eligibility independently. The reviewers screened the titles, abstracts of the manuscripts for subject relevance. Studies that could not be definitely excluded based on abstract information were also selected for full text screening. When agreement could not be reached after all the inclusion criteria were met, a seventh reviewer (LC) was consulted.

The recorded data extracted from the papers were

Table 1 Characteristics of the studies evaluating subjects with osteoporosis that received dental implants

Ref.	Study	No. of subjects	No. of implants	No. of failures	Follow up	Site of implant insertion
Alsaadi *et al*[19]	Retrospective	187	29 OPO/691 CTL	0 OPO/14 CTL	2 yr	388 max/332 mand
Alsaadi *et al*[20]	Retrospective	19 OPO/393 CTL	68 OPO/1446 CTL	9 (13.24%) OPO/92 (6.3%) CTL	2 yr	816 max/698 mand
Amorim *et al*[24]	Prospective	19 OPO/20 CTL	39 OPO/43 CTL	1 (2.56%) OPO/0 CTL	9 mo	Mandible
de Souza *et al*[21]	Retrospective	6 OPO/186 CTL	12 (50%) OPO/495 (71%) CTL With physiologic bone loss	12 (50%) OPO/203 (29%) CTL with additional bone loss	Not mentioned	354 max/368 mand
Dvorak *et al*[25]	Cross-sectional	46 OPO/16 OPE/115 CTL	828 Peri-implantitis	6 (13%) OPO/3 (18.75%) OPE/15 (13%) CTL 11 (23.9%) OPO/4 (25%) OPE/27 (23.5%) CTL	6 ± 4 yr	432 max/396 mand
Eder *et al*[26]	Case report	1 OPO	6	0	5 yr	Mandible
Friberg *et al*[22]	Retrospective	14 OPO	70	2 (2.85%)	3.4 yr	38 max/32 mand
Holahan *et al*[23]	Retrospective	41 OPO/57 OPE/94 CTL	143 OPO/197 OPE/306 CTL	10 OPO/10 OPE/17 CTL	10 yr	268 max/378 mand

OPO: Subjects with osteoporosis; OPE: Subjects with osteopenia; CTL: Control: subjects with standard bone mineral density.

Table 2 Studies showing bone to implant contact on bone tissue around dental implants in osteoporotic patients

Ref.	Study	*N* subjects	*N* implants	BIC (%)
Shibli *et al*[30]	Retrospective	7 with osteoporosis	7	46.00 ± 11.46
		14 without osteoporosis	15	47.84 ± 14.03
Shibli *et al*[28]	Case report	1 with osteoporosis	1	40.07
de Melo *et al*[29]	Case report	1 with osteoporosis	1	62.51
Shibli *et al*[27]	Case report	1 with osteoporosis	1	51.25

BIC: Bone-to-implant contact.

allocated in tables of evidence as follow: citation, publication status, and year of publication; location of the study; study design; characteristics of the subjects; outcome measures; methodological quality of the trials; and conclusions.

Statistical analysis

This study do not use any statistical analysis.

RESULTS

Searching

Searching identified 943 potentially eligible articles. A total of 930 articles were not included in this review. Thirteen full-text articles were examined, but only 12 attended the proposed inclusion criteria. The reasons for exclusion of Becker *et al*[18] was that this article do not presented the data necessary for comparison with the other studies.

Included Studies

Part Ⅰ - clinical findings: In this review it was included five retrospective studies[19-23]; one prospective study[24]; one cross sectional study[25] and a case report[26] (Table 1). No RCT was found for this topic. A total of 133 subjects with osteoporosis, 73 subjects diagnosed with osteopenia and 708 healthy subjects were included in this review. In these subjects were installed 367, 205, 2981 dental implants in osteoporotic, osteopenic and healthy subjects, respectively. Of the total dental implants installed, it was lost 40 (10.9%) dental implant in osteoporotic, 17 (8.29%) in osteopenic and 341 (11.43%) in healthy subjects.

In addition, Dvorak *et al*[25], presented data on prevalence of peri-implantitis. The rate of peri-implantitis was 11 (23.9%), 4 (25%) and 27 (23.5%) for osteoporotic, osteopenic and healthy subjects respectively.

