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MINIREVIEWS

Hallux rigidus: How do I approach it?

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Abstract

Hallux rigidus is a degenerative disease of the first metatarsalphalangeal (MTP) joint and affects 2.5% of people over age 50. Dorsal osteophytes and narrowed joint space leads to debilitating pain and limited range of motion. Altered gait mechanics often ensued as 119% of the body force transmit through the 1st MTP joint during gait cycle. Precise etiology remains under debate with trauma being often cited in the literature. Hallux valgus interphalangeus, female gender, inflammatory and metabolic conditions have all been identified as associative factors. Clinical symptoms, physical exam and radiographic evidence are important in assessing and grading the disease. Non-operative managements including nonsteroidal antiinflammatory drugs, intra-articular injections, shoe modification, activity modification and physical therapy, should always be attempted for all hallux rigidus patients. The goal of surgery is to relieve pain, maintain stability of the first MTP joint, and improve function and quality of life. Operative treatments can be divided into joint-sparing *vs* joint-sacrificing. Cheilectomy and moberg osteotomy are examples of joint-sparing techniques that have demonstrated great success in early stages of hallux rigidus. Arthrodesis is a joint-sacrificing procedure that has been the gold standard for advanced hallux rigidus. Other newer procedures such as implant arthroplasty, interpositional arthroplasty and arthroscopy, have demonstrated promising early patient outcomes. However, future studies are still needed to validate its long-term efficacy and safety. The choice of procedure should be based on the condition of the joint, patient's goal and expectations, and surgeon's experience with the technique.

Key words: Hallux rigidus; Cheilectomy; Arthrodiastasis; Moberg osteotomy; Arthodesis; Interpositional arthroplasty; Arthroplasty

Core tip: Hallux rigidus is the leading form of arthritis

of the foot. Patients experience increasing pain and decreasing motion of the first metatarsalphalangeal joint as the disease progress, leading to significant morbidity and lower quality of life. Multiple treatment options, from cheilectomy to arthrodesis, have been utilized in treating hallux rigidus. Advances in interpositional arthroplasty and implants have introduced new opportunities in giving a more functional outcome. This review will discuss how to approach hallux rigidus in a clinical setting and examine recent evidence in the available treatment options.

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INTRODUCTION

Hallux rigidus is a degenerative disease of the first metatarsophalangeal (MTP) joint. It is the most common form of arthritis in the foot, affecting 1 in 40 people over the age of 50 with a 2:1 predilection for females[1,2]. The first MTP joint plays an important functional role during the gait cycle as it carries approximately 119% of an individual's body weight with each step[3]. Osteophyte formation and degeneration of the cartilage occurs dorsally in early stages of the disease and progresses to involve the entire first MTP joint. Consequently, individuals with hallux rigidus experience joint pain and decreased range of motion (ROM) in the sagittal plane. This leads to altered gait mechanics and significant reduction in activity and quality of life for patients[4,5].

CLASSIFICATION

Multiple different classification systems have been described for hallux ridigus to evaluate and grade the severity of the first MTP joint damage. Beeson *et al*[6] conducted a thorough review of 18 hallux rigidus classification systems reported in literature and found no consistency in the construction of the systems as they lacked reliability and scientific validity. Many of the included parameters were based on subjective clinical experience. The authors concluded that the system proposed by Coughlin and Shurnas[7] most closely approximates a gold standard, as it is based on a combination of objective radiological and clinical findings (Table 1)[6,7].

HALLUX RIGIDUS *VS* HALLUX LIMITUS

An important distinction needs to be made between hallux rigidus *vs* hallux limitus. Hallux rigidus is defined as pain due to an arthritic joint, whereas hallux limitus is defined as functional pain due to soft tissue tightness *(i.e.*, gastrocnemius contracture) or a long and elevated first metatarsal. Patients with hallux limitus will typically have an increased hallux dorsiflexion when the foot is examined in plantarflexion, as this relaxes the gastrocnemius and removes the restricting factor. It must be noted, however, that hallux limitus may progress to hallux rigidus, thus there may be occasions of overlapping features of either condition.

If the contributing factor in hallus limitus is gastrocnemius tightness, then a gastrocnemius recession alone may be performed. If a long or elevated first metatarsal is responsible for the condition, then a shortening or plantarflexion osteotomy of the metatarsal head may be warranted, with or without a gastrocnemius recession.

RISK FACTORS

The etiology of hallux rigidus is not well understood. It has been reported that trauma is one of the main causes for unilateral hallux rigidus[8]. Coughlin and Shurnas observed that hallux rigidus is associated with hallux valgus interphalangeus, and bilateral involvement is associated with a family history and female gender[9]. Development of degenerative changes can also be secondary to repetitive stress or inflammatory or metabolic conditions such as gout, rheumatoid arthritis and seronegative arthropathies[4,10]. Damage of the articular surface of the MTP joint due to osteochondritis dissecans has been proposed as well[10]. Biomechanical and structural factors, such as long first metatarsal, metatarsus elevates, and metatarsus adductus can also lead to increased risk of hallux rigidus[10,11].

EXAMINATION

Clinical examination

Patients with hallux rigidus may present with altered gait patterns or pain on the lateral aspect of the foot. This is secondary to the attempt to reduce loading on the first MTP joint. Patients may also report limitations on wearing certain types of shoes due to dorsal osteophytes on the first metatarsal head and proximal phalanx. Concurrently, patients may experience numbness along the medial border of the great toe as the osteophytes can compress on the dorsomedial cutaneous nerve[8].

Physical examination

The foot must be evaluated in the seated and standing positions. The standing position will provide information regarding the dynamic alignment and function of the hallux. The seated position will relax the soft tissues and help assess ROM.

The first MTP joint is often tender dorsally, with often palpable osteophytes. Since the dorsal osteophytes may compress on the dorsomedial cutaneous nerve, sensation deficits and vascular function of the foot should be recorded.

Evaluating the ROM of the first MTP joint is critical as it may be an indicator of the severity of arthritis. The

Table 1 Coughlin and Shurnas Clinical Radiographic System for Grading Hallux Rigidus

Grade	Dorsiflexion	Radiographic findings	Clinical findings
0	40° to 60° and/or 10% to 20% loss compared with normal side	Normal	No pain; only stiffness and loss of motion on examination
1	30° to 40° and/or 20% to 50% loss compared with normal side	Dorsal osteophyte is main finding, minimal joint-space narrowing, minimal periarticular sclerosis, minimal flattening of metatarsal head	Mild or occasional pain and stiffness, pain at extremes of dorsiflexion and/or plantar flexion on examination
2	10° to 30° and/or 50% to 75% loss compared with normal side	Dorsal, lateral, and possibly medial osteophytes giving flattened appearance to metatarsal head, no more than ¼ if dorsal joint space involved on lateral radiograph, mild-to-moderate joint-space narrowing and sclerosis, sesamoids not usually involved	Moderate-to-severe pain and stiffness that may be constant; pain occurs just before maximum dorsiflexion and maximum plantar flexion on examination
3	⩽ 10° and/or 75% to 100% loss compared with normal side. There is notable loss of metatarsophalangeal plantar flexion as well (often ⩽ 10° of plantar flexion)	Same as in grade 2 but with substantial narrowing, possibly periarticular cystic changes, more than ¼ of dorsal joint space involved on lateral radiograph, sesamoids enlarged and/or cystic and/or irregular	Nearly constant pain and substantial stiffness at extremes of range of motion but not at mid-range
4	Same as in grade 3	Same as in grade 3	Same criteria as grade 3 but there is definite pain at mid-range of passive motion

most common finding is a decreased passive and active ROM, most notably in dorsiflexion. In milder forms of hallux rigidus, pain during passive ROM usually occurs at or near the end points of flexion. However, pain in midrange motion indicates more diffuse level of arthritic change in the joint.

ROM has typically been measured clinically using a goniometer. However, clinical goniometric measurement has been proven to be unreliable and difficult to reproduce in a standardized manner as it is affected by various factors including instrumentation and different patient types[12]. A new reliable and reproducible method for measuring the hallux MTP ROM using dynamic X-rays has been reported by Vulcano *et al*[13]. There was a significant difference between clinical ROM and radiographic ROM, with clinical dorsiflexion being equal to or less than the radiographic dorsiflexion. The difference was more pronounced in patients with a clinical dorsiflexion less than 30 degrees. In addition, radiographic measurements of hallux dorsiflexion had excellent intra- and interobserver reliability[13].

The hallux interphalangeal (IP) joint should also be carefully examined. Should the joint also be arthritic, the surgeon should avoid fusing both IP and MTP joints to prevent abnormal gait patterns.

Radiographic examination

Weight-bearing anteroposterior (AP), lateral and oblique views of the affected foot should be obtained. The degree of joint space narrowing is best observed on the oblique view. In later stages of hallux rigidus, osteophytic formation can be observed in the periarticular area of the metatarsal head and proximal phalanx. It is important to note that the dorsal osteophytes can obstruct the AP view of the joint. This can lead to false impression of more severe osteoarthritis. Deland and Williams noted that osteophytes can also mislead the actual amount of joint space narrowing as it can help maintain the joint space[8]. The dorsal aspect of the joint is generally affected first. Other radiographic findings include joint sclerosis and subchondral cysts. Magnetic resonance imaging (MRI) and computed tomography (CT) images should not be necessary to diagnose the condition or to plan surgery.

TREATMENT

Nonsurgical management

Non-operative treatment for hallux rigidus should be attempted prior to surgical treatments. These treatments include medical therapy, intra-articular injections, shoe modification, activity modification, and physical therapy.

Medical therapy mainly involves oral nonsteroidal anti-inflammatory drugs aimed to reduce swelling and joint pain. However it has been observed that oral medications alone are insufficient to provide pain relief[8].

Intra-articular injections have been shown to provide good relief in some patients with hallux rigidus. Solan *et al*[14] conducted a study evaluating manipulation under anesthesia (MUA) and intra-articular steroid injection in patients with hallux rigidus. They found that patients with Grade 1 hallux rigidus (Karasick and Wapner classification) experienced pain relief of six months while one-third required surgery; grade 2 patients experienced pain relief of three months with two-thirds requiring surgery; grade 3 patients experience minimal benefit as all required surgery. The authors concluded that MUA and intra-articular injections should be recommended to patients with early grades of hallux rigidus[14]. Prolotherapy, or proliferation therapy, (*i.e.*, injection of platelet rich plasma or bone marrow aspirate) has also been shown to decreased pain and stiffness while improving various quality of life parameters[15]. However, the current scientific evidence is too scarce to draw definitive conclusions regarding its effectiveness in treating hallux rigidus.

Shoe modification and orthotics reduce pain by modifying the biomechanics of the first MTP joint. Morton extension and navicular pads have been used to immobilize and alter the loading patterns of the joint. Rocker-bottom soles can help reduce painful dorsiflexion

by allowing the patient to transition from heel strike to toe-off in the gait cycle without requiring the foot or shoe to bend. Shoes with high toe box can help prevent direct contact between the dorsal osteophytes and the shoe thereby taking pressure off the joint.

Physical therapy involves joint mobilization, manipulation and improving the ROM. Gaiting training, ice packs and rest reduce pain and inflammation. The use of extracorporeal shockwave therapy, iontophoresis and ultrasonography therapy have also been proposed[16]. However, evidence supporting the use of these adjunct therapies are still scarce.

Surgical management

When conservative management fails, there are a variety of surgical treatment options available. These techniques can be divided into joint sparing or joint sacrificing techniques. The choice of procedure is based on the condition of the joint, patient's goals and expectations of the surgical outcome, and patient's motivation. The goal of surgery is to relieve pain, improve function, maintain stability of the first MTP joint and improve quality of life.

CHEILECTOMY

Cheilectomy is a joint-sparing technique that involve resection of < 30% of the dorsal metatarsal head. In addition, intraarticular loose bodies and osteophytes localized in the metatarsal head and proximal phalanx are removed, and the medial, lateral and plantar capsules of the metatarsal heads are released. Greater than 30% of the dorsal metatarsal head removal is not advised as the joint can become unstable and the proximal phalanx can sublux. The procedure improves dorsiflexion of the first MTP as well as gait function as it increases the peak ankle push-off power in the sagittal plane[17].

Cheilectomy is the treatment of choice for early stages of hallux rigidus. It is a relatively simple procedure that preserves 1st MTP joint motion, allowing for faster return to daily activities. The reported complication rate for cheilectomy is low (0% to 3%)[18]. Cheilectomy does not compromise future surgical treatments should revision become necessary. However, cheilectomy does not prevent the progression of the disease and is rarely a permanent solution to the problem. Dorsal exostosis has been observed in up to 30% of patients, with continued progression of chondrolysis and joint deterioration[4].

Coughlin and Shurnas[19] reported the longest follow-up study to date for cheilectomy with a mean follow-up of 9.6 years. The study concluded that cheilectomy should be performed for Coughlin and Shurnas Grade I, Grade 2, and Grade 3 with less than 50% metatarsal head cartilage loss. Similarly, Bussewitz *et al*[18] reported an overall success rate of 98.5% in 197 cases with a mean follow-up of 3.2 years. Nicolosi *et al*[20] evaluated the long-term efficacy of aggressive cheilectomy by analyzing patient satisfaction using American Orthopaedic Foot and Ankle Society (AOFAS) scale in 58 patients with mean follow-up period of 7 years. The average improvement in pain relief was 87.71%, and 94.83% of all patients stated that they would undergo the same procedure again. The authors concluded that aggressive cheilectomy should be performed over arthrodesis in patients with Grade Ⅰ to Grade Ⅲ hallux rigidus using the Coughlin and Shurnas classification system.

Cetinkaya *et al*[21] assessed the results of cheilectomy in the treatment of Grade Ⅲ hallux rigidus using the Coughlin and Shurnas classification system for 21 patients (22 toes). There was no revision surgery done, and the visual analog scale (VAS) score improved from 89 preoperative to 29 postoperative. Cetinkaya *et al*[21] concluded that cheilectomy is the preferable method as the first line treatment option for Grade Ⅲ hallux rigidus.

CHEILECTOMY WITH MOBERG OSTEOTOMY

Moberg osteotomy is a dorsal closing-wedge osteotomy of the proximal phalanx. This procedure simulates an increased dorsiflexion that facilitates the third rocker of gait. Futher, the Moberg osteotomy shifts the center of pressure on the first metatarsal head in a plantar direction. As a result, less forces act on the arthritic joint surface[22].

Moberg osteotomy is typically performed in conjunction with a cheilectomy for early stages of hallux rigidus. As noted previously, cheilectomy doesn't prevent further degeneration of the joint and therefore progressive loss of dorsiflexion can occur. Moberg osteotomy can offer decompression of the joint while preserving the movement at the first MTP joint. It has been argued that one potential drawback of the osteotomy is that it could affect dorsal plate positioning in case of arthrodesis revision surgery[23].

In a study of 60 patients (60 toes) with an 8-year follow up, Waizy *et al*[24] compared the results of cheilectomy alone (27 patients) *vs* combined cheilectomy and Moberg osteotomy (33 patients). No revisions or further operations were done in both groups. Four patients had persistent hyperesthesia of the medial side of the great toe and 3 patients had delayed wound healing. Patients who had cheilectomy with Moberg osteotomy reported higher satisfaction than cheilectomy alone (32.6% *vs* 21.7%). The authors concluded that a Moberg osteotomy should be supplemented if dorsiflexion of greater than 70° could not be achieved intraoperatively with cheilectomy alone.

Moberg osteotomy alone has also demonstrated good clinical results in moderate hallux rigidus. Perez-Aznar *et al*[25] evaluated the results of a Moberg osteotomy alone in 40 patients (42 toes) with Coughlin and Shurnas Grade Ⅱ and Ⅲ hallux rigidus. Both AOFAS (51.7 to 88.8) and VAS scores (76.6 to 1.9) improved significantly from pre-op to post-op. Additionally, dorsiflexion improved from 20.3° to 55.7°.

O'Malley *et al*[23] investigated the use of cheilectomy and Moberg osteotomy for the treatment of advanced hallux rigidus. In a cohort of 81 grade Ⅲ hallux rigidus with

a mean follow-up of 4.3 years, significant improvements in dorsiflexion and AOFAS scores were reported. Patient satisfaction was high (85.2%), with 4.9% ultimately requiring arthrodesis. The authors encouraged and recommended cheilectomy with Moberg osteotomy in patients with high grade hallux rigidus with at least 20° of preoperative dorsiflexion.

ARTHRODESIS

Arthrodesis of the 1st MTP joint has been widely accepted as the standard of care for severe, end-stage hallux rigidus due to its perceived safety and efficacy[8,11,26-31]. The procedure is typically performed as open surgery, although few recent reports have demonstrated a percutaneous approach[28,32]. The arthrodesis surfaces can be prepared either in a dome-cup pair configuration or flat and tapered. Dome-cup pair configuration allows for high degrees of adjustability in a three-dimensional plane, making final optimal alignment of the great toe easier.

There are multiple internal fixation techniques to achieve fusion (plates, screws, wires and staples). Ultimately, the choice depends on the surgeon's skills and experiences with a particular fixation technique. Politi *et al*[33] evaluated and compared the strength of fixation of five commonly utilized techniques for arthrodesis and found that the most stable technique was the combination of an oblique lag screw and a dorsal plate. The weakest technique was dorsal plate alone with Kirschner wire fixation. Dening *et al*[34] demonstrated that plate fixation alone has significantly fewer non-unions than a single screw fixation. Hyer *et al*[35] compared the cost and results of two crossed screws and dorsal plating techniques. The two crossed screws represented a simple and less costly technique, with no statistically significant differences in time to fusion, revision surgery or hardware removal rate between the two techniques.

When performing a hallux fusion it is crucial to maintain the load bearing capacity of the first ray in order to prevent lateral transfer of forces towards the lesser metatarsals. The angle of fusion should be within 15° to 40° of extension and 15° and 30° of valgus[36].

Recent studies have reported fusion rates between 77% to 100% with dorsal plating and screw fixation[37]. Arthrodesis has been shown to improve propulsion power, weight-bearing function of the foot, and stability during gait[27]. However, complications such as nonunion have been reported to be as high as 20%[29]. Further, patients may complain of joint stiffness, metatarsalgia and limited footwear options, particularly women desiring to wear high heels.

ARTHROPLASTY

Unlike arthrodesis in which the joint motion is sacrificed to improve pain, partial or total arthroplasty is a surgical option intended to relief pain while preserving the mobility of the first MTP joint. Both total joint arthroplasty and hemiarthroplasty of the proximal phalanx or metatarsal have been developed. Despite the potential benefit of maintaining joint motion while relieving pain, multiple complications have been documented for arthroplasty, including implant failure, soft tissue instability, aseptic loosening of components, pathological wear, limited soft tissue coverage and infection[38,39].

Mixed results have been reported on the long-term outcomes of various types of implants[38-41]. Good short-term and long-term functional outcome and high patient satisfaction level were reported with the use of ToeFit-Plus (Plus Orthopedics AG, Switzerland) implants and silicone implant prosthesis[40,41]. Conversely, a loss of ROM and changes in component alignment over time was demonstrated with the use of an anatomically designed 3-component MTP-I prosthesis (Metis, Newdeal SA, Integra Life Science ILS, New Jersey, United States)[38]. Similarly, high rates of radiolucency, change in angulation, sinkage and malalignment were observed with the use of the second-generation ceramic press fit prosthesis (Press-fit Plus MTP, Moje Keramik-Implantate GmbH and Co KG, Petersberg, Germany)[39]. Because of the poor clinical and radiological results, the authors in the study did not recommend the prosthesis.

Similar to total joint arthroplasty, hemiarthroplasty also helps maintain the motion of the first MTP joint. However, hemiarthroplasty requires less bone resection and ensures maintenance of toe length. As a result, conversion to arthrodesis would be easier if a revision becomes necessary. Like total arthroplasty, studies on hemiarthroplasty have shown mixed results. Gheorghiu *et al*[42] observed a marked decrease in patient satisfaction along with significant decrease in ROM in patients with hemiarthroplasty compared to arthrodesis with a mean follow-up of 3.92 years. On the other hand, Voskuijl and Onstenk[43] found patients with hemiarthroplasty in their study reported greater satisfaction. In addition, symptom intensity and magnitude of disability were found comparable in both hemiarthroplasty and arthrodesis.

While the success and benefit of implants have been documented in the literature, the reports of higher complication rates, unpredictable results and poor survival have led orthopedic surgeons to become cautious with the use of implant arthroplasty. Part of the challenge with arthroplasty is the difficulty in mimicking the native joint and the various anatomical and mechanical stresses it endures. Failure of the arthroplasty is very difficult to manage as significant bone loss was introduced by the procedure in the first place. Additionally, the cost compared to arthrodesis is significantly higher[38]. Therefore, larger cohorts and longer follow-up studies are necessary to draw more definitive conclusions on arthroplasty in hallux rigidus.

INTERPOSITIONAL ARTHROPLASTY

Interpositional arthroplasty is a joint sparing procedure that maintains joint motion in patients with severe hallux rigidus. Keller resection arthroplasty was one of the

pioneer procedures for the treatment of hallux rigidus that involves the resection of up to 50% of the base of the proximal phalanx. The goal of the procedure was to decompress the joint while increasing dorsiflexion. However, the procedure may destabilize the first MTP joint leading to transfer metatarsalgia, excessive shortening of the toe, cock-up deformity, clawing of the IP joint, and high rates of revision[8,44-47]. In addition, pedobarographic evaluations of foot following Keller resection arthroplasty have demonstrated a decrease in the maximum pressure, force and contact area under the operated great toe[45].

Schneider *et al*[45] reported a 90% stable first MTP joint in 78 patients (87 toes) who underwent Keller resection arthroplasty with 23 years of follow-up. The revision rate was reported at 5%. However, it is important to note that even though only one patient required revision with a cock-up deformity, 23% (19 toes) of patients presented with a cock-up deformity. It has been proposed to reserve the Keller resection arthroplasty in patients with advanced hallux rigidus, over the age of 70, and with less physical demand[8,46].

In light of the potential complications, multiple modifications of the Keller resection arthroplasty have been developed. These include a much more limited resection of the proximal phalanx, addition of a cheilectomy, and a placement of a spacer (joint capsule, extensor halluces brevis, tendon autograft, tendon allograft, synthetic matrix, *etc.*). The aim of the modifications is to preserve the bone stock, maintain or increase joint motion, stability and length[48].

Aynardi *et al*[49] retrospectively reviewed 133 patients who underwent interpositional arthroplasty with either autograft or synthetic soft tissue. Ninety percent of patients reported good to excellent outcomes at a mean follow-up of 62.2 mo. Overall failure rate was 3.8%, and a 1.5% infection rate. Six patients reported cock-up deformity of the 1st MTP joint and 23 patients reported metatarsalgia of the 2nd or 3rd MTP joint.