Part Ⅱ - histological findings: Table 2 presents the histological data from the included studies. There are four papers with histological features on osteoporotic subjects. Three are case reports[27-29] and one retrospective study[30]. A total of 10 dental implants were retrieved from osteoporotic subjects and compared against 14 implants removed from non-osteoporotic. The rate of bone-to-implant contact ranged from 46% to 62.51% (mean 49.96%) for osteoporosis group while non-osteoporotic subjects yielded 47.84%, suggesting similar results for both groups.

Individual outcomes

None of the studies analyzed showed a positive correlation between dental implant failure and

osteoporosis. Subjects with osteoporosis presenting a survival rate of the dental implants similar to the non-osteoporotic ones.

DISCUSSION

Osteoporosis has no detrimental effect on implant failure rates neither on percentage of osseointegration. Although RCT were not found in the searched literature, most studies reported similar findings between subjects with and without osteoporosis (Table 1). Complementary, the bone-to-implant contact of dental implants retrieved from osteoporotic jaws did not depict any impact on bone healing.

In osteopenic subjects, the decreased net bone volume, and the bone load bearing capacity could be influenced by a mixture of these modulated cellular activities that are affected by lower levels of estrogen in post-menopausal osteoporosis[10]. Complementary, it may be speculated after establishment of bone tissue anchorage at implant surface, the accumulated rate of bone contacting implants is maintained[30]. Unlike regular bone remodeling occurring in the trabecular area, this phenomenon is not accompanied by an apparent bone turnover or resorption[31]. The overall 10.9% implant failures rate was comparable with previous studies performed in patients without osteopenia/osteoporosis[19-26]. The prevalence of peri-implantitis was also similar among the groups[25], suggesting that the metabolic diseases has no and/or minimal impact on pathogenesis of peri-implantitis, differently as observed in periodontal diseases[32].

The dental implant restorations in the jaws are influenced not only by systemic factors, but also by several local factors such as periodontal conditions, number and distribution of dental implants in the arch, occlusion, and bite forces. Despite some researches present the role of local and systemic factors in the long-term success of dental implants[19], less is known concerning factors influencing the stability of dental implants after abutment connection and occlusal loading. Therefore, the part of endogenous factors on cellular turn over and differentiation is scarce[14].

Systemic conditions associated with osteoporotic and osteopenic subjects have been suggested to contribute to the severity of alveolar bone loss[33].

Thus, the prerogative that dental implant placement might be contraindicated in subjects with osteoporosis/osteopenia is based on the assumption that these pathologies may affect the human jaws in the same fashion which it does affect other parts of the skeleton. In addition, differences in healing kinetics and pathway of bone healing and remodeling may exist between long[10,14]. However, to date, there are no conclusive studies presenting that osteoporosis and/or osteopenia increase the failure rates of dental implants neither peri-implantitis prevalence.

Within the limits of the present systematic review, osteoporosis was associated with higher rates of implant loss in the included studies. Regarding the impact of osteoporosis on bone-to-implant contact, there is a weak evidence to support or refute the hypothesis that osteoporosis may have detrimental effects on bone healing. Consequently, definitive conclusions regarding the impact of osteoporosis on implant-supported restoration cannot be made here. Finally, there are no RCT published for analysis. Therefore, the retrospective nature of the evaluated researchers shall be considered when interpreting the results of this review.

COMMENTS

Background

This systematic review evaluated the clinical and histological findings on subjects with osteoporosis that received dental implants and its relationship to dental implant failures. Two focus questions were raised: (1) "Can osteoporosis be considered a risk factor for dental implant failures?"; and (2) "Does osteoporosis influence bone-to-implant contact rate?" Although osteoporosis has been associated with higher rates of implant loss in the included studies, the bone-to-implant contact, there is a weak evidence to support or refute the hypothesis that osteoporosis may have detrimental effects on bone healing. Consequently, definitive conclusions regarding the impact of osteoporosis on dental implant therapy cannot be made at this time. In addition, there are no randomized clinical trial available for analysis. Therefore, the retrospective nature of the majority of included studies should be considered when interpreting the results of this review.

Research frontiers

Previous studies have been suggested that systemic alterations could act as risk factors to osseointegration process and consequently jeopardize the predictability of dental implant success on osteoporotic patients. Despite these evidences, from a clinical perspective, the literature findings on the topic are sparse and contradictory. Thus, the present systematic review evaluated the clinical and histological findings on subjects with osteoporosis that received dental implants and its relationship to dental implant failures.

Innovations and breakthroughs

Until know, there are no consensus for the impact of osteoporosis in dental implant success. The lack of randomized clinical trials and weak evidence presented in the current literature suggests that further studies are pretty need to clarify this hot topic in Oral Implantology field.

Applications

This review allows the clinician and researchers to rehabilitate partially and totally edentulous subjects with implant-supported restorations.

Peer-review

The topic of review is very interesting.

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P- Reviewer: Charoenphandhu N, Nishio K **S- Editor**: Ji FF
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DOI: 10.5312/wjo.v6.i2.316

World J Orthop 2015 March 18; 6(2): 316-321
ISSN 2218-5836 (online)

CASE REPORT

Total hip arthroplasty for surgical management of advanced tuberculous hip arthritis: Case report

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Author contributions: Tan SM and Chin PL designed the report; Tan SM collected the patient's clinical data and imaging; Chin PL performed the surgery for the patient; Tan SM and Chin PL analyzed the data and wrote the paper.

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Received: May 20, 2014
Peer-review started: May 20, 2014
First decision: July 18, 2014
Revised: November 10, 2014
Accepted: November 17, 2014
Article in press: November 19, 2014
Published online: March 18, 2015

Abstract

Tuberculosis (TB) arthritis of the hip is a debilitating disease that often results in severe cartilage destruction and degeneration of the hip. In advanced cases, arthrodesis of the hip confers benefits to the young, high-demand and active patient. However, many of these patients go on to develop degenerative arthritis of the spine, ipsilateral knee and contralateral hip, necessitating the need for a conversion to total hip arthroplasty. Conversion of a previously fused hip to a total hip arthroplasty presents as a surgical challenge due to altered anatomy, muscle atrophy, previous surgery and implants, neighbouring joint arthritis and limb length discrepancy. We report a case of advanced TB arthritis of the hip joint in a middle-aged Singaporean Chinese gentleman with a significant past medical history of miliary tuberculosis and previous hip arthrodesis. Considerations in pre-operative planning, surgical approaches and potential pitfalls are discussed and the operative technique utilized and post-operative rehabilitative regime of this patient is described. This case highlights the necessity of pre-operative planning and the operative technique used in the conversion of a previous hip arthrodesis to a total hip arthroplasty in a case of TB hip arthritis.

Key words: Tuberculosis; Arthritis; Arthroplasty; Conversion; Arthrodesis

Core tip: Different technical considerations regarding treatment of tuberculosis (TB) hip arthritis and various surgical techniques have been used in the surgical management of TB arthritis. This case report clearly illustrates the pre-operative planning, technical considerations and surgical technique used in the conversion of a arthrodesis into a total hip arthroplasty.

Tan SM, Chin PL. Total hip arthroplasty for surgical management of advanced tuberculous hip arthritis: Case report. *World J Orthop* 2015; 6(2): 316-321 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i2/316.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i2.316

INTRODUCTION

Tuberculosis (TB), one of the most ancient diseases

known to mankind, has remained a public health problem in both developing and developed countries. In 2011, 1533 new cases of TB were notified to the Ministry of Health, Singapore, representing 3.72% increase from the year before[1,2]. Correspondingly, the incidence rate increased from 39.2 cases per 100000 in 2010 to 40.5 cases per 100000 in 2011[2].

Extrapulmonary infection with *Mycobacterium Tuberculosis* has musculoskeletal involvement in up to 19% of cases[3,4] with the spine being the most common skeletal site (50%)[5]. This is followed by the pelvis (12%), hip, knee and tibia (10% each)[5].

TB arthritis of the hip in young individuals are often treated conservatively with physiotherapy, analgesia and rest. In advanced cases, arthrodesis of the hip confers benefits to the young, high-demand and active patient[6,7]. However, many of these patients go on to develop degenerative arthritis of the spine, ipsilateral knee and contralateral hip[8], necessitating the need for a conversion to total hip arthroplasty.

We report a case of advanced TB arthritis of the hip joint in a middle-aged Singaporean Chinese gentleman with a significant past medical history of miliary tuberculosis and previous hip arthrodesis. He presented with an indolent course of low-grade right hip pain for four months associated with symptomatic degenerative arthritis of the spine.