Schenk *et al*[50] compared the outcomes of Keller resection arthroplasty and interpositonal arthroplasty and found no significant difference between the clinical and radiological outcomes of the two procedures. However, these were short term-results with a mean follow-up of 1.26 years. Mackey *et al*[47] compared interpositional arthroplasty with arthrodesis and reported that interpositional arthroplasty had equivalent clinical outcomes to arthrodesis. However, it presented the additional benefit of motion preservation and resulted in a more physiologic pattern of plantar pressure during gait.

Berlet *et al*[48] described the use of a regenerative tissue matrix (RTM) (Wright Medical Technology, Inc., Memphis, TN, United States) as an allograft interpositional spacer for the treatment of advanced hallux rigidus. RTM is a biologically engineered allograft consisting of collagen and extracellular protein matrices. In their preliminary report, 9 patients underwent the procedure and no failures were reported at 10.1 mo follow-up. At 5-year follow-up, none of the patients had subsequent fusion or additional procedures performed on the first MTP joint and all were satisfied with the procedure[51].

Baumhauer *et al*[5] described the use of a synthetic cartilage implant as an allograft interpositional spacer. This synthetic cartilage implant (Cartiva, Inc., Alpharetta, GA, United States) is 8 or 10 mm in diameter and requires minimal bone and joint resection for implantation. The authors compared synthetic cartilage implant and arthrodesis in patients with advanced stage hallux rigidus and concluded that both procedures had equivalent decrease in pain and improvement function at 2-year, with an overall failure rate of 10%.

ARTHODIASTASIS

Arthodiastasis involves extra-articular distraction of a joint. This is based on the principle that offloading the articular surfaces of a joint can provide an environment that stimulates bone healing and fibrocartilage generation[4]. Pain can potentially be reduced, and arthrodesis or arthroplasty is still possible if distraction fails. Distraction of other joints in the body has been well reported, including the hip and ankle[52-54]. Abraham *et al*[55] reported a statistically significant reduction of pain in 9 hallux rigidus patients (10 distractions) using joint distraction with a mean follow up of 2.2 years. All patients were stage Ⅱ or Ⅲ hallux rigidus on the Regnauld classification system, and none of the patients had subsequent procedures on the first MTP joint. The downside of the procedure, however, is the need to carry an external fixator for about 3 mo.

ARTHROSCOPY

The use of arthroscopy in the treatment of hallux rigidus is an emerging technique that has recently been described[56,57]. It is mainly used for grade Ⅰ and Ⅱ hallux rigidus where joint motion still remains. For patients that have failed conservative treatments, arthroscopic debridement and dorsal cheilectomy can be performed as an alternative to an open cheilectomy. Advantages include smaller incisions, reduced operative morbidity and more rapid rehabilitation. In addition, access to the entire joint is easier, which allows for identification of concomitant pathologies in the joint. If visualization of the joint is limited, the dorsomedial portal can be extended and convert the procedure to an open cheilectomy[56]. Arthroscopy of the 1st MTP joint is technically challenging and requires additional surgical training. Complications that have been described include iatrogenic articular cartilage injury, superficial or deep infection, wound dehiscence and sinus tract formation[56].

CONCLUSION

An array of techniques has been developed to address the arthritic changes in hallux rigidus. Surgical treatments can be considered only after failure with non-operative management. Surgical options can be divided into joint sparing and joint sacrificing. Determining the extent of

the degenerative changes in the first MTP joint is critical in selecting which surgical technique to perform. Cheilectomy has demonstrated excellent outcomes for early stages of hallux rigidus, while arthrodesis is the gold standard for end-stage hallux rigidus. Other procedures, such as interpositional arthroplasty, seem to provide promising patient outcomes, but long-term follow-up studies are needed to validate the available results.

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ORIGINAL ARTICLE

Basic Study

Light and electron microscopic study of the medial collateral ligament epiligament tissue in human knees

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Author contributions: Georgiev GP and Landzhov B performed the ultrastructural study and analysed the data from transmission electron microscopy and light microscopy; Iliev A, Kinov P and Slavchev S performed the histologic investigations; Kinov P, Slavchev S and Landzhov B helped in preparing the manuscript; Georgiev GP designed and coordinated the research; Georgiev GP, Iliev A and Kotov G wrote the paper; all authors approved the final version of the article to be published.

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Abstract

AIM

To examine the normal morphology of the epiligament tissue of the knee medial collateral ligament (MCL) in humans.

METHODS

Several samples of the mid-substance of the MCL of the knee joint from 7 fresh human cadavers (3 females and 4 males) were taken. Examination of the epiligament tissue was conducted by light microscopy and photomicrography on semi-thin sections of formalin fixed paraffin-embedded blocks that were routinely stained with haematoxylin and eosin, Mallory stain and Van Gieson's stain. Electron microscopy of the epiligament tissue was performed on ultra-thin sections incubated in 1% osmium tetroxide and contrasted with 2.5% uranyl acetate, lead nitrate, and sodium citrate.

RESULTS

The current light microscopic study demonstrated that the epiligament of the MCL consisted of fibroblasts, fibrocytes, adipocytes, neuro-vascular bundles and numerous multidirectional collagen fibers. In contrast, the ligament body was poorly vascularised, composed

of hypo-cellular fascicles which were formed of longitudinal groups of collagen fibers. Moreover, most of the vessels of the epiligament-ligament complex were situated in the epiligament tissue. The electron microscopic study revealed fibroblasts with various shapes in the epiligament substance. All of them had the ultrastructural characteristics of active cells with large nuclei, well developed rough endoplasmic reticulum, multiple ribosomes, poorly developed Golgi apparatus, elliptical mitochondria and oval lysosomes. The electron microscopy also confirmed the presence of adipocytes, mast cells, myelinated and unmyelinated nerve fibers and chaotically oriented collagen fibers.

CONCLUSION

Significant differences exist between the normal structure of the ligament and the epiligament whose morphology and function is to be studied further.

Key words: Knee; Epiligament; Knee medial collateral ligament; Electron Microscopy; Humans; Microscopy; Photomicrography

Core tip: The epiligament of the medial collateral ligament of the human knee is an important enveloping supporting structure of the ligament proper containing fibroblasts, fibrocytes, adipocytes, mast cells, and neurovascular bundles in a network of collagen fibres that is not limited to the surface of the ligament but also pervades it, as the endoligament, thus providing the cellular elements and blood vessels that participate in the ligament's nutrition and during the process of healing.

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INTRODUCTION

The medial collateral ligament (MCL) of the knee joint, also known as tibial collateral ligament (TCL), is an often injured ligamentous structure of the knee joint[1-3]. Ninety percent of knee ligament injuries involve the MCL or the anterior cruciate ligament (ACL)[4]. The incidence of this injury has increased in recent years and presents a commonly encountered problem in modern sports medicine[5,6]. Most injuries result from a valgus force on the knee from direct contact or with cutting manoeuvres, namely when athletes place a foot in a stable position and then rapidly change the direction of movement[7]. The popularity of sports such as football, skiing and ice hockey has also contributed to the increased incidence of MCL injuries[8]. According to the model of Warren and Marshall, the medial knee is divided into the following three layers: Superficial (Ⅰ), intermediate (Ⅱ), and deep (Ⅲ)[9]. The superficial layer (Ⅰ) consists of the deep crural fascia which invests the sartorius and quadriceps and continues into the deep fascia of the lower extremity, where it covers the gastrocnemius and the popliteal fossa. Layer Ⅱ, or the intermediate layer, includes the superficial MCL (sMCL) and medial patellofemoral ligament (MPFL). Layer Ⅲ is the deep layer and comprises the joint capsule and the deep MCL (dMCL). The superficial and dMCL have similar functions and act as the primary supporting structures of the medial side of the knee[5,10], therefore injuries to these structures merit due attention and adequate treatment[1]. The healing of ligaments after injury is associated with scar tissue formation rather than regeneration[11-14].

The structure of the MCL has been studied extensively, however, very little is known about the thin layer of connective tissue adherent to this ligament, termed the epiligament (EL) [epi-(Greek-on or upon); ligament (Latin-ligare, to bind)]. In 1990, Bray *et al*[15] described the epiligament as a "surrounding adherent connective tissue removed simultaneously with the ligament but which was grossly distinguishable from ligament tissue proper". Our previous studies on the MCL in rat knee models led to the conclusion that the EL tissue plays a key role in the healing of the ligament tissue after injury[13,16,17]. According to Georgiev and Vidinov[18-20] and Georgiev *et al*[12,13,16,21,22] the EL is a donor of fibroblasts, progenitor cells and blood vessels, which proliferate and migrate towards the body of the ligament through the endoligament during the process of ligament recovery. Fibroblasts in the EL tissue normally produce collagen types Ⅰ, Ⅲ, Ⅴ, fibronectin (FN) and matrix metalloproteinases-2 and -9 (MMP-2, -9) which are essential for the normal functioning of the ligament and their synthesis is increased in order to promote adequate repair after injury[13,16,17,21,23]. Therefore, detailed knowledge of the morphology and function of the EL during physiological conditions and post injury is important in deepening our knowledge with regard to ligament healing and may thus lead to proposal of better treatment options in the future. There is plentiful literature data concerning the role of the EL during MCL healing in rats, however its normal anatomy in humans has not been studied yet. In line with this, the aim of this study is to investigate the normal morphology of the MCL EL in humans for the first time in the literature, through light and electron microscopy and to compare it to the ligament substance.

MATERIALS AND METHODS

Several samples of the mid-substance of the MCL of the knee joint of 7 cadavers (3 females and 4 males) were taken from the fresh human cadavers available at the Department of Anatomy, Histology and Embryology at

the Medical University of Sofia. The study was approved by the Medical Legal Office, the Local Ethics Committee and the Institutional Review Board.

After skin incision, the overlying connective tissue was dissected to expose the knee's MCL. The MCL and the external surface of the surrounding EL were precisely dissected and then the pieces were immediately fixed in formalin (Merck Catalogue No. 1040031000) for light microscopy or in 3% glutaraldehyde (Merck Catalogue No. 354400) for 2 h for electron microscopy.

Light microscopic study protocol

After fixation, the samples were embedded in paraffin and cut into semi-thin sections that were stained routinely with HE (Haematoxylin Merck Catalogue No. 105 1741000; Eosin Merck Catalogue No. 1170811000), Mallory stain and Van Gieson's stain. Photomicrographs of representative fields of the light microscopy staining were obtained using Olympus CX 21 microscope fitted with an Olympus C5050Z digital camera (Olympus Optical Co, Ltd).

Electron microscopic study protocol

After fixation, the tissues were rinsed several times with 0.1% phosphate buffer (Merck Catalogue No. 146 5920006) to remove the fixative solution and were incubated in 1% osmium tetroxide (Merck Catalogue No. 1245050500) for 2 h. Then the pieces were dehydrated in EtOH (50%, 70%, 95%, 100%) (Merck Catalogue No. 1009835000) and treated for 30 min with a 2:1 mixture of propylene oxide (Merck Catalogue No. 807027) and epon. The pieces were embedded in Durcupan (Fluka, Buchs, Switzerland). Afterwards, all slices were processed with a dissectional microscope and cut by an ultramicrotome (LKB, Stockholm-Bromma, Sweden). The EL regions were identified on semi-thin sections. Ultrathin sections (60 nm thick) were taken only from the MCL EL and then both were contrasted with 2.5% uranyl acetate, lead nitrate, and sodium citrate. We used a Hitachi 500 electron microscope.

RESULTS

Normal morphology of the MCL EL: Light microscopy

The light microscopic study revealed that human MCL EL is markedly distinctive from the ligament substance and confirmed our previous observations in rats. The external surface of the MCL EL was comprised of fibroblasts, fibrocytes, adipocytes, mast cells and neuro-vascular bundles as well as numerous multidirectional collagen fibres (Figure 1). The EL was relatively rich in blood vessels (Figure 1A). In contrast to the EL, the ligament tissue was poorly vascularised and composed of uniform fascicles that were formed of longitudinally aligned groups of collagen fibres. Each fascicle appeared hypocellular and the scarce cells were interspersed between bundles of collagen fibres. Unlike in the ligament, the collagen fibres in the EL of the midportion of the MCL were quite similar in diameter and were positioned in bundles with various orientation.

Normal morphology of the MCL EL: Electron microscopy

The electron microscopy revealed the presence of various types of fibroblasts in the EL: Spindle-shaped, spinous-shaped, elongated and fibroblasts with irregular shape. They had large nuclei, well developed rough endoplasmic reticulum, multiple ribosomes, poorly developed Golgi complex, individual elliptical mitochondria and oval, individually located lysosomes (Figure 2A-C). The electron microscopy also manifested the presence of adipocytes and mast cells (Figure 1F). The mast cells had well-presented nuclei with peripheral heterochromatin. The cytoplasm contained the specific round or oval granules. The granules were always enclosed by a membrane and separated from other granules by cytoplasmic septa. The matrix of each granule was homogeneous and electron-dense. The electron microscopy revealed that the adipocytes had large lipid droplets which pushed the rest of cytoplasm at the periphery of the cell. The nuclei of the adipocytes were eccentrically located.

Collagen fibres in the EL of the midportion of the MCL were quite similar in diameter and were organized in bundles with various orientation, unlike the parallel pattern of distribution of collagen fibres in the ligament (Figure 2D and E). Again, chaotically oriented small groups of collagen fibres were observed. Both myelinated and unmyelinated nerve fibres were detected.

DISCUSSION

The ligament is built of connective tissue, which comprises two main elements-connective tissue cells and extracellular matrix[11,24]. Collagen fibres in the ligaments are organized in longitudinal groups and form fascicles[11,24,25]. The thin layer of connective tissue separating these fascicles is known as endoligament and is related to another connective tissue structure, containing more blood vessels, which envelops the entire ligament and is known as epiligament[12,13,16-18]. In rabbits, Chowdhury *et al*[26] (1991) examined the external surface of the MCL EL and described two types of cells - spinous-shaped adipocytes and fibroblasts. It is fibroblasts that produce collagen fibers and thus are responsible for the formation of scar tissue[26]. In rats, Georgiev *et al*[12,13,16,17] showed the external portion of the MCL EL to consist of fibroblasts, fibrocytes, adipocytes, neurovascular bundles, and a number of collagen fibres, oriented in varying directions. These cells are located among bundles of collagen fibres. Georgiev *et al*[22] also described the ultrastructural characteristics of the different types of fibroblasts in the EL of the lateral collateral ligament (LCL) in rat knees. In terms of shape, they described spindle-shaped fibroblasts, small elongated fibroblasts and fibroblasts with irregular shape. All of these cells were characterized by the presence of a large nucleus with prominent nucleoli, well-developed rough endoplasmic

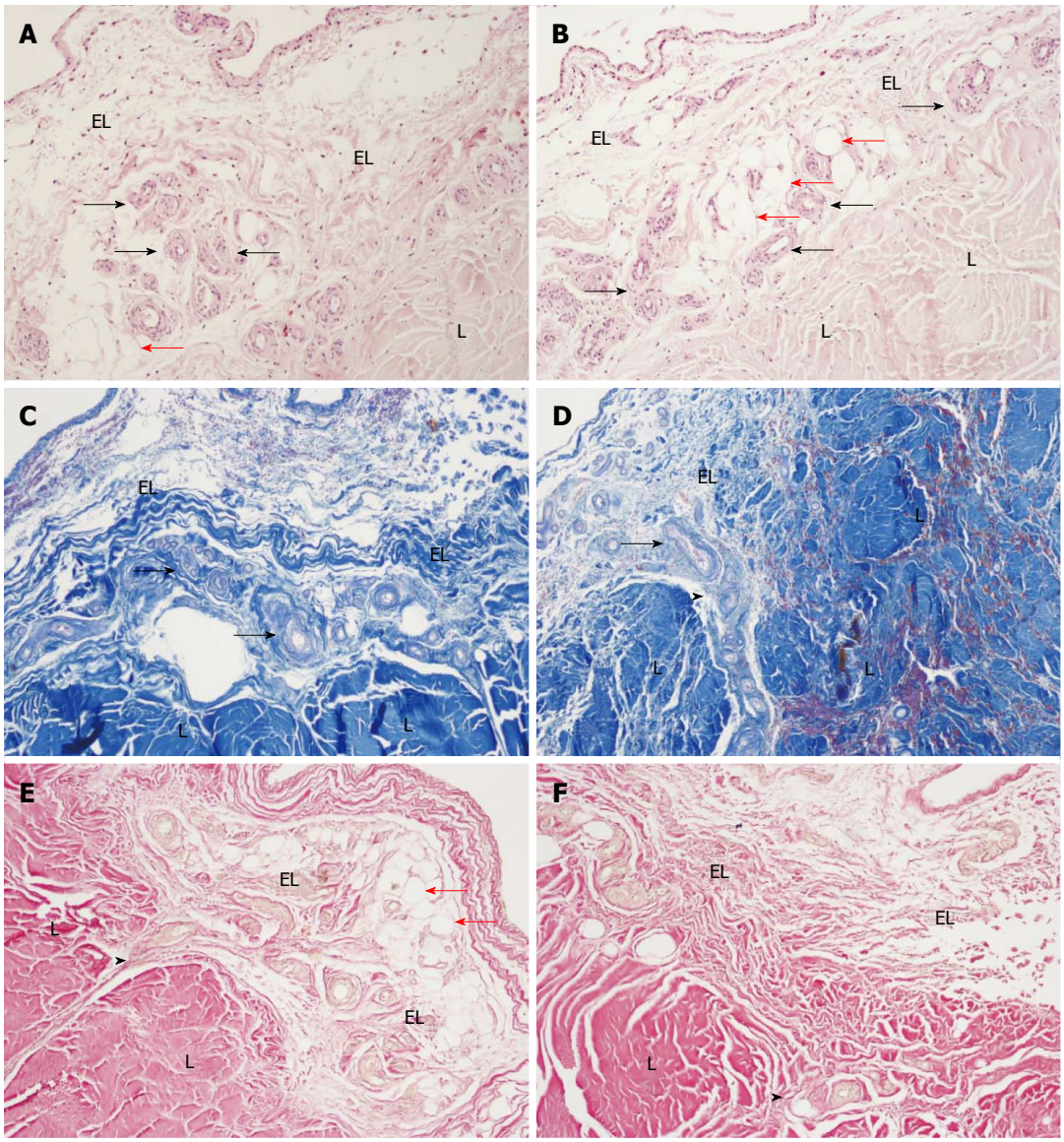

Figure 1 Normal morphology of the medial collateral ligament epiligament tissue in humans. A and B: Normal morphology of the MCL EL tissue. Haematoxylin and eosin stain, × 200. E: Epiligament; L: Ligament; red arrows: Adipocytes; arrows: Vessels in the EL tissue; C and D: Normal morphology of the MCL EL tissue. Mallory stain, × 200. E: Epiligament; L: Ligament; arrows: Vessels in the EL tissue; arrow head: The EL extending into the endoligament; E and F: Normal morphology of the MCL EL tissue. Van Gieson's stain, × 200. EL: Epiligament; L: Ligament; red arrows: Adipocytes; arrow head: The EL extending into the endoligament; MCL: Medial collateral ligament.

reticulum and numerous ribosomes. These ultrastructural characteristics led Georgiev *et al*[22] to conclude that fibroblasts in the EL might take part in the differentiation, phagocytosis and collagen synthesis, possibly thus playing a role in the regeneration of the ligament after injury, which has also been proposed by other authors[11]. Moreover, fibroblasts in the EL may proliferate and migrate through the endoligament into the ligament proper[18,27].

Other rarely observed types of cells are mast cells which have an oval shape and numerous granules with homogeneous density[22]. Adipocytes are organized in cellular lobuli, enveloped by thing connective tissue fibres and represent the building blocks of white adipose tissue[24]. According to Chowdhury *et al*[26] adipocytes synthesize, process and store lipids and thus participate in nutrition and confine specific storage and protective functions to the EL.

In humans, our light microscopic and ultrastructural study confirmed the aforementioned characteristics of the EL tissue and its constituent cells. On light microscopy, we noted the existence of fibroblasts, fibrocytes, adipocytes, neuro-muscular bundles and numerous multidirectional collagen fibres. This greatly resembled the structure of the EL observed in rats[22]. Also, we observed that the main cytological features of the EL were closely related to those in the synovium. This provides further support to the theory that the EL is a specialised form of synovium[11,28]. Electron microscopy revealed a great variety of fibroblasts in terms of shape - spindle-shaped, spinous-shaped, elongated and irregularly-shaped, which confirmed earlier results in rats[22]. We found an abundance of structures in their cytoplasm, namely a well-developed rough

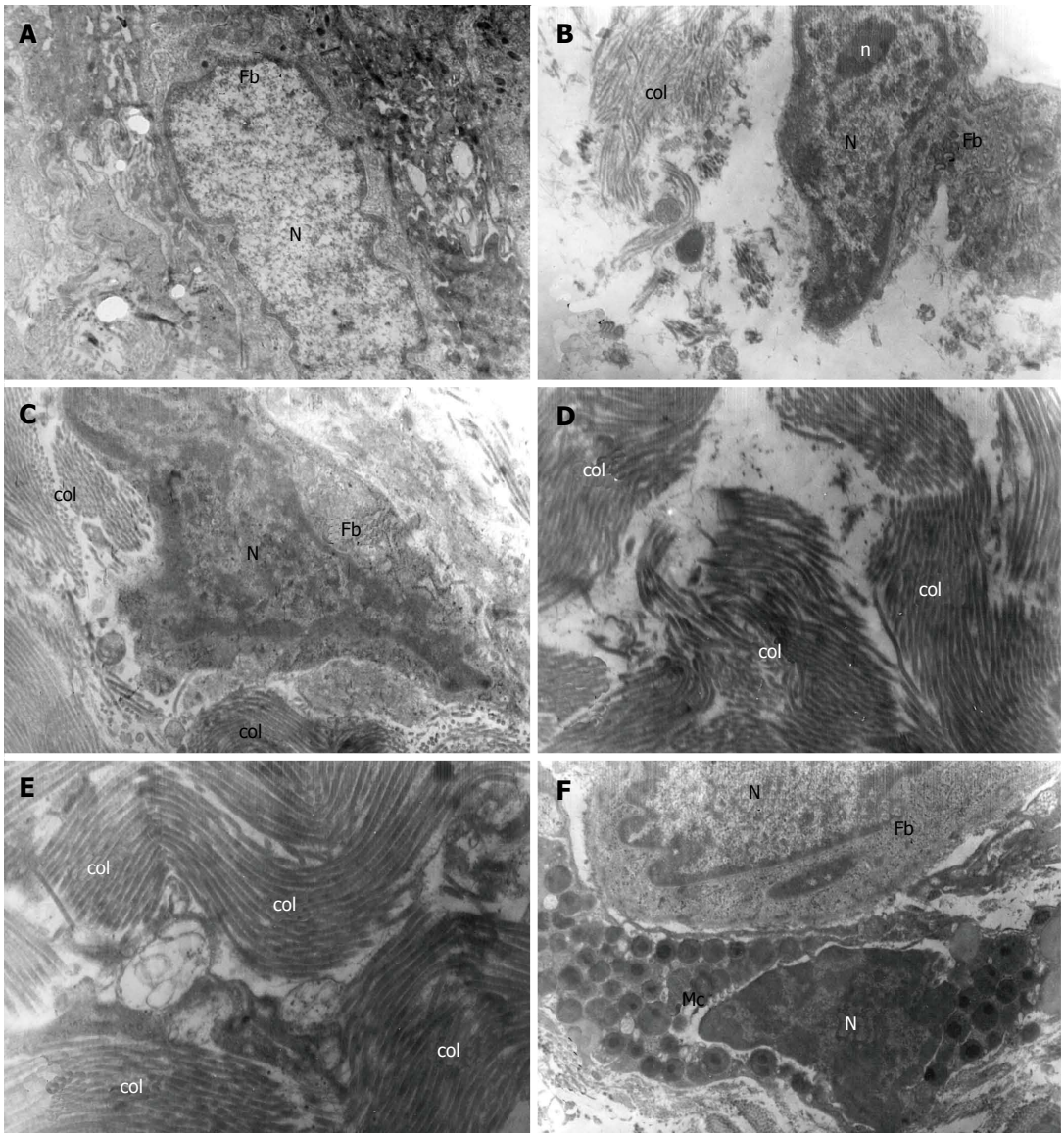

Figure 2 Normal morphology of the medial collateral ligament epiligament tissue in human. A-C: Electron micrograph of a fibroblast (Fb) and its nucleus (N). Mitochondria, lysosomes and rough endoplasmic reticulum are visible in the cytoplasm of the Fb; in the extracellular matrix numerous collagen fibers (col) are presented × 7000; D and E: Electron micrograph of EL collagen fibers (col) in the extracellular matrix oriented in different directions × 7000, × 9000; F: Electron micrograph of a fibroblast (Fb) and its nucleus (N) and a mast cell (Mc) with numerous granules and its nucleus (N), × 9000.

endoplasmic reticulum and multiple ribosomes, which supports the hypothesis that fibroblasts play a key role in the ligament nutrition and healing after injury[11,22].