CASE REPORT

A 51-year-old Chinese Singaporean male mechanic, with a past medical history of miliary tuberculosis complicated by TB peritonitis, left renal pyelonephritis and right hip TB arthritis, presented with right hip pain of four months. This was associated with a complaint of lower back pain. He had previously undergone a right hip synovectomy and a right hip arthrodesis at the respective ages of 2 and 22. In the index hip surgery where synovectomy was performed, tissue sample sent for acid-fast bacilli smears was positive. He was also treated with a course of anti-tuberculous therapy. No subsequent episodes of reactivation were noted. Over an 8-mo period from the time of presentation, he was found to have gradual worsening of symptoms. Subsequently he developed an antalgic gait and experienced difficulty with climbing stairs. A course of conservative treatment including analgesia with physiotherapy did not alleviate his symptoms. There were no recent respiratory symptoms, fever or trauma. No recent travel was noted.

Clinical examination of the right hip revealed generalized tenderness of the right groin with limited range of motion. Hip flexion was restricted to 20°, hip extension to 10° with minimal abduction, adduction, external and internal rotation. A previous surgical scar was seen on the posterior aspect of the right hip. The patient did not have any neurovascular deficit.

Initial radiographs (Figure 1) done of the pelvis and right hip showed minimal right hip fusion with the presence of a Cobra plate used for hip arthrodesis. In addition, there was evidence of screw loosening and breakage seen on the initial radiographs. Based on the Martini *et al*[9] radiographic classification, this patient has Stage Ⅲ TB arthritis. His inflammatory markers were not elevated with a total white cell count of 6.1 $\times 10^9$ with no neutrophilic shift. C-reactive protein was not elevated.

Despite conservative measures, he continued to experience pain in his right hip and lower back, limiting his ability to work. Repeat radiographs done at 5-mo interval (Figure 2) showed further loosening and breakage of the screws. As the inflammatory markers did not show an active infection and the patient did not have any infective symptoms such as fever, no specimens were sent for histological or bacteriological investigations.

The patient underwent removal of right femur cobra plate and a cementless right total hip arthroplasty at 8-mo follow-up after failed conservative therapy. Intraoperative findings included a fused right hip with Cobra plate failure and multiple broken screws. Specimen were taken intraoperatively and sent for microscopy, acid-fast bacilli smears and cultures. These tests returned with negative results.

In our reported case, a direct posterolateral incision was first made and the fascia split before lifting up the vastus lateralis to take down the Cobra plate and broken screws from the previous arthrodesis. This approach was favored because this it was used by the previous surgeon and offers the most direct surgical access to the existing implants. Adopting a different exposure is likely to result in greater tissue damage leading to greater risk of dislocation in an inherently unstable hip. Subsequently, a modified anterior approach was used primarily for the following reasons: (1) to preserve the weak abductors; (2) to remove all broken screws *via* a femoral window; and (3) to confer maximal hip stability by reducing the likelihood of posterior hip dislocation. A long cortical window was made in order to assess and remove the previous prosthesis. Upon complete removal of previous prosthesis, release of the soft tissue envelope was performed-gluteus maximus attachment to femur, iliopsoas and the anterior capsule.

We proceeded to obtain bony landmarks using guide-wires placed in the femoral neck for the femoral neck osteotomy. These landmarks were checked with an image intensifier. It is imperative that a pre-procedure radiographic image is performed to have a complete view of the hip joint. Subsequently, we performed the femoral neck osteotomy with a saw followed by posterior capsule release.

Identification of the true acetabulum was achieved by using the following prominent landmarks such as the fovea, transverse acetabular ligament, greater sciatic notch and pubic rami. The anatomical position of

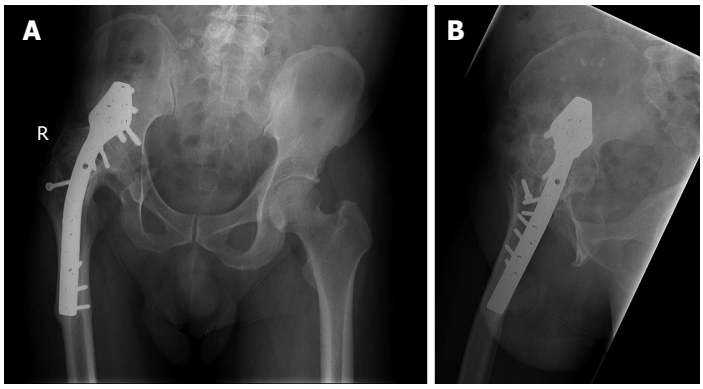

Figure 1 Initial Radiographs at presentation which shows stage Ⅲ tuberculosis arthritis (A) and screw loosening on the right hip (B).