As in the rat and the rabbit, the EL tissue in humans appears to contain a relative abundance of blood vessels[12,24,26,29,30]. Blood vessels in the EL are randomly dispersed in an amorphous structure, built of loose connective tissue[26,30]. They branch extensively, forming anastomotic networks of interconnected vessels[29,30]. Blood vessels in the EL are often accompanied by nerve bundles, but apparently not all blood vessels are organized in a neurovascular bundle[15,26,30].

The healing of ligaments after injury is associated with scar tissue formation rather than regeneration, which shows common mechanisms to the healing processes in other soft tissue structures[31-34]. According to Frank *et al*[32] injury location has an impact on ligament healing. The MCL heals much better and faster than the ACL of the knee joint. This is most likely due to the specific characteristics of the EL, located above the MCL. Georgiev and Vidinov[18-20], Georgiev *et al*[13,16,17,21,22] and Lo *et al*[29], claim that the EL may be the primary donor of connective tissue cells participating in the scar formation as part of the process of ligament healing. Fibroblasts are not static cells and as such can migrate from the EL to the healing ligament[12,13,21,22,26]. According to Chamberlain *et al*[27], ligament injuries stimulate the migration of various cell types from the EL, including neutrophils and cells in the process of mitosis up to the fifth day after injury, which proves that there is a bilateral cooperation between the EL and the ligament with regard to adequate healing of the ligament.

In conclusion, this study illustrates in detail the normal morphology of the MCL EL in humans and demonstrates

its difference from the structure of the ligament tissue for the first time. The electron microscopic study reveals the specific characteristics of the various types of cells in the EL and supports the hypothesis that fibroblasts in particular, together with the abundant blood vessels are essential for the nutrition and healing of the MCL.

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COMMENTS

Background

The epiligament has relatively recently been shown to be a distinct structure enveloping ligaments in mammals and to be the main donor of cells and blood vessels for ligament nutrition and healing not only at its periphery but also within its substance where it penetrates as a ramified network - the endoligament.

Research frontiers

Previous research was performed on rat and rabbit models yielding consistent results.

Innovations and breakthroughs

This is the first light microscopic and ultrastructural study of the epiligament in humans showing it to be structurally, and possibly functionally, similar to that of other mammals.

Applications

Improving the understanding of the biology of the epiligament tissue might further the development and fine-tuning of treatment modalities after ligament injuries.

Terminology

Epiligament: A connective tissue structure enveloping the ligaments and containing cells and blood vessels necessary for the nutrition and healing of the ligament; Endoligament: The ramifications of the epiligament within the ligament substance.

Peer-review

The content is clear and definite, level of structure is logical and accurate. The research method is scientific and reasonable. The article is well-written.

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ORIGINAL ARTICLE

Observational Study

Technical note: Anterior cruciate ligament reconstruction in the presence of an intramedullary femoral nail using anteromedial drilling

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Abstract

AIM

To describe an approach to anterior cruciate ligament (ACL) reconstruction using autologous hamstring by drilling *via* the anteromedial portal in the presence of an intramedullary (IM) femoral nail.

METHODS

Once preoperative imagining has characterized the proposed location of the femoral tunnel preparations are made to remove all of the hardware (locking bolts and IM nail). A diagnostic arthroscopy is performed in the usual fashion addressing all intra-articular pathology. The ACL remnant and lateral wall soft tissues are removed from the intercondylar, to provide adequate visualization of the ACL footprint. Femoral tunnel placement is performed using a transportal ACL guide with desired offset and the knee flexed to 2.09 rad. The Beath pin is placed through the guide starting at the ACL's anatomic footprint using arthroscopic visualization and/or fluoroscopic guidance. If resistance is met while placing the Beath pin, the arthroscopy should be discontinued and the obstructing hardware should be removed under fluoroscopic guidance. When the Beath pin is successfully placed through the lateral femur, it is overdrilled with a 4.5 mm Endobutton

drill. If the Endobutton drill is obstructed, the obstructing hardware should be removed under fluoroscopic guidance. In this case, the obstruction is more likely during Endobutton drilling due to its larger diameter and increased rigidity compared to the Beath pin. The femoral tunnel is then drilled using a best approximation of the graft's outer diameter. We recommend at least 7 mm diameter to minimize the risk of graft failure. Autologous hamstring grafts are generally between 6.8 and 8.6 mm in diameter. After reaming, the knee is flexed to 1.57 rad, the arthroscope placed through the anteromedial portal to confirm the femoral tunnel position, referencing the posterior wall and lateral cortex. For a quadrupled hamstring graft, the gracilis and semitendinosus tendons are then harvested in the standard fashion. The tendons are whip stitched, quadrupled and shaped to match the diameter of the prepared femoral tunnel. If the diameter of the patient's autologous hamstring graft is insufficient to fill the prepared femoral tunnel, the autograft may be supplemented with an allograft. The remainder of the reconstruction is performed according to surgeon preference.

RESULTS

The presence of retained hardware presents a challenge for surgeons treating patients with knee instability. In cruciate ligament reconstruction, distal femoral and proximal tibial implants hardware may confound tunnel placement, making removal of hardware necessary, unless techniques are adopted to allow for anatomic placement of the graft.

CONCLUSION

This report demonstrates how the femoral tunnel can be created using the anteromedial portal instead of a transtibial approach for reconstruction of the ACL.

Key words: Anteromedial drilling; Intramedullary femoral nail; Anterior cruciate ligament reconstruction; Retained hardware

Core tip: The presence of retained hardware presents a challenge for surgeons treating patients with knee instability. In anterior cruciate ligament (ACL) reconstruction, intramedullary (IM) nails may confound tunnel placement, making removal of hardware necessary, unless techniques are adopted to allow for anatomic placement of the graft. We strongly recommend delaying the ACL graft harvest until creation of the femoral tunnel has been successful in these settings. Although unlikely when using anteromedial portal drilling, if the IM rod needs to be removed for anatomic graft placement but cannot be removed, the ACL reconstruction may have to be delayed until this issue is addressed.

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INTRODUCTION

Anterior cruciate ligament (ACL) reconstruction offers patients with knee instability an excellent result following an isolated ACL rupture. However, because this injury often occurs in conjunction with lower extremity trauma, ACL reconstruction may follow surgical fixation of femur and/or tibia fractures[1-5]. When the hardware is located in the distal femur or proximal tibia, it may obstruct the normal placement of the tibial or femoral tunnels. Preoperative planning and intraoperative fluoroscopy can facilitate anatomic placement of the femoral tunnel using the anteromedial portal (AMP) rather than a transtibial (TT) approach in order to avoid removal of retained hardware. It has been shown that the use of AMP may be superior to the TT drilling technique in the setting of acute ACL reonstruction based on physical examination and patient reported outcomes; however these reported improvements have neither reached a minimally clinically important difference nor have been reported in the setting of a femoral fixation hardware[6]. In this technical note, we describe an approach to ACL reconstruction using autologous hamstring by drilling *via* the AMP in the presence of an intramedullary (IM) femoral nail.

MATERIALS AND METHODS

Surgical technique

Preoperative planning: Preoperative imaging including a computed tomography (CT) scan of the distal femur is reviewed to assess the proposed location of the femoral tunnel (Figure 1A and B). Preparations are made to remove all of the hardware (locking bolts and IM nail) by requesting proper instrumentation, personnel and imaging support. While this process confirms that drilling *via* the AMP should avoid the IM nail, we recommend preparing the femoral tunnel before harvesting the hamstring tendons and preparing the graft after femoral drilling has been successfully completed in cases where the size of the femoral tunnel is a concern. Finally, since the femoral tunnel is drilled before harvesting autologous hamstring graft, a cadaveric graft should be available in case the diameter of the harvested hamstrings is insufficient to fill the femoral tunnel.

Operative technique

A diagnostic arthroscopy is performed in the usual fashion. All intra-articular pathology, including meniscal tears and loose bodies, is addressed. The ACL remnant and lateral wall soft tissues are removed from the

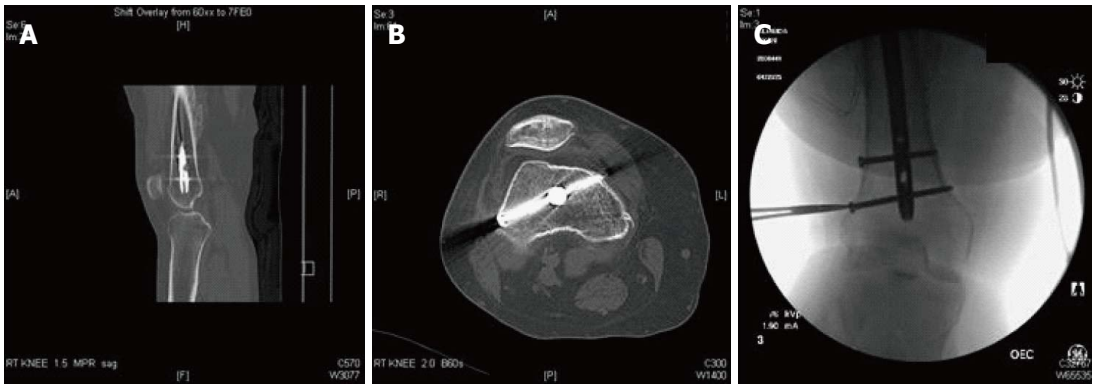

Figure 1 Preoperative imaging of femoral nail. A 380 mm × 11 mm Synthes trochanteric femoral nail was in place from prior and now well-healed femoral neck fracture. Two 5 mm diameter distal locking screws were used. The distal-most locking screw was placed in the distal femur approximately 20 mm superior to the trochlear notch and oriented from posterolateral to anteromedial, in close proximity to the posterlateral femoral cortex and planned femoral tunnel. A: Sagittal; B: Axial CT images; C: Intraoperative fluoroscopic radiograph. CT: Computed tomography.

intercondylar, to provide adequate visualization of the ACL footprint. Femoral tunnel placement is performed using a transportal ACL guide with desired offset (Arthrex, Naples, FL) and the knee flexed to 2.09 rad. The Beath pin is placed through the guide starting at the ACL's anatomic footprint using arthroscopic visualization and/or fluoroscopic guidance. If resistance is met while placing the Beath pin, the arthroscopy should be discontinued and the obstructing hardware should be removed under fluoroscopic guidance. When the Beath pin is successfully placed through the lateral femur, it is overdrilled with a 4.5 mm Endobutton drill (Smith and Nephew, Andover, MA). If the Endobutton drill is obstructed, the obstructing hardware should be removed under fluoroscopic guidance (Figure 1C). In this case, the obstruction is more likely during Endobutton drilling due to its larger diameter and increased rigidity compared to the Beath pin. The femoral tunnel is then drilled using a best approximation of the graft's outer diameter. We recommend at least 7 mm diameter to minimize the risk of graft failure[7]. Autologous hamstring grafts are generally between 6.8 and 8.6 mm in diameter[8]. After reaming, the knee is flexed to 1.57 rad, the arthroscope placed through the anteromedial portal to confirm the femoral tunnel position, referencing the posterior wall and lateral cortex.

For a quadrupled hamstring graft, the gracilis and semitendinosus tendons are then harvested in the standard fashion. The tendons are whip stitched, quadrupled and shaped to match the diameter of the prepared femoral tunnel. If the diameter of the patient's autologous hamstring graft is insufficient to fill the prepared femoral tunnel, the autograft may be supplemented with an allograft. The remainder of the reconstruction is performed according to surgeon preference (Figure 2).

RESULTS

We present a systematic approach to ACL reconstruction in the presence of distal femoral hardware using anteromedial portal femoral drilling followed by autologous hamstring harvest. Like several techniques of femoral tunneling, AMP drilling may provide improved rotation stability, decreased anterior translation and greater coverage of ACL's anatomic footprint compared to TT techniques, but there is little evidence to support a clinical difference[6,9-12]. To this end, clinical outcomes of TT and AMP drilling techniques for ACL reconstruction were directly appraised in a 2016 systematic literature review, however all outcomes suggesting superior result of AMP drilling technique failed to surpass a minimal clinically important difference despite notable improvements based on the physical exam and scoring system results[6].

DISCUSSION

In a biomechanical setting, Steiner *et al*[13] argued that single-bundle ACL reconstructions may be improved if grafts are centered in their anatomical insertions by an independent drilling method *vs* grafts placed by a conventional TT drilling method. The proposed advantage of AMP femoral drilling is the creation of an independent tunnel, which may be oriented to avoid existing hardware. This benefit, depending on the location of the hardware as obstruction, may be unattainable. Ideally, this difficulty would be determined during preoperative planning, as outlined in (Table 1), using CT imaging.

In this case, one distal locking screw was located approximately 2 cm superior to the intercondylar notch, adjacent to posterior femoral cortex and oriented from posterolateral to anteromedial (Figure 1). This screw had to be removed after an unsuccessful attempt at overdrilling the Beath pin (Figure 3). AMP drilling may allow the surgeon to minimize the amount of hardware removed. Because TT femoral drilling techniques result in a more vertically-oriented femoral tunnel that is closer to the midline in the coronal plane. Removal of multiple screws or the entire IM nail may have been necessary.

We strongly recommend delaying the hamstring harvest until creation of the femoral tunnel has been

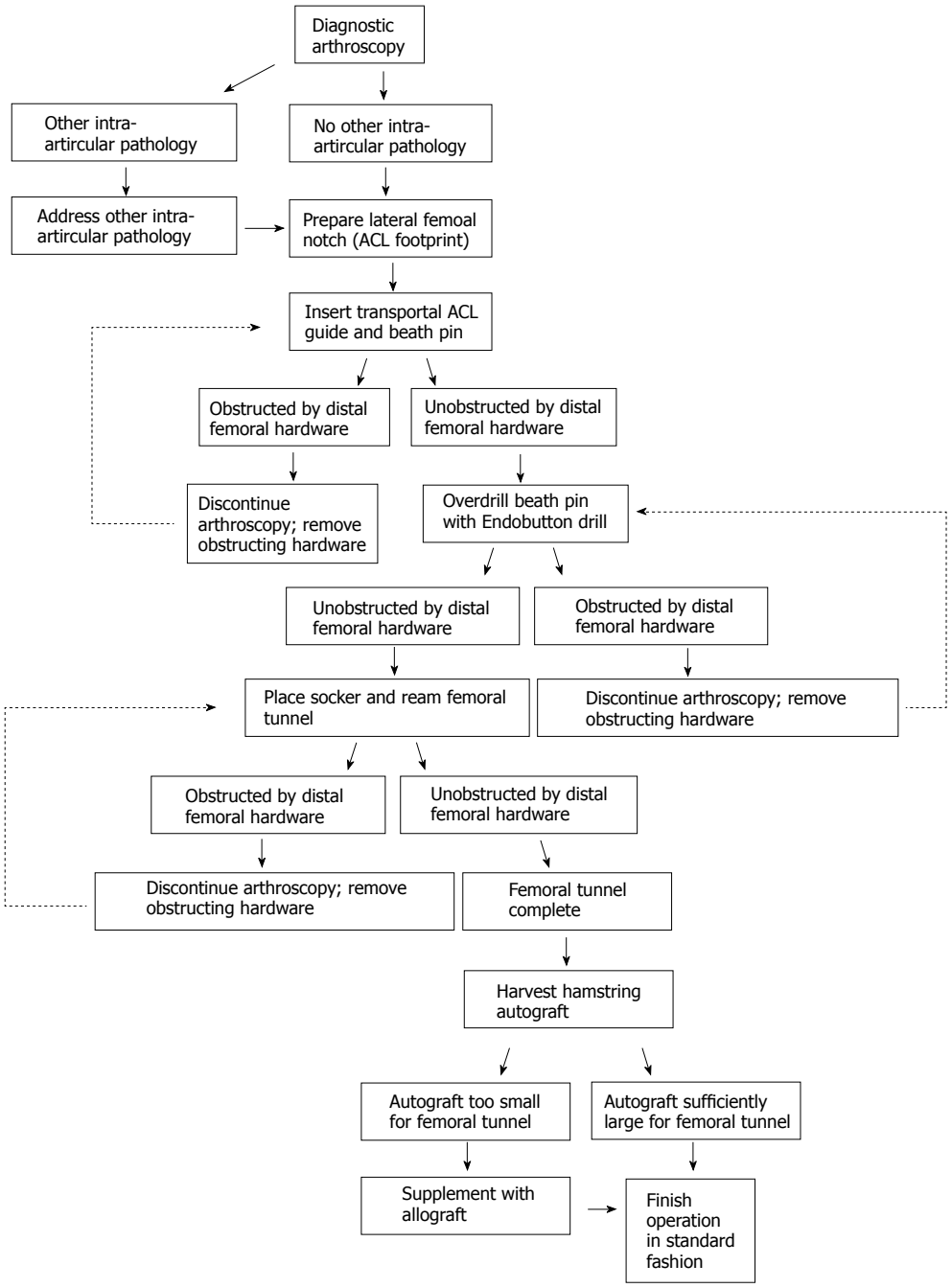

Figure 2 Algorithm for anterior cruciate ligament reconstruction with anteromedial portal femoral drilling and distal femoral hardware. Preoperative planning should guide femoral tunnel trajectory and size. Each step of femoral tunnel preparation may be performed under fluoroscopic guidance to avoid contact with existing hardware. Hardware obstruction is most likely to occur during Endobutton drilling. ACL: Anterior cruciate ligament.

Table 1 Preoperative planning for anterior cruciate ligament reconstruction with distal femoral hardware

Obtain and review radiographic studies including computed tomography scan of distal femur to determine location of hardware which may interfere with femoral tunnel placement
Discuss feasibility and necessity of hardware removal, considering location of individual components and entire construct relative to planned femoral tunnel site, with primary surgeon or consulting trauma surgeon
Arrange for proper instrumentation, fluoroscopy and personnel for removal of hardware
Arrange for access to allograft in case hamstring autograft is insufficient in diameter

successful. Although unlikely when using AMP drilling, if the retained hardware needs to be removed but this process is unsuccessful, the ACL reconstruction may have to be delayed until this issue is addressed.

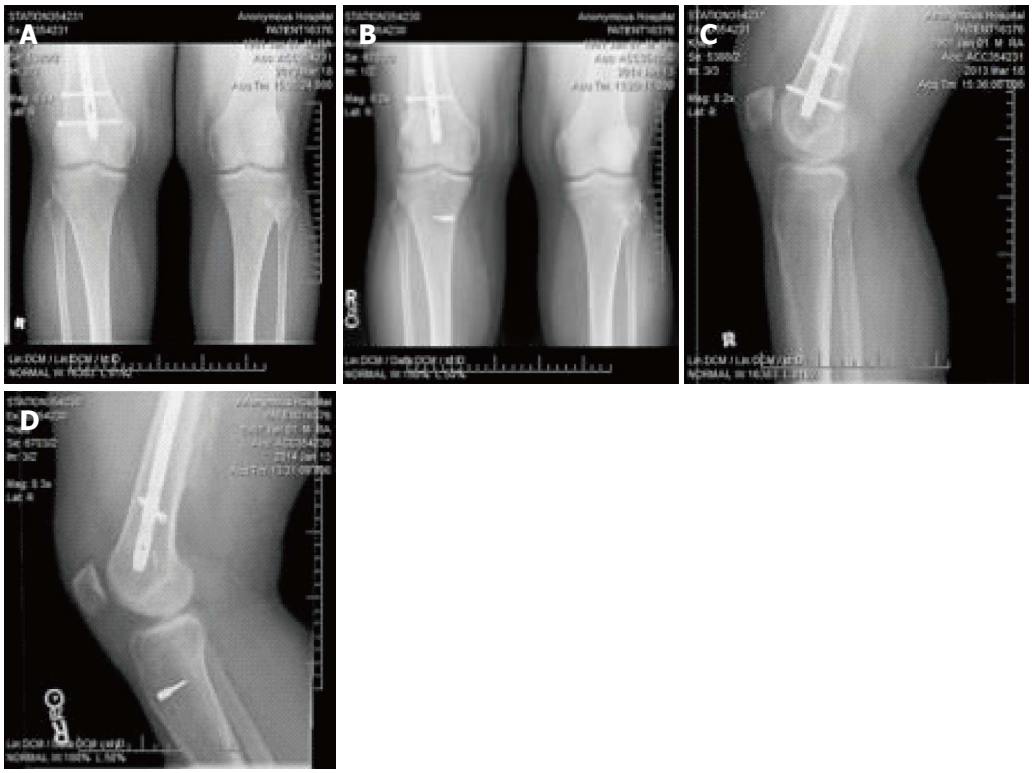

Figure 3 Preoperative and postoperative imaging of distal femoral hardware. Anterior cruciate ligament (ACL) reconstruction required removal of existing distal femoral locking screw located approximately 2 cm superior to the intercondylar notch adjacent to posterior femoral cortex and oriented from posterolateral to anteromedial. A: Preoperative Coronal X-ray; B: Postoperative Coronal X-ray; C: Preoperative Sagittal X-ray; D: Postoperative Sagittal X-ray.

COMMENTS

Background

Anterior cruciate ligament (ACL) reconstruction offers patients with knee instability an excellent result following an isolated ACL rupture. However, because this injury often occurs in conjunction with lower extremity trauma, ACL reconstruction may follow surgical fixation of femur and/or tibia fractures.

Research frontiers

When the hardware is located in the distal femur or proximal tibia, it may obstruct the normal placement of the tibial or femoral tunnels. Preoperative planning and intraoperative fluoroscopy can facilitate anatomic placement of the femoral tunnel using the anteromedial portal (AMP) rather than a transtibial (TT) approach in order to avoid removal of retained hardware.

Innovations and breakthroughs

It has been shown that the use of AMP was superior to the TT drilling technique in the setting of acute ACL reconstruction based on physical examination and patient reported outcomes, however this has not been reported in the setting of a femoral nail.

Applications

The authors strongly recommend delaying the hamstring harvest until creation of the femoral tunnel has been successful. Although unlikely when using AMP drilling, if the retained hardware needs to be removed but this process is unsuccessful, the ACL reconstruction may have to be delayed until this issue is addressed.

Peer-review

This is a short communication with a clear and useful message to other clinicians regarding the best approach to repair ACL injury whilst allowing correct positioning of other implant materials to repair local bone areas.

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ORIGINAL ARTICLE

Prospective Study

Functional outcome of tibial fracture with acute compartment syndrome and correlation to deep posterior compartment pressure

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Abstract

AIM

To measure single baseline deep posterior compartment pressure in tibial fracture complicated by acute compartment syndrome (ACS) and to correlate it with functional outcome.

METHODS

Thirty-two tibial fractures with ACS were evaluated clinically and the deep posterior compartment pressure was measured. Urgent fasciotomy was needed in 30 patients. Definite surgical fixation was performed either primarily or once fasciotomy wound was healthy. The patients were followed up at 3 mo, 6 mo and one year. At one year, the functional outcome [lower extremity functional scale (LEFS)] and complications were assessed.

RESULTS

Three limbs were amputated. In remaining 29 patients, the average times for clinical and radiological union were 25.2 ± 10.9 wk (10 to 54 wk) and 23.8 ± 9.2 wk (12 to 52 wk) respectively. Nine patients had delayed union and 2 had nonunion who needed bone grafting to augment healing. Most common complaint at follow up was ankle stiffness (76%) that caused difficulty in walking,

running and squatting. Of 21 patients who had paralysis at diagnosis, 13 (62%) did not recover and additional five patients developed paralysis at follow-up. On LEFS evaluation, there were 14 patients (48.3%) with severe disability, 10 patients (34.5%) with moderate disability and 5 patients (17.2%) with minimal disability. The mean pressures in patients with minimal disability, moderate disability and severe disability were 37.8, 48.4 and 58.79 mmHg respectively ($P < 0.001$).

CONCLUSION

ACS in tibial fractures causes severe functional disability in majority of patients. These patients are prone for delayed union and nonunion; however, long term disability is mainly because of severe soft tissue contracture. Intra-compartmental pressure (ICP) correlates with functional disability; patients with relatively high ICP are prone for poor functional outcome.

Key words: Compartment syndrome; Leg; Tibial fracture; Deep posterior compartment; Intracompartmental pressure; Functional outcome

Core tip: Anterior and deep posterior compartments are commonly involved in acute compartment syndrome (ACS) of leg after tibial fracture. Assessment of functional outcome in these patients and correlation with deep posterior compartment pressure has never been reported. This study revealed that ACS in tibial fractures causes severe functional disability and about 48% patients were severely disabled at one year. But this study did not find statistically significant relation between fracture union rate and deep compartment pressure value. The intra-compartmental pressure correlates with functional disability. Patients with relatively high pressure are prone for severe residual pain and poor functional outcome.

Goyal S, Naik MA, Tripathy SK, Rao SK. Functional outcome of tibial fracture with acute compartment syndrome and correlation to deep posterior compartment pressure. *World J Orthop* 2017; 8(5): 385-393 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i5/385.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i5.385

INTRODUCTION

Acute compartment syndrome (ACS) is an orthopedic emergency which is commonly noticed in leg bones and forearm bones fracture[1-7]. The reported incidence of ACS is around 3% to 10% following tibial fracture. Prompt diagnosis with early fasciotomy to decompress the tense compartment is crucial in preserving the life and limb of the patient in this grave situation[1-7].

Although a constellation of clinical signs and symptoms are taken into consideration for diagnosis of ACS, these are poorly predictive of compartment syndrome and are often difficult to assess in obtunded patients[2,5,6,8-11]. Measurement of the intra-compartmental pressure (ICP) offers an objective method to confirm the clinical suspicion of compartment syndrome. Various techniques for measurement of compartment syndrome are available in the literature and the most widely accepted threshold for surgical intervention is ICP within 30 mmHg of patient's diastolic blood pressure[12-20]. Adequate and timely fasciotomy is expected to provide good functional and cosmetic results. Delay in decompression of ACS can result in permanent neurological impairment, disabling muscle contractures and delay in fracture union causing severe functional disability[6,8,21-23]. The severity of disability and morbidity, even after fasciotomy in ACS, is dependent on several factors including ICP, time of fasciotomy, adequacy of fasciotomy and demographic profile of the patients[21-23]. Although it is established that anterior and deep posterior compartments are commonly involved in ACS of leg, researchers have used only anterior compartment pressure for diagnosis. Considering the superficial location of anterior compartment, a raised pressure within this compartment may be revealed clinically easily. This may not be true for deep posterior compartment and hence, Matsen *et al*[24] have warned the orthopaedic surgeons that isolated raised deep posterior compartment pressure may be missed in few patients.

This prospective study was designed to measure at least a single baseline deep posterior compartment pressure in patients of tibial fracture complicated by ACS and to correlate the raised pressures to the functional outcome.

MATERIALS AND METHODS

Patient recruitment

Between May 2010 and October 2012, a prospective study was conducted to evaluate the functional outcome of tibial fractures complicated with ACS. The study also aimed at correlating the outcome with initial deep posterior compartment pressure. Patients of > 18 years old with tibial fracture and clinical suspicion of ACS were recruited in this study after getting their written informed consent. Patients with associated ipsilateral limb injury, vascular injury (Doppler confirmed absent blood flow), poor general status (GCS $\leqslant$ 13, patients in shock (SBP < 90 mmHg or MAP < 70 mmHg), pathological fractures or pre-existing disease in the limb (prior surgery, neuromuscular disorders; polio, *etc.*) were excluded. Institutional ethical committee permission was obtained before recruiting patient in this study.

Patient evaluation

All patients were evaluated initially by an orthopedic surgeon. Demographic profiles and injury mechanisms were mentioned in a predesigned proforma. Appropriate

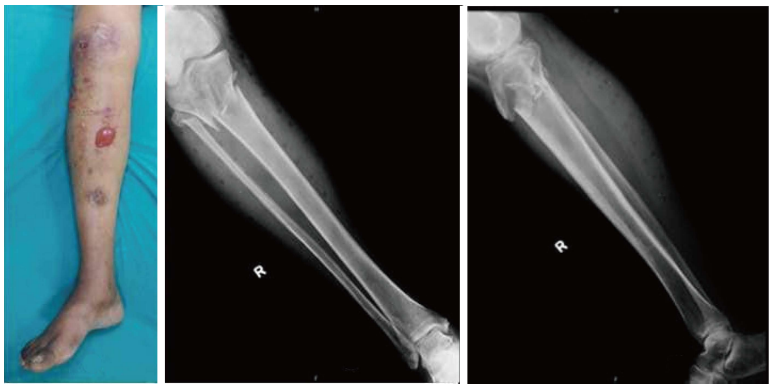

Figure 1 Clinical photograph and radiograph of a patient with right proximal tibial fracture and compartment syndrome.

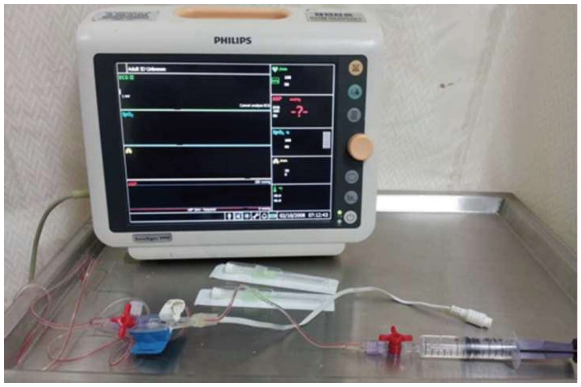

Figure 2 Equipment used for compartment pressure measurement; 18G *iv* cannula, saline filled line with electronic transducer and *Philips VM8* monitor.

radiographs were taken to assess the fracture pattern and classified as per OTA classification and Schatzker classification for proximal tibial fractures. Doppler was done to confirm that there was no vascular injury in these patients.

The patients were evaluated clinically for signs and symptoms of ACS by two attending orthopaedic surgeons. If there were any signs or symptoms of ACS, then the deep posterior compartment pressure of the injured leg was measured and documented. The diagnosis of ACS was established if there were at least 3 clinical signs/symptoms (Figure 1), a differential pressure (ΔP) of less than 30 mmHg between the diastolic and compartment pressures (McQueen and Court-Brown 1996) or a combination of both clinical and pressure indications. Fasciotomy was performed in patients diagnosed with ACS.

Technique for measuring the compartment pressure

The pressure in the limb was measured in the deep posterior compartment of leg using modified Whiteside's technique. The patient was positioned supine and limbs flat at rest on the bed. All measurements were made within 5 cm of the level of the fracture[25]. Under strict aseptic conditions a straight cannulated 18-gauge intravenous needle was inserted at an angle of approximately 45° relative to the skin surface skirting the posterior border of tibia to reach the posterior compartment. An arterial-line transducer (PHILIPS V-08) connected to a monitor was placed at the same level as the needle, saline flushed through the system to remove air, and the monitor was kept at zero. Half milliliter of normal saline was injected to allow the compartment to equilibrate with interstitial fluids. Measurement was recorded from the monitor after values were stabilized, usually within 20 to 30 s (Figure 2).

Clinical and functional outcome evaluation

The patients were followed up regularly at an interval of two weeks till the fasciotomy wound was healed. After that they were followed up at 3 mo, 6 mo and one year. Time of clinical (no pain at fracture site with full weight bearing) union and radiological union (bridging trabeculae at the fracture site) and complications encountered during post-operative period were recorded in the predesigned proforma. Fractures which did not unite till 6 mo' time were considered as delayed union and, if there was no progressive radiological evidence of union for further three consecutive months, it was considered as nonunion (> 9 mo since the time of injury). At the end of one year, the patients were examined particularly for any pain, toe deformity, ankle stiffness, residual paralysis of leg muscles, paraesthesia and limb contracture. Functional limitation of the patient to sit with 90° knee flexion, sitting cross-leg, squatting, walking, running and climbing stairs was evaluated on a Likert-Scale. Overall functional assessment of the limb was done using lower extremity functional scale (LEFS). LEFS score was calculated for each patient using questionnaire and percentage of disability calculated. The mean score was 51.03 (out of 80) corresponding to 63.78% of maximal function. The patients were categorized into five groups of disability based on their percentage of maximal function (LEFS/80 × 100): Bedbound - 0% to 20% score, crippled - 20% to 40% score, severe disability - 40% to 60% score, moderate disability - 60% to 80% score, minimal disability - 80% to 100% score).

Statistical analysis

Data was analyzed using commercial statistical package SPSS (Version 16, SPSS Inc, Chicago, IL) for MS-Windows. The data summary was presented in a descriptive fashion as mean, standard deviation, skewness and Kurtosis, *etc*. to describe the clinical characteristics and functional and

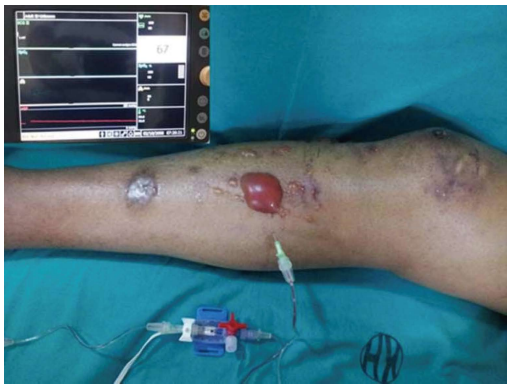

Figure 3 Deep posterior compartment pressure of 67 mmHg in the same patient (clinical photograph in Figure 1).

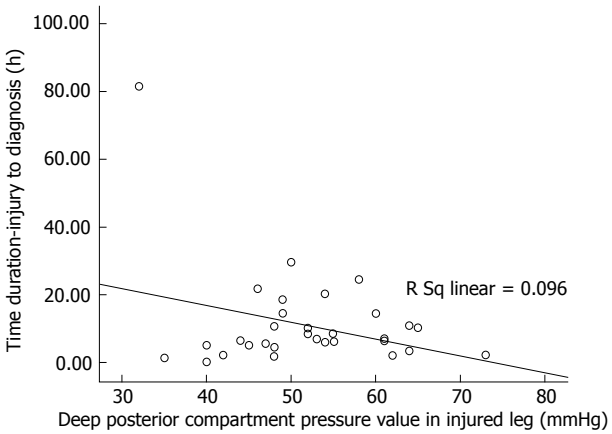

Figure 4 Correlation of time since injury to pressure values.

radiological outcome. The relationship of the radiological union and functional outcome were analyzed and related to the fracture pattern, delay in fasciotomy, pressure threshold and clinical diagnosis of ACS.

Differences between variables were analysed using Pearson's χ^2 test. The strength of association was carried out using Karl Pearson's or Spearman's rank correlation coefficient. Various comparisons were made either using independent *t*-test or analysis of variance (ANOVA). Difference was considered significant with a *P* value of < 0.05. The statistical review of this study was performed by a biomedical statistician before submission.

RESULTS

Six hundred and three patients with tibial fractures were treated during this period. Of which, 48 patients with ACS met the inclusion criteria; 6 did not consent to participate in the study and data of 10 patients were incomplete. Remaining 32 patients were evaluated to assess functional outcome of ACS of leg. The mean age of the patients was 40.3 years (range, 25 to 64 years). There were 30 males and 2 females. Only one patient presented to us after 72 h of injury and remaining patients presented to our service after an average delay of 9.0 h (median 6.75 h, range 0.25 to 29.5 h). There were 16 diaphyseal and 16 proximal tibial fractures in this study. Among proximal tibial fracture patients, 15 had tibial plateau fracture (10 Schatzker type Ⅵ, 3 Schatzker type Ⅴ, One type Ⅳ and one type Ⅰ) and only one had extra-articular fracture. There were six open fractures and all were Gustilo Anderson type Ⅰ injury.

Twenty-four patients (75%) had tense palpable swelling and 30 (93.75%) had pain on passive stretch. Paraesthesia and paralysis in the affected limb was noticed in 20 (62.5%) and 21 (65.63%) patients respectively. Three patients (9.38%) had pulselessness and only one patient (3.13%) had pallor in the leg. Clinical diagnosis (3 signs/symptoms) of ACS was established in 20 patients.

The mean ICP of deep posterior compartment of leg was 51.84 mmHg (range 32 to 73 mmHg). All patients had absolute ICP above 30 mmHg, and 26 (81%) patients had ICP above 45 mmHg (Figure 3). Mean differential pressure was (ΔP) 23.97 + 13.389; 25 patients (78.1%) had ΔP above 20 mmHg and 15 patients (46.9%) had ΔP above 30 mmHg. Twenty patients had at least 3 clinical signs/symptoms and diagnosed clinically. They all underwent fasciotomy. Twelve patients who did not fit the clinical criteria for ACS had ΔP within 30 mmHg of diastolic pressure, but only 10 patients underwent fasciotomy; among the other two patients, one patient had > 48 h delay and the other showed clinical improvement; hence fasciotomy was avoided in both patients. Both single and double incision fasciotomy was used in equal frequency (15 each).

In our set of patients, there was an asymmetrical distribution for the time delay; therefore we considered median value (5.00 h, mean 7.91 h) for analysis. Seven (21.86%) fractures were definitely fixed at the time of fasciotomy and remaining patients were temporarily stabilized using external fixator (12, 37.5%) or POP (13, 40.6%). Ultimately, three patients had to undergo amputation as a result of complication of ACS and remaining patients were treated with IM nailing (14, 48.3%), plate osteo-synthesis (13, 44.8%) or external fixator (2, 6.9%) as a method of fracture fixation.

Analysis of variables affecting pressure values

The effect of age on compartment pressure was analyzed by diving the patients into two groups (≥ 35 years and < 35 years). Patients < 35 years old had mean pressure of 52.33 mmHg compared to 51.25 mmHg in older age group (*P* = 0.777, independent sample *t*-test). The pressure values were also compared between the two age groups and it was found that older age patients were more within the diagnostic threshold for ACS, though again no statistical difference was seen. Gender, mechanism of injury, open/closed fracture and the site (diaphyseal or proximal tibia) of injury had no effect on pressure values (*P* > 0.05). We found that ICP was decreasing with the progression of time (Figure 4),

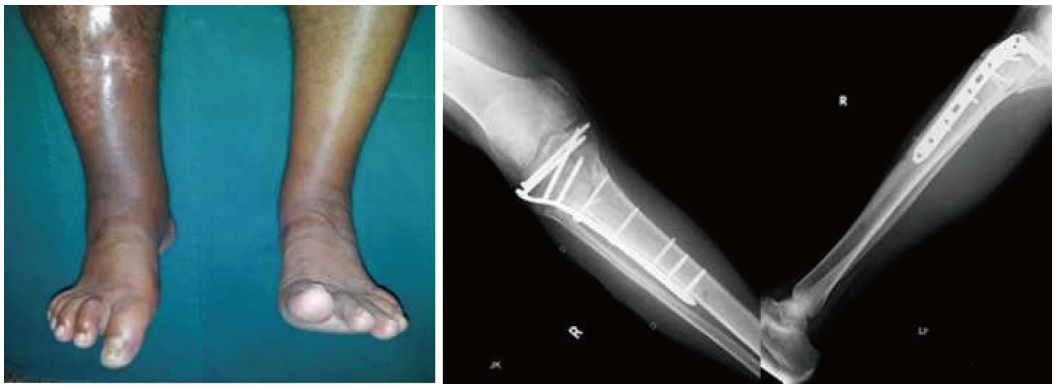

Figure 5 Residual right side toe deformity and ankle stiffness in a patient (shown in Figure 1) at follow up, X-ray of fracture union of this patient.

Table 1 Complications in tibial fracture patients with acute compartment syndrome (*n* = 29)

Complication	No. of patients (%)
Amputation (*n* = 32)	3 (9.4)
Infection (fasciotomy wound)	5 (17.2)
Toe deformities (*e.g.*, clawing)	8 (27.6)
Ankle stiffness (affecting function)	19 (76.0)
Residual paralysis (EHL/FHL/ankle DF/ankle PF)	18 (62.1)
Paraesthesia or nerve dysfunction	3 (10.3)
Limb contracture	5 (17.2)
Muscle herniation (fasciotomy site)	2 (6.9)
Pain (apart from fracture site)	15 (51.7)
Others (DVT, limb edema)	9 (31.0)

DVT: Deep vain thrombosis.

Table 2 Disability in tibial fracture patients with acute compartment syndrome (*n* = 29)

Function	No. of patients (%)	
(*n* = 29)	(None/mild)	(Moderate/severe)
Sitting 90°	27 (93.1)	2 (6.9)
Cross legged sitting	22 (75.9)	7 (24.1)
Squatting	17 (58.6)	12 (41.4)
Walking	24 (84.8)	5 (17.2)
Running	13 (48.8)	16 (55.2)
Stair climbing	19 (65.5)	10 (34.5)

contrary to the expectation, with pearson co-efficient -0.310; but it was not statistically significant (P = 0.084).

Functional outcome and complications

For follow up and outcome assessment, 3 patients who had to undergo amputation were not considered. Average follow up period was 93.1 wk (range 54 to 123 wk). Average time for clinical union was 25.2 ± 10.9 wk (ranging from 10 to 54 wk) and radiological union was 23.8 ± 9.2 wk (ranging 12 to 52 wk) (Figure 5). Nine patients had delayed union and 2 had nonunion who needed bone grafting to augment healing. Most common complaint at follow up was ankle stiffness (76%), which caused difficulty in walking, running and/or squatting (Tables 1 and 2, Figure 5). Out of 21 patients who had paralysis at diagnosis, 13 (62%) did not recover. Additional 5 patients developed paralysis at follow up even after fasciotomy (Table 1).

On LEFS evaluation, there were 14 patients (48.3%) with severe disability, 10 patients (34.5%) with moderate disability and 5 patients (17.2%) with minimal disability (Table 2).

Analysis of variables affecting functional outcome

Six out of 13 (46.2%) proximal tibial fractured patients and 5 out of 16 (31.2%) diaphyseal fractured patients had delayed union or nonunion, statistically no significant difference was observed between the type of fracture (P = 0.706). Eight patients with clinical ACS (3 signs/symptoms) and 3 patients without clinical ACS had delayed union or nonunion. Although it appears that patients diagnosed with clinical ACS had propensity to undergo delayed union or nonunion, there was no statistical difference (P = 0.332). The mean ICP in patients with normal union was 54.36 mmHg and it was 49.48 mmHg in patients with delayed union or nonunion (P = 0.214). So there was no effect of ICP on fracture union. Relatively high ICP was also noted in patients with residual disability and complications, but apart from persistent pain (P = 0.019), none of other group had statistically significant difference in pressures (Table 3).

Functional scores were expected to be poor in patients with higher pressure values. The mean LEFS score in our patients was 51 (63.75%) which corresponded to moderate disability. We found pressure values to be higher in patients with lower LEFS score, also there was a negative correlation between the same. Significant difference in pressure was found in LEFS groups (Figure 6). The mean pressures in patients with minimal disability (n = 5), moderate disability (n = 10) and severe disability (n = 13) were 37.8, 48.4 and 58.79 mmHg respectively (one way ANOVA, P < 0.001).