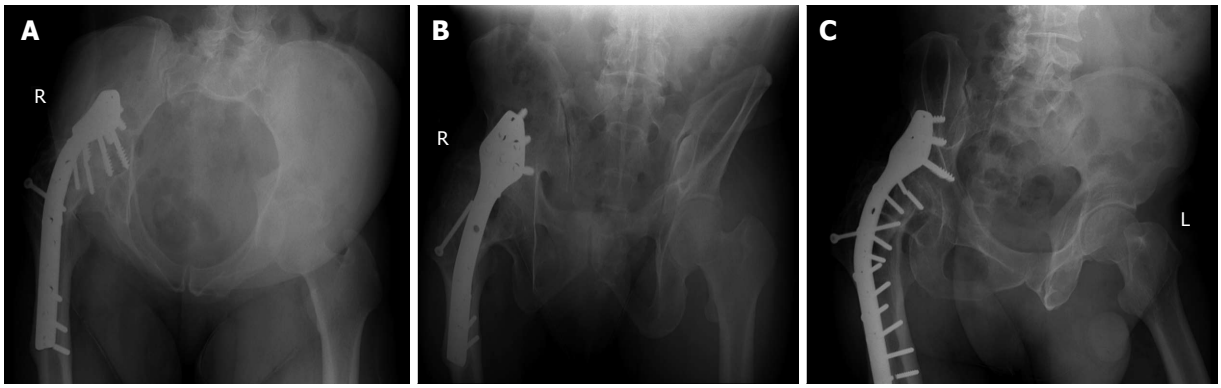

Figure 2 Radiographs at 5-mo follow up which revealed broken screws (A and B) and further loosening (C).

the true acetabulum can be further ascertained intra-operatively with the use of the image intensifier. Once the true acetabulum position has been ascertained, we deepened and enlarged the acetabulum progressively, beginning with the smallest-sized acetabular reamer and continuing till both the medial wall and floor of the acetabulum were encountered. In our reported case, the joint fusion was largely fibrous and this allowed a distinct envelope to be identified. We chose a TM acetabular cup and screw fixation. The choice of fixation was made with the consideration that the acetabulum was osteoporotic likely from stress shielding. In addition, in this inherently unstable hip joint, the possibility of conversion to a constrained hip prosthesis can be considered in a subsequent procedure.

The approach for the femoral component is similar to a conventional total hip arthroplasty. Key to this step was the release of soft tissue releases and their reattachment. As we have a long cortical window from the removal of the broken screws, a fully-beaded, coated, long bow stem was used to bypass the window. The use of defunctioning wires distal to the cortical window prevented propagation of a potential femur split. A bow stem was selected in order to achieve better rotational control of the femoral stem. A large, 32-mm diameter head was used to increase the stability with an ultra-high molecular weight polyethylene liner. Meticulous inspection for bony impingements was done and any impingement was chilectomized.

Post-operative radiographs at 4-mo interval (Figure 3) showed good anteversion of the acetabular component with bony ingrowth, no evidence of femoral or acetabular component loosening and no evidence of limb length discrepancy.

Postoperatively, this patient was started on a progressive rehabilitation regime, beginning with limited range of motion exercises. He was placed on a hip brace and started on partial-weight bearing exercises with the use of a walking frame for 6 wk post-operatively. Subsequently, he began full-weight bearing exercises. At 3-mo follow up interval, he was able to ambulate without any walking aids. He had no more complaints of right hip pain or lower back pain. On examination, he no longer exhibits an antalgic gait and shows significant improvement in hip abduction and external rotation movements. No significant limb length discrepancy was noted.

Using the Oxford Hip Questionnaire[10], the patient had an improved score of 17 post-operatively compared to 22 pre-operatively. The patient also had improved scores in terms of pain, stiffness and physical function based on WOMAC Arthritis Questionnaire.

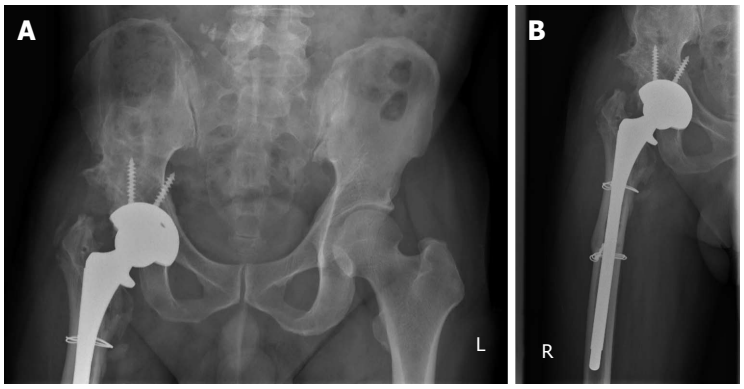

Figure 3 AP (A) and lateral radiographs of the right hip (B) at 4-mo post-operation.

DISCUSSION

TB arthritis of the hip is a very disabling disease. Known for its insidious onset, lack of early characteristic radiographic findings and often lack of constitutional or pulmonary involvement, it presents a diagnostic challenge for the orthopaedic surgeon.

The potential risk of reactivation has led to the controversy surrounding the timing of total hip arthroplasty and the use of anti-tuberculous chemotherapy. Whilst some authors advocated the use of anti-tuberculous therapy in prevention of TB reactivation, most authors did not routinely use anti-tuberculous therapy in managing these patients pre- and post-operatively. Two key factors for TB reactivation were identified: (1) the period of quiescence from the initial infection till the time of surgery; and (2) complete curettage and debridement of infected tissue. Hardinge *et al*[11] reported 21 cases of TB hip arthritis treated with total hip arthroplasty with quiescent periods between active infection and time of surgery ranging from 1 to 20 years. In this series where no chemoprophylaxis was given, no recurrence was reported. Similarly, Eskola *et al*[12] reported no recurrence in 18 patients who underwent cementless total hip arthroplasty for TB hip arthritis. Anti-tuberculous therapy was used in only 7 of these patients and surgery was performed on an average of 34 years from the time of onset. A study done by Joshi *et al*[13] in 2002 also showed no reactivation of tuberculosis in 60 patients who had hip arthrodesis converted to total hip arthroplasty. The mean time interval between hip fusion and conversion to total hip arthroplasty was 27 years. Oztürkmen *et al*[14] advocated the use of 1-year anti-tuberculous therapy post-operatively. In this series of 12 patients, none had TB recurrence.

In the case reported, the time of total hip arthroplasty was 49 years after the initial onset of infection which provides a significant quiescent time interval between active infection and arthroplasty. The time interval between arthrodesis to conversion to total hip arthroplasty was 29 years. Furthermore, the inflammatory markers were not elevated and intraoperative cultures were negative for acid-fast bacilli, hence anti-tuberculous chemotherapy was not instituted prophylactically both pre-operatively and post-operatively.

Conversion total hip arthroplasty from hip arthrodesis is a surgical challenge and have been reported to have high complication rates[15-17]. The initial work-up requires the careful exclusion of an active tuberculous reactivation of joint infection. This can be achieved with the use of serial inflammatory markers, tissue and blood cultures. An assessment of the gluteus muscles to evaluate abductor muscles function is key to predicting implant stability post-operatively[18]. The use of magnetic resonance imaging (MRI) stands superior to ultrasound evaluation of the glutei muscles. The presence of fatty degeneration within the glutei muscles often indicates permanent disability. Nerve conduction studies and electromyography further compliment this assessment. Another important consideration is that of limb length discrepancy[19] that often presents post-operatively due to the massive shortening of the affected limb. Depending on the amount of discrepancy, measures ranging from the use of platform shoes to shortening osteotomy of the contralateral limb may be necessary to correct the deficit.

In terms of surgical exposure, difficulties include utilizing an approach that facilitates minimal damage to the atrophied abductor muscles, osteotomy to take down the arthrodesis, delivering femur out of the wound with minimal soft tissue trauma, determining the site and depth of the true acetabulum, altered positions of anatomical landmarks, reconstruction of the abductor mechanism, stability, limb length discrepancy and post-operative rehabilitation of the abductor muscles. Other important factors that mitigate the decision for a particular approach include previous surgical exposure, stability of the prosthesis and the need for removal of any existing implants.