Thirty patients (30/32) had fasciotomy to decompress the compartment and 3 of these eventually ended up with amputation. We considered delay of more than 6 h to be significant and evaluated the outcome of patients. The average delay in fasciotomy was 9.8 h in patients who underwent amputation and 7.7 h in

Table 3 Mean pressure values (mmHg) in patients with complications (n = 29)

	Pain	Ankle/toe deformity	Residual paralysis	Running difficulty	Squatting difficulty
Yes	55.4 (15)	51.9 (18)	53.7 (18)	52.2 (16)	52.2 (12)
No	47.5 (14)	51.1 (11)	48.2 (11)	50.8 (13)	51.1 (17)
P value	0.019	0.827	0.125	0.753	0.702

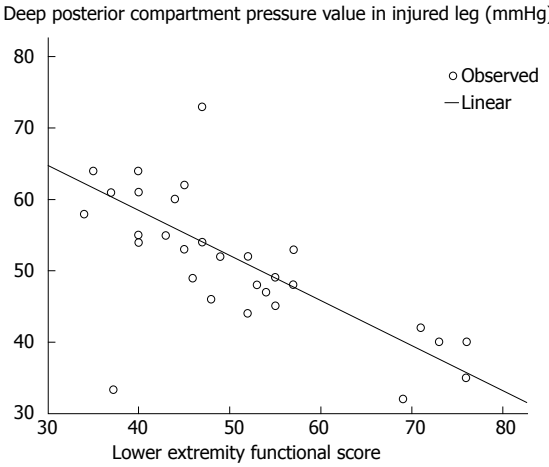

Figure 6 Negative correlation plot of lower extremity functional scale with rising pressure (Pearson's R = -0.814, *P* < 0.001).

patients who didn't end up with amputation; but, there was no statistically significant difference in these two groups (independent *t*-test, *P* = 0.564). There were 14 patients who were late for > 6 h in fasciotomy; 4 had good functional outcome (LEFS score > 60%) and 10 had poor outcome (LEFS score < 60% or amputation). Among remaining 16 patients who had fasciotomy done within 6 h, 9 patients had good functional outcome and 7 had poor outcome. Although it appears that delay in fasciotomy for more than 6 h effects the eventual functional outcome, it was not statistically significant in this study (Pearson's χ^2 = 2.330, *P* = 0.159). Both delay in fasciotomy and total time since injury showed negative relationship with LEFS with a slightly better correlation of time from injury to fasciotomy, but it was not statistically significant (Figure 7). No difference was found in single incision and double incision fasciotomy on LEFS outcome (*P* = 0.856).

DISCUSSION

ACS in tibial fracture is a serious complication and absence of prompt intervention can cause considerable morbidity or, even mortality[1-7]. Clinical judgment is based on subjective appraisal of the limb condition and there is a risk of missing the diagnosis or getting late. ICP of the anterior compartment has helped the surgeon in establishing the diagnosis. However, some reports have stressed on measurement of deep posterior compartment pressure as this compartment get involve equally or may involve in isolation[25]. In this study, we have evaluated the functional disability of the patient objectively and correlated it with deep posterior compartment pressure.

There are few limitations in this study. The number of patients was small and there was no control group. The technique of compartment measurement was not validated with a standard technique. Only single baseline deep compartment pressure was measured and it was correlated with functional outcome. Despite these limitations, this study has strength as it was based on prospective evaluation of patient and the measuring technique was reliable[26,27]. Several authors have reported that continuous pressure monitoring does not influence outcome in tibial fracture complicated with ACS[8,28-30]. Therefore, single deep posterior compartment pressure measurement was used as an adjunct to diagnosis and the effects of elevated pressure was evaluated. For clinical union, an ability to bear full weight without any pain at the fracture site was considered, however the residual effect of ACS may have some influence on the decision. Because of contracture some patients may have pain on weight bearing and that might have caused a longer clinical union (25 wk) time than the radiological union (24 wk).

Young males with high energy injuries of tibial shaft are prone for development of ACS[1,2,5]. But, we did not observe any statistically significant difference between proximal tibia and tibial shaft fractures. Also, patients < 35 years and older did not have any effect on ACS occurrence, this was because the mean age of our patients was 40 years and there was equal incidence of diaphyseal and proximal tibial fractures; majority (41%) of proximal tibial fractures were high impact injuries with severe comminution (OTA 41C1-3) and open fractures.

Systemic hypotension, vascular injuries and patients with decreased alertness pose difficulty in diagnosing compartment syndrome and interpretation of elevated pressure[6,31], therefore these patients were excluded. Diagnosis of ACS and the decision for fasciotomy was based on clinical judgement without any objective criteria. Ulmer proposed presence of 3 or more clinical symptoms to diagnose ACS[9]. Applying only these criteria, we would have diagnosed only 20 patients with diagnosis of compartment syndrome and missing the remaining patients. The patients usually have different threshold of pain, and clinical symptoms are also variable, thus we used pressure measurement to assess their risk of compartment syndrome. However, absolute ICP was not found to be diagnostic of ACS when considered alone. We found that applying the threshold of pressure difference from diastolic blood pressure (DBP) within 30 mmHg identified ACS in more than 75% cases. Using absolute ICP of 30 mmHg may result in overtreatment. Delta P within 20 mmHg of DBP would have resulted in

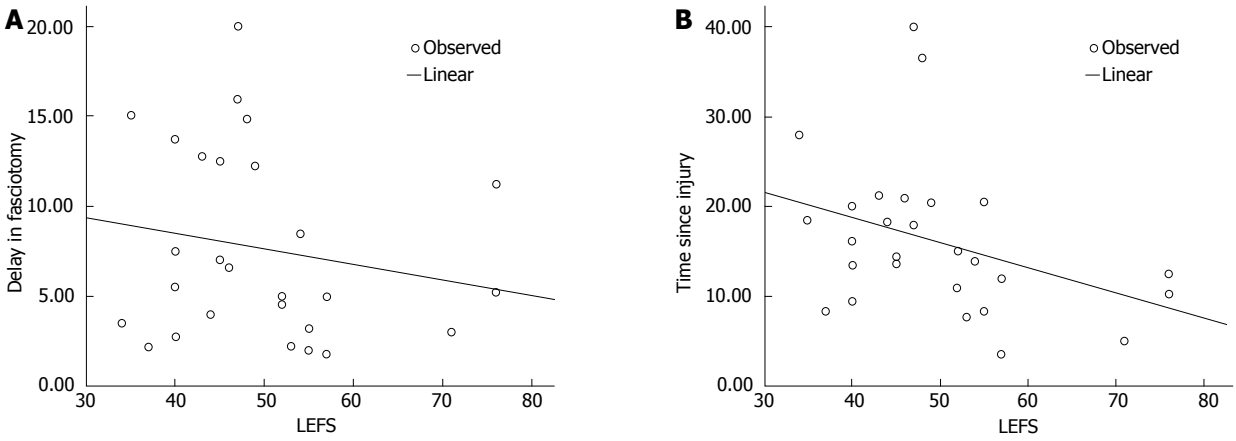

Figure 7 Correlation of (A) fasciotomy delay (Pearson's R= -0.182, *P* = 0.928) and (B) time since injury (Pearson's R = -0.369, *P* = 1.984) with lower extremity functional scale. LEFS: Lower extremity functional score.

missing 25%-70% patients of ACS. The duration of onset of compartment syndrome was not possible to predict from the time since injury in this study and we found decrease in compartmental pressure with progression of time. However, decreased LEFS score was found with the progression of time.

The long term functional outcome of ACS in tibial fractures can be evaluated on two broad aspects; first, the impact on fracture-healing and second about the impact on soft tissue leading to contracture. Increase in ICP compromises the perfusion of neuro-muscular tissues causing ischemia and cell death. Initial traumatic micro and macro muscle fibre damage, loss of haematoma from the fracture site because of fasciotomy, secondary neutrophilic microvascular dysfunction and reperfusion injury also contributes to the poor fracture healing, muscular contracture and persistent neuralgic pain[23,31,32]. We noticed 38% delayed or non-unions with a mean union time of 24 wk. A recent systematic review by Reverte *et al*[23], reported the mean time of tibial fracture union in ACS to be 31.7 wk and the incidence of delayed union and nonunion was 25% (in patients > 18 years). Other available literature reported the incidence of delayed union and nonunion to be 55%[22,23]. Our finding on fracture union is almost comparable to the available literature. Three factors such as fracture site, mode of diagnosis and ICP value were analysed to evaluate their effects on fracture healing. Although it seemed that proximal tibial fracture and clinically diagnosed ACS patients were at risk of delayed union and nonunion, it was statistically insignificant.

We found that the major long term functional disability of compartment syndrome is mainly because of soft tissue contracture. Ankle stiffness (76%) and toe deformities (62%) because of soft tissue contractures were the most common complications. Residual persistent pain was also seen in 55% of pain. The cause of pain in these patients may be multifactorial. Soft tissue contracture causes restriction of knee, ankle and toes movement and elicits pain on stretching or weight bearing. Ischemic damage of nerve fibre inducing neuralgic pain may also be contributory. Although a majority of patients were able to sit (with knee bending 90 degree and cross leg), climb stair and walk, there was difficulty in running and squatting. About 55% of patients were unable to run and 42% patients were unable to squat. A statistically significant correlation between persistent pain and raised ICP was noted, however none of the other sequelae/complications of ACS showed significant association.

The functional disability in ACS of leg has never been evaluated objectively. We found a severe functional disability in majority of patients because of residual disability as evaluated on LEFS. Fifty percent of patients had severe disability and 30% had moderate disability. More than 55% patients had LEFS score of less than 60% maximal functional capacity. We found lower LEFS scores had significant correlation with higher ICP (R = 0.814, $P < 0.001$). Outcome of ACS is most importantly determined by timing and adequate decompression of all the compartments. Both single and double incision fasciotomy have been proved to be effective. In our study also we did not find any difference in outcome of either surgical technique ($P > 0.05$). The average delay in fasciotomy in our study was 7.91 h which is higher than critical delay of 6 h and, this delay correlated with poor outcome scores; although not significantly ($P > 0.05$). We also noted that despite fasciotomy more than 50% patients still had poor outcome. This could be because of several reasons like, 40% of these had delay of more than 6 h, 3 patients ended up with amputation after fasciotomy. We also noted that the average time to diagnosis of ACS from the time of injury was about 9 h which could have contributed to significant tissue damage by the time ACS was diagnosed.

To conclude, ACS in tibial fractures leads to severe functional disability in majority of patients. These patients are prone for delayed union and nonunion; however, long term disability is mainly because of severe soft tissue contracture. ICP correlates with functional disability; patients with relatively high ICP are prone for poor functional outcome.

COMMENTS

Background

The intracompartmental pressure affects the union and functional capability of patients in tibial fracture complicated with acute compartment syndrome (ACS).

Research frontiers

Tibial fractures with compartment syndrome are prone for delayed union and nonunion. These patients usually suffer from functional disabilities because of soft tissue contracture, neuralgic pain and residual paralysis. There is no literature about correlation of deep posterior compartment pressure of leg and functional outcome in tibial fracture with ACS. An objective assessment of the disabilities in such patients is lacking.

Innovations and breakthroughs

The deep posterior compartment pressure of the leg was measured in patients with clinically diagnosed compartment syndrome after a tibial fracture using modified Whiteside's technique. The union rate, union time and functional disabilities in these patients were correlated to the pressure value. The average times for clinical and radiological union were 25 wk (10 to 54 wk) and 24 wk (12 to 52 wk) respectively. Thirty-eight percent patients had delayed union or nonunion. Most common complaint at follow up was ankle stiffness (76%) that caused difficulty in walking, running and squatting. On lower extremity functional scale evaluation, there were 48% patients with severe disability, 35% with moderate disability and 17% with minimal disability. The mean pressures in patients with minimal disability, moderate disability and severe disability were 37.8, 48.4 and 58.79 mmHg respectively.

Applications

Compartment syndrome in tibial fractures leads to severe functional disability in majority of patients. These patients are prone for delayed union and nonunion; however, long term disability is mainly because of severe soft tissue contracture. The deep posterior compartment pressure correlates with functional disability; patients with relatively high pressure are prone for poor functional outcome.

Peer-review

The authors evaluated patients with tibia fracture and compartment syndrome. The authors found the correlation between compartment pressure and the functional disability. The article is well-written.

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ORIGINAL ARTICLE

Randomized Clinical Trial

Frozen shoulder - A prospective randomized clinical trial

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Author contributions: Mukherjee RN, Nag HL and Mittal R planned and conducted this study; Pandey RM helped with the biostatistics for this study; Mukherjee RN and Mittal R wrote this article.

Institutional review board statement: The ethics committee of All India Institute of Medical Sciences, New Delhi, approved the study.

Informed consent statement: All the patients were informed about the study before including them in the study. The informed consent was explained to them in their native language and a written consent was obtained as advised by the ethic committee of our institute. The identity of any of the patients was not disclosed.

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Abstract

AIM

To compare the results of arthroscopic capsular release with intra-articular steroid injections in patients of frozen shoulder.

METHODS

Fifty-six patients with frozen shoulder were randomised to one of two treatment groups: Group 1, complete 360 degree arthroscopic capsular release and group 2, intra-articular corticosteroid injection (40 mg methyl prednisolone acetate). Both groups were put on active and passive range of motion exercises following the intervention. The outcome parameters were visual analogue scale (VAS) score for pain, range of motion and Constant score which were measured at baseline, 4, 8, 12, 16 and 20 wk after intervention.

RESULTS

All the parameters improved in both the groups. The mean VAS score improved significantly more in the group 1 as compared to group 2 at 8 wk. This greater improvement was maintained at 20 wk with *P* value of 0.007 at 8 wk, 0.006 at 12 wk, 0.006 at 16 wk and 0.019 at 20 wk. The Constant score showed a more significant improvement in group 1 compared to group 2 at 4 wk, which was again maintained at 20 wk with *P* value of 0.01 at 4, 8, 12 and 16 wk. The gain in abduction movement was statistically significantly more in arthroscopy group with *P* value of 0.001 at 4, 8, 12, 16 wk and 0.005 at 20 wk. The gain in external rotation was statistically significantly more in arthroscopy group with *P* value of 0.007 at 4 wk, 0.001 at 8, 12, and 16 wk and 0.003 at 20 wk. There was no statistically significant difference in

extension and internal rotation between the two groups at any time.

CONCLUSION
Arthroscopic capsular release provides subjective and objective improvement earlier than intra-articular steroid injection.

Key words: Adhesive capsulitis; Frozen shoulder; Capsular release; Corticosteroid; Idiopathic stiff shoulder; Intra articular injection; Steroid injection; Arthroscopic arthrolysis; Constant score

Core tip: The treatment of frozen shoulder is selected depending on the preference of the treating physician, since there are no guidelines or protocols. The physicians, physiotherapists, occupational therapists and orthopedicians who are not trained in shoulder arthroscopy often select non-surgical methods. On the other hand, shoulder arthroscopists prefer arthroscopic arthrolysis. We conducted a randomised clinical trial to compare the results of arthroscopic arthrolysis and intra-articular steroid injection in frozen shoulder. Both modalities resulted in significant improvement in pain, range of motion and Constant score. However the improvement in surgery group preceded those in injection group by 4-8 wk.

Mukherjee RN, Pandey RM, Nag HL, Mittal R. Frozen shoulder - A prospective randomized clinical trial. *World J Orthop* 2017; 8(5): 394-399 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i5/394.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i5.394

INTRODUCTION

Frozen shoulder also termed as adhesive capsulitis of shoulder, is a common cause of shoulder pain and global stiffness of the glenohumeral joint. It is estimated to affect 2%-5% of the population[1]. Frozen shoulder has been described as a self-limiting condition, lasting on average 2-3 years[2-4]. Some studies, however, have reported that 20%-50% of the sufferers continue to have pain and restricted movement beyond 3 years[5,6]. Though it is a self-limiting condition, patients find it impractical and difficult to wait for such a long period as it interferes with the activities of daily life.

A variety of treatment strategies for adhesive capsulitis have been developed to alleviate pain and enhance range of motion (ROM) of the shoulder. The commonest modalities to achieve this are physiotherapy[7] and corticosteroid injections[8] either through local injection or systemically. Other options include manipulation under general anaesthesia[9-11], scalene block, arthrographic capsular distension[12-14] and surgical intervention (arthroscopic and open arthrolysis).

Arthroscopic capsular release for the treatment of adhesive capsulitis has gained popularity for its high safety and efficacy reported in literature[15-18]. Our study aims to compare the results of arthroscopic capsular release with those of intra-articular corticosteroid injection[19-21] which seems to be the most commonly prescribed treatment for adhesive capsulitis of shoulder at present, and ascertain whether arthroscopic capsular release can provide a speedier recovery compared to the more commonly prescribed intra-articular steroid injections. Our null hypothesis was that the two modalities would provide equal outcomes.

MATERIALS AND METHODS

Patient selection

The criteria to include patients in this study were idiopathic stiffness of the shoulder with global restriction of shoulder movements for at least six months and normal findings on plain radiograph. Global restrictions would imply decrease in active and passive movements in all directions. Patients with prior history of trauma, surgery or injections to the shoulder were excluded from the study. Patients who had received any form of treatment to the affected shoulder other than physiotherapy were also excluded.

Patients

Sample size was calculated using Master 2.0 software. All the patients were explained about the study in their native language and a written consent was obtained before enrolment in the study. Sixty such patients were randomly allocated to one of the two study groups using computer tables. The patient inclusion and dropouts from the study groups is described in the consort diagram (Figure 1). In group 1, complete 360-degree arthroscopic capsular release of the affected shoulder was performed under general anaesthesia in lateral position in 28 patients. These patients underwent pre-operative magnetic resonance imaging (MRI) examination to rule out any intra-articular pathology. Arthroscopic capsular release involved excising the tissues in the rotator interval up to the coracoids process, division of the superior, middle and inferior glenohumeral ligaments and release of the anterior, posterior, superior and inferior capsule of the shoulder joint. Subacromial bursa was not viewed. In group 2, single dose of 40 mg methylprednisolone acetate along with 3 mL of 2% lignocaine was injected into the affected shoulder without image guidance through the posterior approach in 28 patients. The intervention in the both study groups was followed by active and passive range of motion exercises. Both groups of patients were given a combination of a NSAID with tramadol as analgesics for pain control.

Outcome measures

The clinical outcome measures used in the study were: Visual analogue scale (VAS) score for pain (0-10), range of motion and Constant score (0-100). The parameters were initially recorded before the intervention (baseline) and then after the intervention at 4, 8, 12, 16 and 20

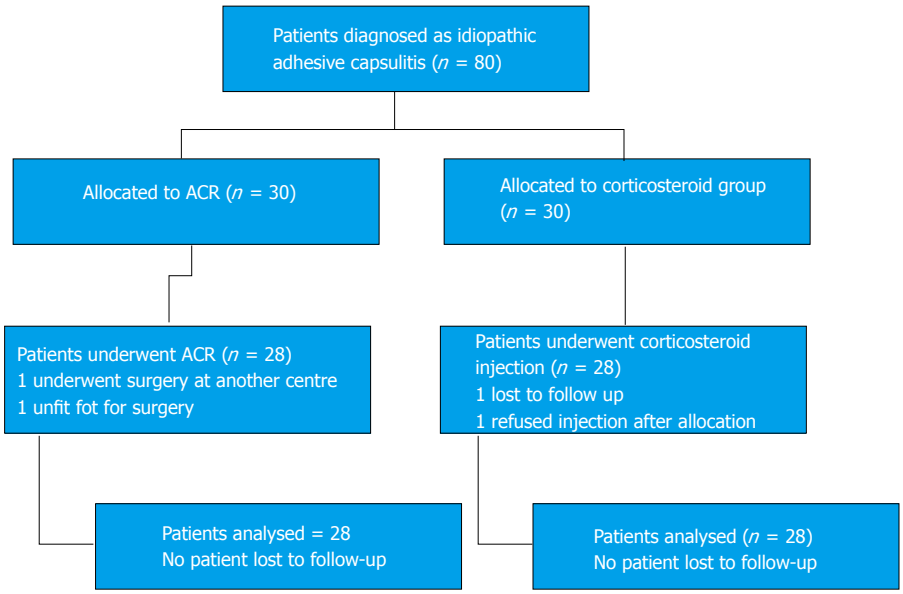

Figure 1 Consort diagram.

wk. The outcome parameters in both the study groups were compared with each other. Any complications encountered in the study were also noted.

Arthroscopic findings

Twenty-seven out of the 28 patients who underwent arthroscopic capsular release showed fibrous contracture of the rotator interval, suggesting that it is the most important pathology associated with the development of adhesive capsulitis. Synovitis was present in all the patients. Twenty-four patients had global synovitis involving the rotator interval, the joint capsule, subscapularis tendon and the rotator cuff and 4 patients had synovitis limited only to the rotator interval. Apart from the above findings, which are suggestive of adhesive capsulitis, 4 patients had partial tear of the rotator cuff on the articular side and 1 patient had a type 2 superior labrum anterior to posterior (SLAP) lesion, which were not diagnosed preoperatively. These lesions were not detected on pre-operative MRI also. The partial cuff tears were debrided and SLAP was left as such. These 4 patients were not excluded from the study because the intra-articular lesions were not symptomatic, but were incidental findings. The arthroscopic group did not experience any post-operative infection or neurovascular damage. There was one case of articular cartilage scuffing of glenoid and one case of the humeral head.

Statistical analysis

Statistical analysis was carried out using SPSS software version 20. Data was presented as number (%) or mean ± SD as appropriate. The baseline characteristics were compared using χ^2 test (categorical variables) and Student's *t* test (continuous variables). The outcome parameters such as VAS, range of motion and Constant score measures at baseline, 4, 8, 12, 16 and 20 wk were compared between the two groups using Student's *t* test. The change in outcome parameters within each group was detected using a general linear model. *P* value of < 0.05 was considered statistically significant.

Table 1 Changes in visual analogue scale scores in both groups

Duration	VAS score in group (mean ± SD)		*P* value
	ACR	Corticosteroid	
Baseline	7.1 ± 1.8	7.1 ± 1.8	1
4 wk	4.4 ± 1.6	5.1 ± 1.7	0.101
8 wk	3.6 ± 1.7	4.8 ± 1.7	0.007
12 wk	3.0 ± 1.6	4.2 ± 1.6	0.006
16 wk	2.5 ± 1.8	3.7 ± 1.5	0.006
20 wk	2.0 ± 1.7	3.2 ± 1.5	0.019

VAS: Visual analogue scale.

RESULTS

Demography

The mean age of the patients included in the study was 50.4 ± 9.0 years (capsular release group, 48.1 ± 9.6 years, and corticosteroid group, 52.6 ± 7.9 years). Out of the 56 patients in the study, 23 patients were male and 33 patients were female with 18 male patients in the capsular release group and 15 male patients in the corticosteroid group. Twenty-four patients had involvement of the dominant side and 32 patients had involvement of the non-dominant (17 patients in the capsular release group involving the non-dominant and 15 patients in the corticosteroid group involving the non-dominant side). The condition most commonly associated with adhesive capsulitis in the study was diabetes mellitus. Sixteen patients out of the 56 patients recruited in the study had diabetes mellitus. The age, sex, shoulder affected and the patients with diabetes mellitus were similarly distributed in the two groups. The average duration of symptoms was 6.3 mo (6.5-9.5 mo).

Clinical parameters

VAS score: The mean VAS score showed significant

Table 2 Change in range motion in both groups

Movement type	Study group	Movement in degrees (mean ± SD)					
		Baseline	4 wk	8 wk	12 wk	16 wk	20 wk
Forward flexion	ACR	99.8 ± 13.4	133.3 ± 19.1	140.1 ± 18.6	145.5 ± 17.4	151.2 ± 16.4	152.9 ± 14.6
	Corticosteroid	100.8 ± 16.7	118.9 ± 17.4	126.4 ± 16.9	132.5 ± 17.3	138.9 ± 17.6	143.9 ± 16.6
	P value	0.79	0.005	0.006	0.007	0.009	0.05
Extension	ACR	34.1 ± 7.5	42.6 ± 8.1	45.0 ± 7.6	48.0 ± 6.8	49.8 ± 7.0	50.6 ± 7.2
	Corticosteroid	34.4 ± 7.4	41.6 ± 6.3	43.7 ± 5.3	46.7 ± 6.1	49.2 ± 5.5	50.0 ± 5.4
	P value	0.86	0.58	0.48	0.47	0.53	0.68
Abduction	ACR	78.3 ± 13.2	113.2 ± 20.4	121.6 ± 21.8	127.6 ± 21.3	131.9 ± 19.8	135.6 ± 18.5
	Corticosteroid	78.0 ± 18.8	94.6 ± 20.2	100.0 ± 22.4	107.5 ± 21.2	109.2 ± 26.9	118.3 ± 22.0
	P value	0.93	0.001	0.001	0.001	0.001	0.005
Adduction	ACR	28.0 ± 5.6	37.3 ± 6.1	39.1 ± 5.9	41.7 ± 5.1	43.9 ± 5.5	45.9 ± 5.0
	Corticosteroid	28.7 ± 6.3	33.2 ± 5.4	35.8 ± 5.9	38.2 ± 6.6	41.2 ± 5.5	43.0 ± 5.8
	P value	0.65	0.01	0.04	0.02	0.07	0.07
Internal rotation	ACR	28.9 ± 6.4	39.8 ± 8.4	42.5 ± 8.9	44.8 ± 9.1	48.3 ± 9.0	50.4 ± 7.5
	Corticosteroid	32.6 ± 8.3	38.7 ± 6.7	41.0 ± 5.6	44.2 ± 6.1	46.4 ± 4.6	47.8 ± 5.5
	P value	0.06	0.6	0.47	0.79	0.31	0.16
External rotation	ACR	39.1 ± 6.2	56.4 ± 11.4	61.4 ± 12.9	65.7 ± 13.2	69.8 ± 12.7	73.4 ± 14.2
	Corticosteroid	42.6 ± 8.2	49.1 ± 7.7	51.4 ± 8.9	54.8 ± 8.2	59.2 ± 8.8	62.6 ± 9.9
	P value	0.07	0.007	0.001	0.001	0.001	0.003

Table 3 Changes in Constant score in both groups

Duration	Constant score in group (mean ± SD)		*P* value
	ACR	Corticosteroid	
Baseline	29.5 ± 6.2	30.4 ± 8.3	0.64
4 wk	50.3 ± 10.7	43.4 ± 9.5	0.01
8 wk	56.0 ± 11.9	47.6 ± 10.3	0.01
12 wk	61.0 ± 12.3	53.0 ± 9.9	0.01
16 wk	66.5 ± 13.0	58.4 ± 11.2	0.01
20 wk	70.2 ± 12.1	62.6 ± 11.6	0.03

improvement at baseline, and at 4, 8, 12, 16 and 20 wk in both groups. The improvement in VAS was statistically significant in the capsular release group at 8, 12, 16 and 20 wk as compared to injection group (Table 1).

Range of motion: All the movement measured in the study, *i.e.*, forward flexion, extension, abduction, adduction, external rotation and internal rotation, showed significant improvement in both groups during the follow-up at 4, 8, 12, 16 and 20 wk (Table 2). Forward flexion, abduction and external rotation showed a statistically significant improvement in the capsular release group as compared to that in the injection group and the improvement was maintained till the end of 20 wk.

Constant score: The Constant score showed significant improvement at each follow-up in both groups. However, improvement was more significant in the surgical release group than in the injection group. No difference was found in the change of clinical parameters between the patients with and without diabetes mellitus in either groups (Table 3).

DISCUSSION

Despite the wide variety of treatment options available and the amount of research done, the results still appear to be inconclusive about the effectiveness of different interventions for adhesive capsulitis. There is no definitive guideline as to when to change from one treatment modality to another. But it is generally acceptable to wait for 3 mo before declaring any conservative treatment ineffective. Physiotherapy and intra-articular injections of corticosteroids continue to be the commonest mode of treatment for this condition. Injections into shoulder joint is most frequently administered without any image guidance in general practice even though multiple studies have shown that even in expert hands, a large number of injections may be out of the joint. In order to replicate the general practice, no image guidance was performed during the injections in this study. Arthroscopic capsular release has shown to provide early relief of symptoms[22] and is increasingly being performed for the treatment of adhesive capsulitis of shoulder.

Baums *et al*[17], Smith *et al*[18] and Le Lievre *et al*[23] have demonstrated a significant early improvement in pain, range of motion and overall shoulder function following arthroscopic capsular release. In the Indian population, similar results have been shown by Sabat and Kumar[22]. Jerosch *et al*[24], Warner *et al*[25], Ogilvie-Harris *et al*[26] have shown the safety and effectiveness of arthroscopic capsular release for the treatment of adhesive capsulitis of shoulder. However, we could only find one study by De Carli *et al*[27] which compared arthroscopic capsular release with intra articular corticosteroid injections. The results of our study are in agreement with those by De Carli *et al*[27] in which arthroscopic capsular release resulted in an early relief of pain and increased shoulder range of motion.

Our study showed continuous improvement in all parameters in both the groups and it stared as early as 4 wk after the intervention. The scores of different parameters in the injection group at 20 wk were achi-

eved 4-8 wk earlier in the surgery group. In contrast to the Constant score which showed significant difference between the two groups as early as 4 wk, the VAS score for pain showed significant difference between the two groups in the 8th week. The initial period of pain following surgery could be the possible reason for this slightly delayed significant improvement in VAS score in the arthroscopic group. Extension and internal rotation of the shoulder were the only two parameters where there was no significant difference between the two groups.

Our study had some notable strengths. These include a strict inclusion and exclusion criteria, random allocation of the patients to both study groups and a frequent follow-up at a 4-wk interval. The limitations of our study included the lack of a control group, a relatively small sample size, short-term follow-up of only 20 wk and lack of blinding in the study.

In conclusion, our null hypothesis was proved wrong as both the modalities of treatment give good clinical improvement both subjectively and objectively but arthroscopic capsular release can give improvement earlier as compared to intra- articular steroid injections. However, intra-articular corticosteroids injection is a much less invasive and cheaper option and continues to be an effective modality to alleviate the symptoms in patients with adhesive capsulitis of shoulder. Hence we conclude that intra-articular steroids should be more routinely recommended as the first-line therapy for treatment of idiopathic adhesive capsulitis of shoulder. Arthroscopic capsular release may be recommended as a first-line treatment to patients who do not wish to wait for the results of intra-articular steroid injections. It may also be used for the failures of conservative treatment.

COMMENTS

Background

Frozen shoulder is a common condition and many treatment options are available, but with no clear guidelines. This study compares the outcomes of the two very common methods of treatment - injection steroid (non-surgical method) and arthroscopic arthrolysis (surgical method).

Research frontiers

Researchers are trying to make an animal model mimicking frozen shoulder. Many recent studies have evaluated non-operative methods of treatment and quality of life in patients with frozen shoulder.

Innovations and breakthroughs

The study emphasizes that injection of a steroid in the shoulder without any image guidance gives significant relief in frozen shoulder. This is the situation in most of the actual clinical settings. It improves pain and range of motion, which are the main problems in frozen shoulder. It dispels the belief that image guidance is a must for the intra-articular injection. It also re-establishes the findings of De Carli *et al* that arthroscopic arthrolysis yields outcomes similar to steroid injection but they occur 2 wk earlier.

Application

The fact that the benefits of arthroscopic arthrolysis precede those of injection of steroid by 4 to 8 wk, may help in selection of treatment modalities depending on the patient profile. This may also be the baseline for future researches.

Peer-review

It is an interesting research.

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SYSTEMATIC REVIEWS

Predicting lower limb periprosthetic joint infections: A review of risk factors and their classification

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Author contributions: George DA and Romano CL designed the research; George DA, Scarponi S, Gallazzi E and Romano CL performed the research; Drago L and Haddad FS contributed to the results analysis and discussion; George DA, Scarponi S and Gallazzi E analyzed the data; George DA wrote the paper; Drago L, Haddad FS and Romano CL edited the paper.

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Abstract

AIM

To undertook a systematic review to determine factors that increase a patient's risk of developing lower limb periprosthetic joint infections (PJI).

METHODS

This systematic review included full-text studies that reviewed risk factors of developing either a hip or knee PJI following a primary arthroplasty published from January 1998 to November 2016. A variety of keywords were used to identify studies through international databases referencing hip arthroplasty, knee arthroplasty, infection, and risk factors. Studies were only included if they included greater than 20 patients in their study cohort, and there was clear documentation of the statistical parameter used; specifically *P*-value, hazard ratio, relative risk, or/and odds ratio (OR). Furthermore a quality assessment criteria for the individual studies was undertaken to evaluate the presence of record and reporting bias.

RESULTS

Twenty-seven original studies reviewing risk factors relating to primary total hip and knee arthroplasty infections were included. Four studies (14.8%) reviewed PJI of the hip, 3 (11.21%) of the knee, and 20 (74.1%) reviewed both joints. Nineteen studies (70.4%) were retrospective and 8 (29.6%) prospective. Record bias was identified in the majority of studies (66.7%). The definition of PJI varied amongst the studies but there was a general consensus to define infection by previously validated methods. The most significant risks were the use of preoperative high dose steroids (OR = 21.0, 95%CI: 3.5-127.2, $P < 0.001$), a BMI above 50 (OR = 18.3, $P < 0.001$), tobacco use (OR = 12.76, 95%CI: 2.47-66.16, *P*

= 0.017), body mass index below 20 (OR = 6.00, 95%CI: 1.2-30.9, *P* = 0.033), diabetes (OR = 5.47, 95%CI: 1.77-16.97, *P* = 0.003), and coronary artery disease (OR = 5.10, 95%CI: 1.3-19.8, *P* = 0.017).

CONCLUSION

We have highlighted the need for the provider to optimise modifiable risk factors, and develop strategies to limit the impact of non-modifiable factors.

Key words: Periprosthetic joint infection; Risk factor; Predictive; Hip arthroplasty; Knee arthroplasty

Core tip: This systematic review determines the most statistically significant factors that increase a patient's risk of developing lower limb periprosthetic joint infections. Reviewing all relevant papers until November 2016 through international databases, we have included 27 original studies. The results include multiple factors relating to the patient and the Institute, as well as post-operative predictors and causes of infection. This ultimately reiterates the importance of optimising the patients pre-operatively by addressing modifiable risk factors (such as their immunosuppression, nutrition, diabetes, and smoking), and develops strategies to limit the impact of non-modifiable factors.

George DA, Drago L, Scarponi S, Gallazzi E, Haddad FS, Romano CL. Predicting lower limb periprosthetic joint infections: A review of risk factors and their classification. *World J Orthop* 2017; 8(5): 400-411 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i5/400.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i5.400

INTRODUCTION

Chronic periprosthetic joint infections (PJI) have received increasing interest in the medical literature as the profession has acknowledged the real-life implications to the patient and the health service[1,2]. The treatment of PJI is costly to the health service with strain upon limited resources as multiple operations and trials of antibiotic therapy may be attempted. But the cost to the patient is greatest, with loss or reduced joint function, deterioration in their physical and psychological health, and loss in trust with the profession.

Prevention is key. Despite improved outcomes following the various treatment modalities for treating established infections today, the patient has to endure the consequences of the infection[3]. Prior to the initial surgery it is imperative the patient is medically optimised and any reversible risk factors be corrected. Such risk factors are well known such as diabetes[4], systemic infections[5], and immunocompromise[6].

However, risk factors vary and are dependent upon the patient cohort, and often findings from isolated studies are not transferable. Therefore, we undertook a systematic review of the literature to determine overall predictive factors that increase a patient's risk of developing a lower limb PJI, and determine which risk factors are most predictive of infection.

In this review, we categorised risk factors in order to better understand the relative role of the host, of the healthcare provider, and of post-surgical conditions, the latter acting more as prognostic factors since the surgical procedure has already taken place. To this aim, we have subdivided known risk factors for PJI in three groups: (1) those relating to the host (host-related risk factors); (2) those that are related to the treatment provider and to the surgical environment (provider-related risk factors); and (3) those that arise from clinical interventions, increasing the patient's inherent risk (post-surgical risk factors). We have then compared the absolute number of risk factors in each main category, scored them according to their relative weight and divided in "modifiable" and "non-modifiable" risk factors.

MATERIALS AND METHODS

This systematic review included full-text studies that reviewed risk factors of developing either a hip or knee PJI following a primary arthroplasty published from January 1998 to November 2016. These were identified through international databases, such as EMBASE, PubMed/MEDLINE, MEDLINE Daily Update, MEDLINE In-Process, Google Scholar, SCOPUS, CINAHL, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.

A variety of keywords were used either alone or in combinations to identify the studies. This included references to hip infections (total hip replacement; THR; periprosthetic hip infection, hip arthroplasty infection), knee infections (total knee replacement; TKR; periprosthetic knee infection, knee arthroplasty infection), general joint infections (PJI, PPI), and "risk factors". We did not use specific keywords to search for individual risk factors, such as diabetes, *etc*.

Studies were only included if the risk factors were calculated by involving greater than 20 patients in their study cohort, and there was clear documentation of the statistical parameter used, and were only included if the P-value was quoted and one or more of the following; hazard ratio (HR), relative risk (RR), or/and odds ratio. Studies were excluded if they referred to recurrent infection following a revision procedure, hip or knee fracture, and a risk factor was excluded if the *P*-value was greater than 0.05. Results from combined studies, as seen in meta-analysis, were also excluded.

Two investigators, DAG and CLR, independently searched and reviewed the literature and determined if the study should be included based on their title and abstract. Once the two lists were compared, if the same material was presented in more than one study, only the most recent one was included.

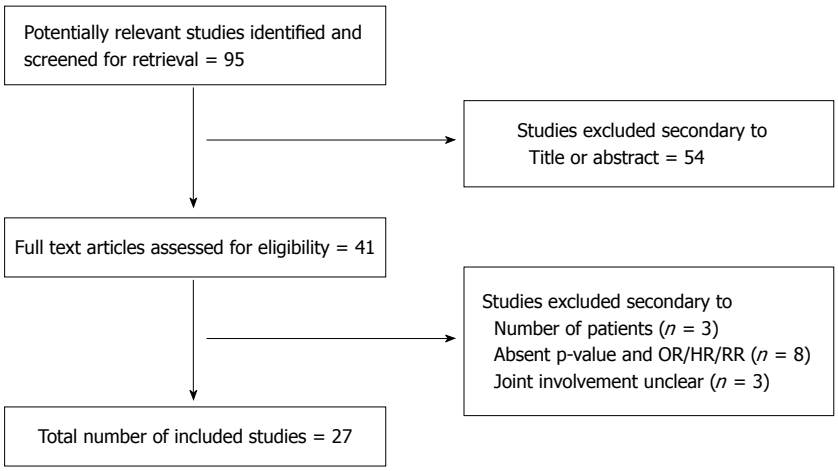

Figure 1 Flowchart summarizing the results of the literature search. RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 1 Study characteristics including number of patients, statistical method used, site (hip, knee or both), and duration of patient follow-up

Ref.	Year	Patients (*n*)			Statistical method used	Site	Follow-up (mo)		
		Infected (cases)	Non-infected (controls)	Total			Min	Max	Mean
Berbari *et al*[9]	1998	462	462	924	OR, CI, *P*	Both	-	-	-
Lai *et al*[10]	2007	51	-	-	OR, CI, *P*	Both	-	84	-
Parvizi *et al*[11]	2007	78	156	234	OR, CI, *P*	Both	-	-	-
Pulido *et al*[12]	2008	63	9182	9245	HR, CI, *P*	Both	12	72	43
Malinzak *et al*[13]	2009	43	8451	8494	OR, *P*	Both	24	192	74.4
Ong *et al*[14]	2009	887	39042	39929	OR, *P*	Hip	-	108	-
Berbari *et al*[5]	2010	339	339	678	OR, CI, *P*	Both	-	-	-
Peel *et al*[15]	2011	63	126	189	OR, CI, *P*	Both	-	-	-
Bozic *et al*[16]	2012	-	-	40919	HR, CI, *P*	Hip	12	-	-
Jämsen *et al*[17]	2012	52	7129	7181	HR, CI, *P*	Both	0	12	12
Bozic *et al*[4]	2012	-	-	83011	OR, CI, *P*	Knee	12	-	-
Dale *et al*[18]	2012	2778	429390	432168	RR, CI, *P*	Hip	0	60	60
Greenky *et al*[19]	2012	389	15333	15722	OR, CI, *P*	Both	36	108	62.4
Namba *et al*[20]	2013	404	55812	56216	HR, CI, *P*	Knee	-	-	-
Somayaji *et al*[21]	2013	5	254	259	OR, CI, *P*	Both	12	124	24
Coelho-Prabhu *et al*[22]	2013	339	339	678	OR, CI, *P*	Both	2	24	-
Maoz *et al*[23]	2014	47	3625	3672	OR, CI, *P*	Hip	12	48	24
Gómez-Lesmes *et al*[24]	2014	32	1299	1331	OR, CI, *P*	Knee	-	3	-
Yi *et al*[25]	2014	126	375	501	OR, CI, *P*	Both	3	-	-
Wu *et al*[26]	2014	45	252	297	OR, CI, *P*	Both	12	144	28
Sousa *et al*[27]	2014	43	2454	2497	OR, CI, *P*	Both	1	12	12
Jiang *et al*[28]	2014	-	-	306946	HR, *P*	Hip	6	-	-
	2014	-	-	573840	HR, *P*	Knee	6	-	-
Duchman *et al*[29]	2015	8062+	70129+	78191	OR, CI, *P*	Both	-	-	-
Chrastil *et al*[30]	2015	-	-	13272	HR, CI, *P*	Both	24	120	-
Crowe *et al*[31]	2015	26	3393	3419	OR, CI, *P*	Both	-	12	-
Debreuve-Theresette *et al*[32]	2015	45	90		OR, CI, *P*	Both	-	-	-
Bohl *et al*[33]	2015	-	-	49603	RR, CI, *P*	Both	-	1	-

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

The quality assessment criteria for the inclusion of the individual studies was adapted from George *et al*[7]. to reflect the information we expect to be present in each study. Therefore we evaluated the presence of (1) record bias reflecting the source of data, and whether the analysis was retrospective or prospective; and (2) reporting bias; each study's definition of PJI (the measured outcome).

Figure 1 demonstrates the overall selection process according to the Prisma model[8]. DAG, CLR, SS and EG compared the overall findings and any discrepancies were solved by reclassification as mutually agreed.

RESULTS

Included studies

In all, 27 original studies reviewing risk factors relating to primary total hip and knee arthroplasty infections were included. The number of risk factors identified ranged from 1 to 18. Four studies (14.8%) reviewed PJI on the hip, 3 (11.21%) on the knee, and 20 (74.1%) reviewed both joints. The statistical methods used to determine significance are also shown in Table 1[4,5,9-33].

The quality of the included studies is demonstrated in Table 2. Nineteen studies (70.4%) were retrospective

Table 2 Paper quality, defined by presence of record and reporting bias

Ref.	Design	Record bias	Reporting bias (outcome measure); definition of infection
Berbari *et al*[9]	Retrospective	No	2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint
Lai *et al*[10]	Retrospective	No	2 or more cultural examination positive for the same microorganism; clinical diagnosis
Parvizi *et al*[11]	Prospective	No	Criteria based upon 3 of 5 features[1]
Pulido *et al*[12]	Retrospective	Yes	Criteria based upon 3 of 5 features[1]
Malinzak *et al*[13]	Retrospective	No	Unknown
Ong *et al*[14]	Retrospective	Yes	Diagnostic code in Medicare database
Berbari *et al*[5]	Prospective	Yes	2 or more cultural examination positive for the same microorganism; acute inflammation on histopathological examination; sinus tract; purulence around the prosthesis/joint
Peel *et al*[15]	Prospective	Yes	Criteria based upon 3 of 5 features[1]
Bozic *et al*[16]	Retrospective	Yes	Diagnostic code in Medicare database
Jämsen *et al*[17]	Prospective	Yes	CDC definition of surgical site infection[3]
[1]Bozic *et al*[4]	Retrospective	Yes	Diagnostic code in Medicare database
Dale *et al*[18]	Retrospective	Yes	Clinical as reported by the surgeon after surgery
Greenky *et al*[19]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Namba *et al*[20]	Retrospective	Yes	CDC definition of surgical site infection[3]
Somayaji *et al*[21]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Coelho-Prabhu *et al*[22]	Retrospective	Yes	2 or more cultural examination positive for the same microorganism; sinus tract; purulence around the prosthesis/joint
Maoz *et al*[23]	Retrospective	Yes	CDC definition of surgical site infection[3]
Gómez-Lesmes *et al*[24]	Prospective	Yes	Criteria based upon 3 of 5 features[1]
Yi *et al*[25]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Wu *et al*[26]	Retrospective	Yes	MSIS definition[2]
Sousa *et al*[27]	Retrospective	No	Criteria based upon 3 of 5 features[1]
Jiang *et al*[28]	Prospective	Yes	Diagnostic code in Medicare database
Duchman *et al*[29]	Prospective	Yes	Criteria based upon 3 of 5 features[1]
Chrastil *et al*[30]	Retrospective	Yes	Diagnostic code in Medicare database
Crowe *et al*[31]	Retrospective	Yes	CDC definition of surgical site infection[3]
Debreuve-Theresette *et al*[32]	Retrospective	No	CDC definition of surgical site infection[3]
Bohl *et al*[33]	Prospective	Yes	American College of Surgeons National Surgical Quality Improvement Program definition

[1]Refers to 3 of 5 of the following criteria: (1) abnormal serology (ESR > 30 mm/h; CRP > 1 mg/dL); (2) strong clinical and radiographic suspicion for infection; (3) positive joint aspiration culture for infection; (4) evidence of purulence during the subsequent surgical intervention; and (5) positive intraoperative culture; [2]Musculoskeletal Infection Society (MSIS) definition; [3]Defined as (1) deep infection; (2) purulent drainage; (3) dehiscence; (4) fever; and (5) localized pain. CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

and 8 (29.6%) prospective. Record bias was identified in the majority of studies (66.7%). The definition of PJI varied amongst the studies but there was a general consensus to define infection by previously validated methods.

This included the presence of 2 or more cultural positive results for the same microorganism (plus other features on infection) in 4 studies (14.8%), the CDC definition in 5 studies (18.5%), the Medicare code for infection in 5 studies (18.5%), and 9 studies (33.3%) based their definition on patients meeting 3 of the following 5 features; (1) abnormal serology (ESR > 30 mm/h; CRP > 1 mg/dL); (2) strong clinical and radiographic suspicion for infection; (3) positive joint aspiration culture for infection; (4) evidence of purulence during the subsequent surgical intervention; and (5) positive intraoperative culture.