In a study in done in 2007, Morsi[19] used a trans-trochanteric approach in 19 cases undergoing conversion to total hip arthroplasty from previous hip arthrodesis. He cited 4 reasons for using such an approach: (1) to facilitate the procedure; (2) to preserve the weak

abductors; (3) the greater trochanter may be over the axis of entry of the femoral component into the medullary canal as a result of previous arthrodesis; and (4) trochanteric advancement was required to adjust the tension of the abductors for better stability and function. At a mean of 7.1 years follow-up, 1 out of 19 cases had failed. This was a result of recurrent dislocation which required revision.

Correction of limb length discrepancy is important in the alleviation of lower back pain, restoration of normal gait pattern and prevention of scoliosis. It is critical to note that in patients who have had fused hips for long periods, a significant correction of limb length discrepancy may result in exacerbation of back pain due to fixed obliquity of the pelvis and scoliosis[19]. Optimal correction of the limb length discrepancy should be based on the mobility of both pelvis and lower back.

Conversion of a fused hip should be performed by an experienced surgeon well versed in the different surgical approaches and techniques to the hip. The procedure may potentially involve large amounts of blood loss and prolonged operative timing. As such, the use of mechanical foot pumps, warming blankets and cell savers are measures that should be considered in the prevention of deep venous thrombosis, hypothermia and significant hemorrhage.

This case highlights the necessity of pre-operative planning and the operative technique used in the conversion of a previous hip arthrodesis to a total hip arthroplasty in a case of TB hip arthritis.

COMMENTS

Case characteristics

A 51-year-old Chinese Singaporean male mechanic, with a past medical history of miliary tuberculosis complicated by tuberculosis (TB) peritonitis, left renal pyelonephritis and right hip TB arthritis, presented with right hip pain of four months.

Clinical diagnosis

Hip arthritis.

Differential diagnosis

Tuberculous hip arthritis, osteoarthritis, avascular necrosis.

Laboratory diagnosis

Inflammatory markers were not elevated with a total white cell count of 6.1 × 10^9 with no neutrophilic shift. C-reactive protein was not elevated.

Imaging diagnosis

Radiographs done of the pelvis and right hip showed right hip fusion with the presence of a Cobra plate used for hip arthrodesis. In addition, there was evidence of screw loosening and breakage. Based on the Martini and Ouaches radiographic classification, this patient has Stage Ⅲ TB arthritis.

Pathological diagnosis

Tissue samples were taken intraoperatively and sent for microscopy, acid-fast bacilli smears and cultures, which returned with negative results.

Treatment

The patient underwent removal of right femur cobra plate and a cementless right total hip arthroplasty at 8-mo follow-up after failed conservative therapy.

Related reports

Eskola *et al* reported no TB recurrence in 18 patients who underwent cementless total hip arthroplasty for TB hip arthritis. Joshi *et al* also showed no reactivation of tuberculosis in 60 patients who had hip arthrodesis converted to total hip arthroplasty. Conversion total hip arthroplasty from hip arthrodesis is a surgical challenge and have been reported to have high complication rates as reported by Kreder *et al* and Strathy *et al* in their respective studies on patients with ankylosed hips undergoing total hip arthroplasty.

Term explanation

Arthrodesis, also known as fusion of the joint, is commonly performed for young patients with TB hip arthritis. This often results in limited range of motion of the affected hip joint. Conversion to total hip arthroplasty in which the fused joint is taken down and implanted with both an acetabular and femoral component to increase the range of motion of the hip joint and provide a better functional outcome, especially for the young, high-demand patients.

Experiences and lessons

This case highlights the necessity of pre-operative planning and the operative technique used in the conversion of a previous hip arthrodesis to a total hip arthroplasty in a case of TB hip arthritis.

Peer-review

The case report by Tan and Chin is well done and highlights an important operative technique that makes a big difference in patients with extrapulmonary tuberculosis with skeletal involvement, specifically hip involvement.

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P- Reviewer: Ayieko J, Drain P, Garcia-Elorriaga G, Silva GAV
S- Editor: Song XX **L- Editor**: A **E- Editor**: Liu SQ

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