One study used the MSIS criteria, which includes: (1) a sinus tract; (2) positive culture results from 2 or more tissue or fluid samples; and (3) 4 of the following 6 criteria are present: (Ⅰ) elevated CRP/ESR; (Ⅱ) elevated synovial WCC; (Ⅲ) high synovial PMN leukocyte percentage; (Ⅳ) presence of purulence in the joint; (Ⅴ) positive culture result from one sample from the affected joint; and (Ⅵ) PMN leukocyte count of more than 5 per high-powered field in 5 high-powered fields on histologic analysis at 400 × magnification[34].

Host-related risk factors

Risk factors relating to the host have been shown in Table 3, and are the most abundant group of risk factors identified. The majority of the risk factors are systemic referring to patient co-morbidities that are negatively associated with patient outcome following a primary THR or TKR, such as presence of diabetes mellitus[4,9,17,20,26], immunocompromised[5,15,21], concomitttent systemic infection[5,10,27,31], cardiology[4,16,21] and gastroenterology disorders[22,28], high ASA (American Society of Anesthesiologists) grade[12,15,20] and mal-nutrition[13,17,21,23,25,26,33].

Patient demographics also have been shown to have an impact upon risk of PJI, including age[16], rural residence[16], race[20], male gender[14,18,20,31], and alcohol[26] or tobacco use[23,29,31,32]. Previous operations to the joint (excluding revisions arthroplasty as this was excluded from analysis) increased the risk of PJI[5,32].

Table 3 Host-related risk factors

	Ref.	Statistical parameter					Site
		HR	OR	RR	95%CI	*P* value	
General							
Age: 65-75 yr (compared to 45-65)	[26]		3.36		1.30-8.69	0.013	Hip/knee
Comorbidities (total number)	[10]		1.35		1.10-1.66	0.005	Hip/knee
Charlson index + 5 (compared to 0)	[14]		2.57		1.96-3.37	< 0.001	Hip
Place of residence (rural)	[26]		2.63		1.13-6.10	0.025	Hip/knee
Hispanic race (compared to White)	[20]	0.69			0.49-0.98	0.038	Knee
Alcohol abuse	[26]		2.95		1.06-8.23	0.039	Hip/knee
Tobacco use	[29]		1.47		1.21-1.78	0.001	Hip/knee
	[31]		3.4		1.23-9.44	0.029	Hip/knee
	[32]	3.91	3.4		1.19-12.84	0.032	Hip/knee
Tobacco use (S aureus colonization)	[23]		12.76		2.47-66.16	0.017	Hip
Gender							
Female	[14]		0.83			0.009	Hip
Male	[18]			1.9	1.80-2.10	< 0.001	Hip
	[20]	1.89			1.54-2.32	< 0.001	Knee
	[31]		3.55		1.60-7.84	0.002	
Endocrine disorders							
Diabetes mellitus	[4]		1.19		1.06-1.34	0.0025	Knee
	[26]		5.47		1.77-16.97	0.003	Hip/knee
	[22]	1.46			1.27-1.68	0.0007	Hip
	[9]		4		1.13-14.18	0.032	Hip/knee
	[20]	1.28			1.03-1.60	0.025	Knee
	[17]	2.31			1.12-4.72	< 0.001	Hip/knee
	[15]		1.4		0.90-2.10	0.06	Hip/knee
	[5]		1.8		1.20-2.80	0.006	Hip/knee
	[13]		3.1			0.02	Hip/knee
	[44]		2.21		1.34-3.64	0.001	Knee
Pre-op BM > 6.9 mmol/L	[17]	2.25			0.60-8.50	0.073	Hip/knee
Pre-operative hyperglycemia	[30]	1.44			1.09-1.89	0.008	Hip/knee
Psychiatric disorders							
Depression	[4]		1.28		1.08-1.51	0.0035	Knee
	[16]	1.6			1.32-1.93	0.0039	Hip
Psychosis	[16]	1.74			1.38-2.20	0.0044	Hip
	[4]		1.26		1.02-1.57	0.0331	Knee
Haematological disorders							
Preoperative anaemia	[16]	1.36			1.15-1.62	0.0005	Hip
	[19]		1.95		1.41-2.69	< 0.001	Hip/knee
	[4]		1.26		1.09-1.45	0.0014	Knee
Coagulopathy	[16]	1.58			1.24-2.01	0.0002	Hip
Malignancy							
Metastatic malignancy	[4]		1.59		1.03-2.47	0.0369	Knee
Tumour 5 yr before implant	[5]		3.1		1.30-7.20	< 0.01	Hip/knee
Cardiovascular disorders							
Congestive heart failure	[4]		1.28		1.13-1.46	< 0.0001	Knee
	[16]	1.57			1.33-1.84	0.0409	Hip
Cardiac arrhythmia	[16]	1.48			1.30-1.70	0.0012	Hip
Coronary artery disease	[21]		5.10		1.30-19.8	0.017	Hip/knee
Valvular disease	[4]		1.15		1.01-1.31	0.039	Knee
Peripheral vascular disease	[4]		1.13		1.01-1.27	0.0381	Knee
	[16]	1.44			1.24-1.68	0.0032	Hip
Gastroenterology disorders							
Liver cirrhosis	[28]	5.4				< 0.001	Hip
	[28]	3.4				< 0.001	Knee
Hepatitis B virus (amongst males)	[44]		4.32		1.85-10.09	< 0.001	Knee
OGD with biopsy	[22]		2.8		1.10-7.10	0.03	Hip/knee
Respiratory disorders							
Chronic pulmonary disease	[4]		1.22		1.10-1.36	< 0.0001	Knee
	[31]		4.34		1.28-14.70	0.041	Both
Pulmonary circulation disorders	[4]		1.42		1.06-1.91	0.0205	Knee
Renal disorders							
Renal disease	[4]		1.38		1.11-1.71	0.0038	Knee
Renal function (mL/min)	[15]		1		0.90-1.00	0.05	Hip
Rheumatoid arthritis							
Rheumatoid arthritis	[15]		3.3		0.80-13.90	0.09	Hip/knee
	[4]		1.18		1.02-1.37	0.0277	Knee
	[16]	1.71			1.42-2.06	< 0.0001	Hip

ASA grade						
ASA score	[15]		2.2	1.30-4.00	0.006	Hip/knee
Mean score	[11]		2.07	1.08-1.97	0.03	Hip/knee
3 (compared to 1 or 2)	[20]	1.65		1.33-2.00	< 0.001	Knee
> 4	[12]	1.95		1.00-3.70	0.04	Hip/knee
Body mass index						
Obesity	[4]		1.22	1.03-1.44	0.0219	Knee
	[16]	1.73		1.35-2.22	< 0.0001	Hip
BMI (kg/m^2)	[15]		1.1	1.00-1.10	0.05	Hip
	[12]	3.23		1.60-6.50	0.001	Hip/knee
< 20	[21]		6	1.20-30.9	0.033	Hip/knee
25-30	[5]		0.4	0.30-0.70	< 0.001	Hip/knee
⩾ 28 (compared to 18.5-28)	[26]		2.77	1.20-6.40	0.017	Hip/knee
31-39	[5]		0.5	0.30-0.70	< 0.001	Hip/knee
35 (compared to < 35)	[20]	1.47		1.17-1.85	0.001	Knee
	[32]	1.84		1.11-3.05	0.007	Both
> 40	[23]		4.13	1.30-12.88	0.01	Hip
	[13]		3.3		0.045	Knee
	[17]	6.41		1.67-24.59	< 0.001	Hip/knee
> 50	[13]		18.3		< 0.001	Hip/knee
Malnutrition	[25]		2.3	1.50-3.50	< 0.001	Hip/knee
Serum albumin < 3.5 g/dL	[33]		2	1.50-2.80	< 0.001	Hip/knee
Immunocompromise						
Immunocompromise	[5]		2.2	1.60-3.00	< 0.001	Hip/knee
Inflammatory disease	[18]		1.4	1.10-1.70	0.001	Hip
Prednisone dose exceeds 15 mg/d	[21]		21	3.50-127.2	< 0.001	Hip/knee
Systemic steroid therapy	[15]		3.3	0.80-13.90	0.09	Hip/knee
Infection						
Distant organ infection	[5]		2.2	1.50-3.25	< 0.001	Hip/knee
Nasal *S. Aureus* Infection	[31]		3.95	1.80-8.71	< 0.001	Hip/knee
Nasal MRSA Infection	[31]		8.24	3.23-21.02	< 0.001	Hip/knee
Asymptomatic bacteriuria	[27]		3.23	1.67-6.27	0.001	Hip/knee
Genitourinary infection	[10]		2.8	1.01-7.77	0.048	Hip/knee
Operative indication						
Hip fracture	[18]		2.1	1.90-2.40	< 0.001	Hip
Post-traumatic osteoarthritis	[20]	3.23		1.68-6.23	< 0.001	Knee
Prior operation on the index joint	[5]		1.9	1.30-2.60	< 0.001	Hip/knee
Per additional surgery	[32]		2.88	1.45-5.80	0.018	Hip/knee
Avascular necrosis	[18]		1.7	1.40-2.10	< 0.001	Hip

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Provider-related risk factors

Risk factors relating to the provider are shown in Table 4. Prolonged operative duration of greater than 115 minutes in hip arthroplasty is a strong predictor of infection[5,14,23], as is non-same day surgery[23]. During knee arthroplasty, exposure to the joint requiring quadriceps release significantly increases the risks of infection[20].

Protective measures include the use of antibiotic surgical prophylaxis systemically[5] and locally as irrigation[20], but antibiotic impregnated cement may or may not be protective[18,20]. In addition, bilateral procedures during the same operation have been shown by some studies to increase the risk[12], whilst in others decrease it[20].

Post-surgical risk factors

Post-operatively patients may present with a superficial infection to the joint with a warm, cellulitic, and sometimes discharging wound, which is a high predictor of an underlying PJI[5,11,9,15]. Table 5 demonstrates other factors that have a high correlation with a PJI, including receiving a blood transfusion[11,12,15] (especially if the blood has been stored for greater than 14 d[24]), post-operative urinary tract infection (UTI)[5,12], and onset of cardiac arrhythmias[12].

Risk factor impact

Several risk factors were shown to have greater significance than others, and a vast majority of the risk factors were directly related to the patient (host-factors). The most significant risks were the use of preoperative high dose steroids (OR = 21.0, 95%CI: 3.5-127.2, $P < 0.001$)[21], a BMI above 50 (OR = 18.3, $P < 0.001$)[13], tobacco use (OR = 12.76, 95%CI: 2.47-66.16, $P = 0.017$)[23], BMI below 20 (OR = 6.00, 95%CI: 1.2-30.9, $P = 0.033$)[21], diabetes (OR = 5.47, 95%CI: 1.77-16.97, $P = 0.003$)[26], and coronary artery disease (OR = 5.10, 95%CI: 1.3-19.8, $P = 0.017$)[21].

Modifiable risk factors

We further categorised the resultant risk factors into whether or not they were modifiable, reflecting the opportunity of the surgeon to optimise their patient preoperatively and to reduce the risk of developing a PJI (Table 6).

DISCUSSION

It is extremely difficult to predict if a patient will develop a

Table 4 Provider-related risk factors

	Ref.	Statistical parameter					Site
		HR	OR	RR	95%CI	*P* value	
Antibiotic use							
Antibiotic surgical prophylaxis	[5]		0.5		0.30-0.80	0.003	Hip/knee
Antibiotic irrigation	[20]	0.67			0.48-0.92	0.014	Knee
Surgical technique							
Exposure requiring quadriceps release	[20]	4.76			1.18-19.21	0.029	Knee
Use of wound drain tube	[15]		0.09		0.01-0.80	0.03	Knee
Side of surgery							
Simultaneous bilateral surgery	[12]	5.85			2.50-13.90	< 0.0001	Hip/knee
	[20]	0.51			0.31-0.83	0.007	Knee
Single side (compared to bilateral)	[13]		3.1			0.0024	Hip/knee
	[13]		4			0.009	Knee
Cement							
Antibiotic-laden cement	[20]	1.53			1.18-1.98	< 0.001	Knee
Non-antibiotic cement	[8]			1.5	1.30-1.80	< 0.001	Hip
Hybrid (compared to uncemented)	[8]			1.6	1.40-1.80	< 0.001	Hip
Operative duration							
Length of operation (> 115 min)	[23]		3.38		1.23-9.28	0.018	Hip
(> 210 min)	[14]		1.78		1.40-2.26	< 0.0001	Hip
(≥ 240 min)	[5]		2.7		1.50- 5.00	0.002	Hip/knee
Hospital factors							
Hospital volume < 100 (*vs* > 200/yr)	[20]	0.33			0.12-0.90	0.03	Knee
Medicare buy-in	[14]		1.34			0.005	Hip

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 5 Post-surgical risk factors

	Ref.	Statistical parameter				Site
		HR	OR	95%CI	*P* value	
Anaesthetic factors						
Intensive care length of stay (d)	[15]		0.5	0.20-1.00	0.06	Knee
Haematological						
Blood transfusion	[12]	2.11		1.10-3.90	0.02	Hip/knee
	[15]		2.1	1.00-4.20	0.04	Hip/knee
	[11]		1.63	1.14-2.33	0.007	Hip/knee
Transfusion if RBCs stored > 14 d	[24]		5.9	2.60-13.20	< 0.001	Knee
Perioperative blood loss (*via* drain tube)	[15]		1	1.00-1.01	0.008	Hip
Cardiac						
Postoperative atrial fibrillation	[12]	6.22		1.40-28.5	0.02	Hip/knee
Postoperative myocardial infarction	[12]	20.4		2.10-199.9	0.009	Hip/knee
Hospital factors						
Longer hospital stay	[12]	1.09		1.00-1.10	0.0003	Hip/knee
Non same-day surgery	[23]		4.16	1.44-12.02	0.008	Hip
Wound complications						
All wound complications	[11]		27	11.00-91.6	0.0002	Hip/knee
Wound discharge	[5]		18.7	7.40-47.2	< 0.001	Hip/knee
	[15]		6.3	1.30-30.7	0.02	Knee
	[15]		5.4	2.00-15.0	0.001	Hip
	[15]		5.7	2.40-13.3	<0.001	Hip/knee
	[11]		32.2	8.7-119.17	< 0.0001	Hip/knee
Haematoma	[5]		3.5	1.30-9.50	0.01	Hip/knee
Surgical site infection	[1]		35.9	8.30-154.6	< 0.01	Hip/knee
Superficial incisional SSI	[15]		3.7	1.10-11.9	0.03	Knee
	[15]		5	1.60-15.9	0.007	Hip
	[15]		4.3	1.90 - 9.90	0.001	Hip/knee
NNIS risk index 2	[9]		3.9	2.00-7.50	< 0.01	Hip/knee
Urinary						
Postoperative urinary infection	[12]	5.45		1.00-8.70	0.04	Hip/Knee
	[5]		2.7	1.04-7.10	0.04	Hip/Knee

RR: Relative risk; HR: Hazard ratio; OR: Odds ratio.

Table 6 Classification of risk factors and probability of infection (main factors)

	Risk factor	Minimum increase	Maximum increase	Statistical parameter	Ref.
Host-related risk factors					
Modifiable	Systemic steroids	3.3	21	OR	[15,21]
	Tobacco use	3.4	12.76	OR	[23,32]
	Nasal MRSA infection	-	8.24	OR	[31]
	BMI < 20	-	6	OR	[21]
	Coronary artery disease	-	5.1	OR	[21]
	COPD	1.22	4.34	OR	[4,31]
	BMI > 40	-	4.13	OR	[23]
	Pre-operative BM	-	2.25		[17]
Non-modifiable	Diabetes	1.4	5.47	OR	[15,26]
	Liver cirrhosis	-	5.4	HR	[28]
	Male	1.89	3.55	HR,OR	[20,31]
	Age	-	3.36	OR	[26]
	Rheumatoid arthritis	1.18	3.3	OR	[4,15]
	Malignancy	-	3.1	OR	[5]
Provider-related risk factors					
Modifiable	Quadriceps release (TKR)	-	4.76	HR	[20]
	Non-same day procedure	-	4.16	OR	[23]
	Prolonged operation	1.78	3.38	HR	[14,23]
Non-modifiable	Prolonged storage of blood	2.6	13.2	OR	[24]

BMI: Body mass index; RR: Relative risk; HR: Hazard ratio; OR: Odds ratio; COPD: Chronic obstructive pulmonary disease; TKR: Total knee replacement.

post-operative infection following lower limb arthroplasty. Multiple prospective and retrospective studies have reviewed the risks associated with their patient cohort developing such infections. This paper was undertaken to combine these risks and determine if there was a consensus to which factors puts a patient at highest risk, and categorise them if they related directly to the host (patient), provider (the surgical team and their Institute), or occurred during the post-operative period.

Little is known about the interaction between, or synergistic effect, of specific patient risk factors[35], as it is likely they have a multiplicity effect, rather than additive risk, as shown by Tomás[6]. In their cohort if a patient had two (or more) significant factors the probability of infection development was 14-times higher, whereas having three (or more) factors the probability was increased 16-times.

Several themes have emerged following this systematic review of the literature, specifically the patient's immunological and systematic responses to infection, other sources of infection, antibiotic use, and provider factors.

Immunological response

The most frequently quoted risk factor was diabetes mellitus[4,9,17,20,22,26], which had one of the highest odds ratios[26]. Almost all the other highest odds ratio, or hazard ratio, also belonged to medical conditions ultimately impairing a patients immunity, as demonstrated from high dose pre-operative steroids[21], malnutrition (reflective of high alcohol intake[26], BMI below 20[21] and above 50[13]), and tobacco use[23]. Malignancy[4,5], rheumatoid arthritis[4,15,16], and liver cirrhosis[28] can also impair a patient's immunity.

Immunosuppression has long been known to increase a patient's risk of systemic infection, and has widely been documented in arthroplasty patients. Ragni *et al*[36] demonstrated this in human immunodeficiency virus-positive hemophiliacs with CD4 counts of 200 mm^3 or less undergoing orthopaedic surgery. Post-operative infection occurred in 10 (15.1%) of 66 patients[36]. Local steroid injection causing focal immunosuppression about the joint has also been shown to increase the risk, compared to those that have not received any joint injections in hip arthroplasty cases[37].

In rheumatoid patients treated with immunosuppressive drugs (including biologic agents) undergoing all orthopeadic procedures, a statistically significant higher risk of infection was seen in this patient cohort compared to a degenerative/post-traumatic group (OR = 2.58, 95%CI: 1.91-3.48, $P < 0.001$)[38]. Furthermore this risk was significantly increased in patients taking multiple disease-modifying antirheumatic drugs (DMARDs) ($P = 0.036$) or tumor necrosis factor α (TNFα) inhibitors ($P = 0.032$), especially if the last dose of TNFα inhibitor was given < 1 administration interval before surgery[38].

Infection response

While not directed specifically to immunosuppression, other co-morbidities have a role in reducing the patients systemic response to infection. Cardiac dysfunction[4,16,21], renal failure[4,15], anaemia[4,9,16] and coagulopathy[16] have all been shown to increase the risk of infection. This may be directed through specific cellular pathways[39], but may demonstrate the insult the surgical procedures has in causing a secondary inflammatory insults, worsening multiple organ dysfunction[40,41].

Deranges in renal function, with progressively higher poor glomerular filtration rate (GFR) in either the acute or chronic stages, reduces the ability to remove unwanted and hazardous chemicals from the blood, and places the patient at a higher risk. Lieberman *et al*[42] demonstrated

a high rates of infection in patients on chronic renal dialysis (19%), however in a separate patient series no significant increase in infection risk was seen[43].

Infection source

We believe that if a patient is known to have systemic infection, or a localised infection but distant to the operative joint, the risk of haematological spread of infection to the implant is highly likely. We have demonstrated a statistically significant increased risk of PJI in patients with a pre-operative confirmation of a genitourinary infection[10,27], nasal *S. Aureus* and *MRSA* infections[31], or other distant organ infections[6], such as hepatitis B[44].

Conditions that further increase this risk are those that may make the patient more susceptible for the introduction of a new pathogen, such as chronic pulmonary disease[4,31] with known high rates of pneumonia, peripheral vascular disease[4,16] with high risk of skin ulceration and introduction of skin contaminates, and recent oesophagogastroduodenoscopy (EGD) with biopsy[22], risking the introduction of gut flora to the blood system.

Furthermore, perioperative blood transfusion increases the risk of PJI in both hip and knee arthroplasty[11,12,15], and allogeneic blood transfusion has been shown to instigate a detrimental immunomodulation reaction, and decreases T-cell-mediated immunity, and may enhance the acute inflammatory response[45,46]. Stored blood can cause a significant increase in inflammatory cytokine release from the stored neutrophils, and superoxide release results in delaying neutrophil apoptosis and risks cytotoxicity[47,48].

This has been confirmed in a recent systematic meta-analysis of 6 studies demonstrating the association between allogeneic blood transfusion and an increased risk for a SSI after total hip and knee arthroplasty. Data was included from over 20000 patients, and the blood transfusion group had a significantly higher frequency of infection (pooled OR = 1.71, 95%CI: 1.23-2.40, P = 0.002) compared to the non-exposed group[49].

Antibiotic use

The use of antibiotic-impregnated cement was shown by Dale *et al*[18] to protect against revisions due to infection, whereas Namba *et al*[20] identified an increased risk. Such conflicting outcomes are common in the literature regarding the use of antibiotic-impregnated cement in primary procedures. A prospective randomized study with 2948 cemented total knee arthroplasties failed to see an improvement of PJI rates by using bone cement loaded with erythromycin and colistin compared to controls[50], whereas the Norwegian Arthroplasty Register has demonstrated a synergistic effect of systemic and cement antibiotics[51]. However there is a general consensus that antibiotic-impregnated cement has a greater role in revision cases[52], and is recommended as standard practice in these high-risk cases[53].

Systemic antibiotics given at anaesthetic induction are generally the standard of care, and continued post-operatively for a further two doses in the United Kingdom, and for two days in Italy (authors experience). The choice of antibiotic varies in each Institute to reflect the prominent pathogen and patient cohort. Multiple studies have demonstrated the benefits of antibiotics given during the procedure to reduce the risk of post-operative infection[51,54].

Provider factors

Concerning the relative impact of the hospitals yearly volume of procedures, we found only one retrospective review of joint registry data, that suggests that the fewer total knee arthroplasties undertaken per year will result in a lower rate of infection[20]. This particular finding needs, in our opinion, further validation, since it contradicts other reports demonstrating better outcomes from greater volumes of surgery and greater experience of the surgeons, as exemplified by the Hospital for Special Surgery, New York[55], while other studies have shown no difference between the two[56].

Furthermore, the use of a drain post-operatively has been shown by Peel *et al*[15] to reduce the risk of PJI following knee arthroplasty, however multiple meta-analyses and prospective, randomised, controlled trials have demonstrated no significant difference in post-operative infections between the wounds treated with a drain and those without[57,58].

Modifiable risk factors

When the risk factors were further categorised into modifiable or not, the vast majority of factors were non-modifiable. Many risk factors increased a patient's risk by less than 5 times (OR < 5), and very few increased the risk by more than 10 times.

However, the presence of non-modifiable risk factors still requires attention, and may be more important than modifiable ones. Alternate methods should be adopted to reduce the patient's burden and may include a combination of implant modifications (such as silver or disposable microbiological coatings)[59,60], antibiotic impregnated cement or bone graft[61,62], or other novel therapies[63] to provide a personalized and more effective prophylaxis.

It is the responsibility of the operating team to act upon these, and modify or optimise the patient prior to surgery. For example, intensive insulin therapy, maintaining tight blood glucose concentrations between 80 and 110 mg/dL, has been shown to decrease infection-related complications and mortality[64]. Normal renal function should be sought, nutrition improved, cardiac investigations and interventions should be offered, local and systemic infections appropriately treated, as should chronic anaemia, and patients should be informed to withhold DMARDs and stop tobacco smoking and alcohol use preoperatively.

Risk-analysis tools

Indeed, determining individual patients risks is an important step in personalized informed consent. Surgeons may quote published rates or their own, but the risk

is individual and should reflect all the aforementioned factors, which may have consequences in the medico-legal evaluation in case of damage evaluation after PJI.

Previous attempts to combine such measures in a scoring system have been attempted by The Mayo Clinic[65] who based the data on their cohort of patients at baseline and at one month. Bozic *et al*[35] developed a risk calculator using data from 11 years worth of Medicare claims. A similar tool has been developed in the Chinese population[26].

The main disadvantage of such tools is the calculations relate to a specific set of patients, and may not reflect the general public risks, as they have not been externally validated. In addition the data is unlikely to appreciate advances in perioperative care over the time period, and may not capture patients with late onset PJI if follow-up is short.

Limitations

A wide variety of studies were included in this systematic review, which gives an overview of risk factors for hip and knee PJI but the quality of each study is generally poor. As previously discussed, only 8 studies (29.6%) were prospective, and one third of studies demonstrated record bias. Reporting bias was also seen amongst the studies, as a variety of diagnostic criteria were used. This is common amongst studies reviewing PJI as there is no gold standard measure to determine presence of infection, nor an agreement to the medical, or surgical management, for these patients[53].

Our search criteria only highlighted studies with "risk factor" in the title, and therefore we did not search for studies looking at individual risk factors. Therefore studies, some of high quality, may not have met our inclusion criteria. Furthermore, we were unable to undertake a meta-analysis due to the heterogeneity of the data.

In conclusion, as demonstrated, current data is conflicting as the influence of the risk factors vary widely, and we believe more emphasis is required regarding the multiplicity effects of risk factors. We need larger studies and novel tools to investigate single and combined risk factors, and to identify key areas of improvement and modification for these patients.

The literature has demonstrated significant variation in the number and type of risk factors that places a patient at higher risk of developing a PJI, which is heavily weighted towards the patient. However the provider has a role in addressing the modifiable risk factors pre-operatively to optimise their patient, and develop new strategies to limit the impact of non-modifiable factors.

COMMENTS

Background

Several studies have previously shown the impact of various risk factors on the probability of developing an infection after joint replacement. The heterogeneity of the available data notwithstanding, in this systematic review a detailed analysis of the respective weight of known risk factors, classified as host-, provider- or post-surgical-related, is performed; moreover, a further distinction in modifiable or not-modifiable risk factors is proposed.

Research frontiers

A classification and ranking of known risk factors may open new frontiers in prevention and control of peri-prosthetic infections. Furthermore, it can be helpful to improve the information to the patient prior to surgery, to drive personalised prophylaxis and to better evaluate the cost-to-benefit ratio of new technologies, like antibacterial coatings, designed to reduce bacterial adhesion on implanted biomaterials.

Innovations and breakthrough

This systematic review sheds new lights on the relative impact of various risk factors that increase a patient's risk of developing lower limb periprosthetic joint infections (PJI). This ultimately reiterates the importance of optimising the patients pre-operatively by addressing modifiable risk factors (such as their immunosuppression, nutrition, diabetes, and smoking), and develops strategies to limit the impact of non-modifiable factors.

Applications

The data obtained in this systematic review may form the basis for the development of specific software, like the "PJI Risk App", an application for smartphones, specifically designed to calculate the risk of developing a peri-prosthetic infection in a given patient. This in turn may be useful for surgeons and their patients to understand the specific risk of undergoing joint replacement and eventually to better tailor antibiotic prophylaxis.

Peer-review

In this manuscript authors reviewed provider risk factors of chronic PJI. This study is interesting and the objective very clear.

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SYSTEMATIC REVIEWS

Dementia and osteoporosis in a geriatric population: Is there a common link?

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Abstract

AIM

To determine the existence of a common pathological link between dementia and osteoporosis through reviewing the current evidence base.

METHODS

This paper reviews the current literature on osteoporosis and dementia in order to ascertain evidence of a common predisposing aetiology. A literature search of Ovid MEDLINE (1950 to June 2016) was conducted. The keywords "osteoporosis", "osteoporotic fracture", "dementia" and "Alzheimer's disease" (AD) were used to determine the theoretical links with the most significant evidence base behind them. The key links were found to be vitamins D and K, calcium, thyroid disease, statins, alcohol and sex steroids. These subjects were then searched in combination with the previous terms and the resulting papers manually examined. Theoretical, *in vitro* and *in vivo* research were all used to inform this review which focuses on the most well developed theoretical common causes for dementia (predominantly Alzheimer's type) and osteoporosis.

RESULTS

Dementia and osteoporosis are multifaceted disease processes with similar epidemiology and a marked increase in prevalence in elderly populations. The existence of

a common link between the two has been suggested despite a lack of clear pathological overlap in our current understanding. Research to date has tended to be fragmented and relatively weak in nature with multiple confounding factors reflecting the difficulties of *in vivo* experimentation in the population of interest. Despite exploration of various possible mechanisms in search for a link between the two pathologies, this paper found that it is possible that these associations are coincidental due to the nature of the evidence available. One finding in this review is that prior investigation into common aetiologies has found raised amyloid beta peptide levels in osteoporotic bone tissue, with a hypothesis that amyloid beta disorders are systemic disorders resulting in differing tissue manifestations. However, our findings were that the most compelling evidence of a common yet independent aetiology lies in the APOE4 allele, which is a well-established risk for AD but also carries an independent association with fracture risk. The mechanism behind this is thought to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele which may be amplified by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies.

CONCLUSION

Robust evidence remains to be produced regarding potential links and regarding the exact aetiology of these diseases and remains relevant given the burden of dementia and osteoporosis in our ageing population. Future research into amyloid beta, APOE4 and vitamins K and D as the most promising aetiological links should be welcomed.

Key words: Osteoporosis; Fracture; Dementia; Thyroid disease; Alzheimer's disease; Elderly; Vitamin D; Vitamin K; Calcium; Statins; Alcohol; Sex steroids

Core tip: A potential pathological link between osteoporosis and dementia has been explored in observational studies, but there exists a lack of large scale randomised controlled trials. We hypothesise that dementia and osteoporosis have common yet independent aetiologies. The most compelling evidence lies in the APOE4 allele, a well-established risk factor for Alzheimer's disease. APOE4 is associated with fracture, independent of dementia and falling. The mechanism behind this is postulated to be reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele. This may be augmented by the nutritional deficiencies associated with dementia, known to include vitamins K and D.

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INTRODUCTION

Dementia and osteoporosis are complex disease processes with similar epidemiology. Alzheimer's disease (AD) is the most common form of dementia and increases from 16% in 75-year-old to 84-year-old to 48% in over-85s[1]. Osteoporosis affects 25% of women and 10% of men over 60[2]. The two diseases co-exist in a subsection of the population, especially amongst females[3]. Indeed, an odds ratio of 6.9 for fracture prevalence between people with and without AD has been reported[4]. Thus a common link has been suggested despite no apparent pathological overlap.

The pathogenesis of AD lies in three complex mechanisms[5]. The development of amyloid senile plaques causes neuronal death and phosphorylation of Tau proteins. Tau disassembles the microtubules resulting in neurofibrillary tangles and ultimately neuronal degeneration. Amyloid and Tau localise in the synapses, causing excessive calcium entry into post-synaptic neurons, necrosis and apoptosis. Despite extensive research into the disease, current treatment options are limited by their cost and efficacy. Their action lies in palliation of symptoms and most are only effective in a subsection of AD sufferers.

Osteoporosis is a progressive skeletal disease characterised by reduced bone density and micro-architectural bone destruction. This leads to increased bone fragility and susceptibility to fracture. Like dementia, the pathophysiology of osteoporosis is multifactorial and extends far past the traditional theory of nutritional calcium depletion. Indeed, both diseases have been associated with a number of other metabolic disturbances such as decreased vitamin D concentration and elevated serum parathyroid hormone, in addition to postulated common genetic variations such as the APOE4 allele[2].

The burden of elderly care is a significant challenge to healthcare systems throughout the world and will only continue to grow in the coming decades. AD is the leading cause of loss of autonomy and independency in the elderly, and is associated with a number of comorbidities[6]. Osteoporotic fractures have huge impact in terms of morbidity and mortality. Both diseases form part of the frailty syndrome, a collection of signs and symptoms associated with significant disability and public expenditure[7]. Here we hypothesize that osteoporosis and dementia share a common predisposing aetiology. We propose that this is multifactorial, involving genetic, metabolic, endocrine and environmental factors. Elucidation of a common link between the two diseases could prove vital in the development of novel treatments for these complex medical and social problems.

MATERIALS AND METHODS

A comprehensive literature search of Ovid MEDLINE (1950

to June 2016) was conducted. The keywords "osteoporosis", "osteoporotic fracture", "dementia" and "Alzheimer's disease" were used initially to determine the theoretical links with the most significant evidence base behind them. From manual study of key papers the lead investigators selected these to be vitamins D and K, calcium, thyroid disease, statins, alcohol and sex steroids. These subjects were searched in combination with the previous terms. Manual examination of titles and abstracts was used to exclude irrelevant articles. Theoretical, *in vitro* and *in vivo* research were all used to inform this review which focuses on the most well developed theoretical common causes for dementia (predominantly Alzheimer's type) and osteoporosis.

RESULTS

Vitamin D

Approximately 1 billion adults are vitamin D deficient worldwide, and the prevalence is especially marked in older people, ranging from 50%-80%[5]. Vitamin D has long been known for its effects on phosphocalcic metabolisms and bone[5], thus vitamin D deficiency is well established as a risk factor for the development of osteoporosis[8]. In contrast, the association between vitamin D and dementia requires clarification.

In 1995, Kipen *et al*[8] found significantly lower vitamin D in women with dementia compared to cognitively-intact controls. A subsequent cross-sectional study found a vitamin D deficiency of < 10 ng/mL doubled the risk of cognitive impairment[9]. A similar association between severe vitamin D deficiency (here defined as < 25 nmol/L at baseline) and mild cognitive impairment has been seen in elderly subjects over 65 years of age[10].

A recent large Danish prospective study looked at participants who were free of cognitive impairment at enrolment and found that a decline in serum levels of vitamin D were associated with increased risk of participants developing AD[11]. A more diverse American prospective study with a shorter length of follow up also found an association between baseline vitamin D deficiency (defined by the authors as serum levels < 50 nmol/L) and likelihood of participants developing AD and other all-cause dementias, an association that remained despite adjustment for mediators such as diabetes and hypertension[12]. Both these studies looked at healthy participants who were ambulatory at enrolment[11,12]. However reduced exposure to sunlight in patients with AD has been implicated as the main cause of vitamin D deficiency in patients with dementia[13]. Patients with dementia are often immobile or housebound, and may be unable to gain sufficient sunlight exposure. Furthermore, generalised malnutrition either due to changes in functional ability, appetite disturbance, or disease may compound this problem.

In addition to environmental and functional changes, a decline in renal function accompanies the process of aging with the incidence of chronic kidney disease quoted as up to 35.8% in the geriatric population[14]. Chronic renal disease results in impaired 1,25 dihydroxycholecalciferol production, the physiologically active metabolite within the body. Patients with suboptimal production of 1,25 dihydroxycholecalciferol may have this confirmed by low serum levels, and evidence of a secondary hyperparathyroidism[15].

Aside from well-established physiological effects on bone metabolism, vitamin D has been found to play a pivotal role in both the normal function and protection of the central nervous system (CNS). As a neurosteroid hormone, vitamin D receptors are found in the neurons and glial cells of the CNS[5]. The binding of 1,25 dihydroxycholecalciferol to these receptors results in a number of neuroprotective mechanisms. These can be categorised as direct, immune and homeostatic.

Directly, vitamin D inhibits the synthesis of nitric oxide synthase, an enzyme which promotes neuron alterations, and increases the synthesis of neurotrophic agents such as nerve growth factor[5]. In addition, neuron-glial cell cultures treated with vitamin D show increased expression of genes known to limit the progression of AD[16]. Vitamin D is also known to increase the number of macrophages and leukocytes in the brain. *In vitro* studies of macrophages from AD patients showed that stimulation with vitamin D increased phagocytosis and clearance of amyloid[17]. Vitamin D plays an important role in the homeostasis of calcium and the avoidance of hyperparathyroidism by upregulating calcium channels and the synthesis of calcium-binding proteins[5]. The importance of calcium and parathyroid status is discussed later.

Despite evidence *in vitro,* conclusive evidence of a link between vitamin D and dementia in patients is lacking (Table 1). In cross-sectional studies, vitamin D deficiency has been shown to double the risk of presenting with cognitive impairment[9]. However, the nature of cross-sectional studies means that no cause and effect link can be made. Clearly, dementia may be the cause of reduced mobility and therefore reduced exposure to sunlight. A recent BMJ editorial criticised the perceived reliance on cross-sectional studies in relation to vitamin D as an aetiological factor in AD. It cited "a range of interpretational difficulties" such as reverse causality, confounding, classification bias and differences in assay methods[18].

Nevertheless, in longitudinal studies, low baseline vitamin D levels have been found to predict incident cognitive decline in the elderly. A study of 858 Italians over the age of 65 showed that those who were "severely deficient" in vitamin D had a 1.6-fold increased risk of a substantial cognitive decline over 6 years, thus providing a temporal association[19]. Another longitudinal study looking at time to progression to AD along with vitamin D treatment status, found that time to progression was longer in those treated with vitamin D (5.4 ± 0.4 years, P = 0.003) than in those who were not supplemented (4.4 ± 0.16 years, P = 0.003) but only in those who went on to develop severer manifestations of the disease[20]. This study however was limited again by an observational

Table 1 Studies investigating the association between vitamin D and cognition

Study design	Ref.	Population	Results
Cross-sectional study	[88]	80 community-dwelling women 40 with mild AD 40 cognitively-intact	Vitamin D deficiency was associated with impairment on two of four measures of cognitive performance
	[89]	32 community-dwelling patients	Significant positive correlation between vitamin D concentrations and MMSE scores
	[90]	9556 community-dwelling patients	Lower 25(OH)D levels were not associated with impaired performance on various psychometric measures
	[91]	225 older outpatients diagnosed as having probable AD	Significant positive association between MMSE test scores and serum 25-hydroxyvitamin D(3) levels
Case-control study	[92]	5596 community-dwelling women	Significant positive association between vitamin D intakes and cognitive performance
	[93]	69 community-dwelling patients	A significant negative correlation between dietary intake of vitamin D and poor performance on cognitive tests
	[94]	148 community-dwelling patients	No significant positive association between cognitive performance and serum 25-hydroxyvitamin D(3) levels
Longitudinal study	[95]	1138 community-dwelling men	Independent association between lower vitamin D levels and odds of cognitive decline
	[19]	175 community-dwelling patients	1.60-fold risk of losing at least 3 points on MMSE in 6 yr with low baseline vitamin D
Pre-post study	[96]	63 frail nursing home residents 25 in intervention group 38 in control group	No treatment-induced improvement in ambulation, cognition or behaviour was observed
	[21]	13 community-dwelling patients with mild to moderate AD	Significant improvement in ADAs-cog score
Randomised controlled trial	[21]	32 community-dwelling patients with mild to moderate AD 16 in intervention group 16 in control group	Neither cognition nor disability changed significantly after high-dose D

AD: Alzheimer's disease.

study design and exclusion of some confounders from analysis, for example treatment with psychotropic medication[20]. Pre-post studies, where cognitive function was measured before and after supplementation of vitamin D, found an improvement in cognition concomitant with the increase in vitamin D concentrations[5]. There is only one, small randomised controlled trial on this topic, where 32 individuals with mild to moderate AD received low-dose vitamin D supplementation for 8 wk, before being randomised to either continue with the low dose (plus placebo) or to receive an additional high-dose supplement for a further 8 wk. Cognition was tested using a number of validated scales. Despite promising results from a smaller pilot study, the authors found that supraphysiological doses of vitamin D were no better than physiological doses at improving cognition or disability in this group, but acknowledge the limitations of such a small sample size[21].

Vitamin K

Vitamin K is the collective term for a group of fat-soluble vitamins responsible for gamma-carboxylation of glutamate at various sites in the body. In the liver, vitamin K plays a vital role in the modification of prothrombin and other proteins responsible for haemostasis[1]. In addition, vitamin K promotes bone health by means of site-specific carboxylation of osteocalcin (a marker of bone formation) and other bone matrix proteins such as matrix Gla-protein and protein S[22]. In vitamin K deficiency, undercarboxylated osteocalcin is associated with osteoporosis and increased risk of fracture[1]. A meta-analysis of 3 trials involving patients with neurological disease (AD, stroke and Parkinson's Disease) showed that when vitamin K is replaced, there is a decreased risk of fractures compared to non-treatment[23].

As with vitamin D, the link between vitamin K and osteoporosis is well-established, whilst any connection to dementia remains both multifactorial and largely theoretical. Numerous observational studies from Japan have indicated that vitamin K deficiencies contribute to reduced bone mineral density in patients with AD[22]. A number of reasons have been postulated for the association between vitamin K deficiency and dementia including that of reverse causality.

It is plausible that, rather than vitamin K deficiency causing dementia, it is the dementia which affects vitamin K levels through malnutrition. Suboptimal dietary intake is evident even in the early stages of AD compared to cognitively intact age-matched controls[24]. In humans, vitamin K_1 is dietary, whilst K_2 is synthesised by gut bacteria[3]. In a cross-sectional study of 100 women with varying degrees of AD, BMI, bone mineral density and vitamin K_1 levels were significantly lower in severe AD compared to mild AD[3]. However, vitamin K_2 levels were not significantly decreased, indicating a nutritional cause. Another study analysed the dietary vitamin K intakes of 31 patients with mild AD, compared to 31 controls.

Vitamin K intakes were significantly less in patients with AD, even after adjusting for energy intake[25].

Nevertheless, vitamin K does also appear to have a direct effect on the brain. Vitamin K-dependent gamma-carboxylation of glutamate in the liver and bone has already been discussed. This process is also apparent in the brain, by which growth-arrest-specific gene (*Gas6*) is biologically activated. Yagami *et al*[26] investigated the effect of *Gas6* in primary cultures of rat cortical neurons. *Gas6* was shown to protect against AD by the rescue of cortical neurons from amyloid-induced apoptosis[26]. In addition, vitamin K is involved in sphingolipid synthesis. Sphingolipids are an important constituent of the myelin sheath and the neuron cell membrane, and alterations in sphingolipid metabolism have been identified in the brains of patients with mild AD[25].

Alternatively, dementia and vitamin K deficiency may share a common cause. As previously discussed, apolipoprotein E4 (APOE4) is an allele that has been well-established as a risk factor for AD[3]. APOE is found in chylomicrons which bind to vitamin K in plasma[1]. APOE binds to a hepatic LDL receptor and LDL receptor-related protein (LRP); the variant APOE4 binds particularly quickly, thus reducing plasma vitamin K levels[1]. The concentration of vitamin K is therefore lower in the circulating blood of APOE4 carriers[1] and women expressing the APOE4 allele have been shown to have a significantly increased risk of osteoporotic hip fractures compared with those with other APOE genotypes[27]. Another genotype, consisting of two copies of the apolipoprotein allele E2, has also been associated with increased frequency of vertebral fractures, suggesting further that apolipoprotein polymorphisms may play a role in bone mineral density and fracture risk[28].

Although the association between vitamin K and dementia appears strong, there is little outside of cell work to prove a causal relationship. The evidence thus far lies in observational studies[22] and a small number of randomised controlled trials in which vitamin K supplementation has been proven to reduce the risk of fractures in patients with neurological disease[23]. This effect is assumed to be bone-mediated, and the possibility of improved cognitive function is not explored.

Calcium and hyperparathyroidism

Calcium has long been known to contribute to bone health. In combination with vitamin D, calcium promotes osteoblast differentiation and formation of mineralised bone, thus impairment in calcium signalling can contribute to the pathophysiology of osteoporosis[29]. Likewise, the role of calcium homeostasis in the pathophysiology of dementia has been extensively investigated for almost three decades. The "calcium hypothesis" of the late 1980s[30] postulates that "in the aging brain, transient or sustained increases in the average concentration of intracellular free calcium contribute to impaired function, eventually leading to cell death". This hypothesis was supported by a range of animal and human studies, the earliest of which have been well-described by Disterhoft *et al*[30]. For example, administration of magnesium, a calcium channel antagonist, to aging rats was shown to reduce calcium influx in hippocampal neurons and reverse functional and learning difficulties. Similarly, nimodipine, an isopropyl calcium channel antagonist that readily crosses the blood-brain barrier, was found by a recent Cochrane review to be of "some benefit in the treatment of patients with features of dementia due to unclassified disease or to AD, cerebrovascular disease, or mixed Alzheimer's and cerebrovascular disease" although the authors stressed this benefit could only be applied to short-term outcomes[31].

The role of calcium in the pathophysiology of impaired cognition is complex. Calcium is required for the function of all cells in the body, including neurons. The neurons of aged animals have been found to exhibit enhanced calcium activity compared to their younger counterparts[32]. This has been attributed to an excess of calcium influx *via* voltage-gated calcium channels. Indeed, an increased density of these channels has been positively correlated with cognitive decline in animals. Further, in humans, enhanced intracellular calcium release from the endoplasmic reticulum has been found in the ageing brain, and research into this phenomenon continues[32].

To propose that changes in calcium transport and metabolism forms the basis of link between osteoporosis and dementia seems counterintuitive, as the former may result from falling calcium levels, whist the latter has been attributed to high intracellular calcium. One possible mechanism is that calcium deficiency and the resultant secondary hyperparathyroidism results in bone loss whilst shifting calcium from the skeleton to the soft tissue, and from the extracellular to the intracellular compartments[33]. Indeed a recent cross-sectional study has found association between high levels of PTH with low bone mineral density, which persisted even in participants where serum calcium levels were not overtly deficient[34].

Increased parathyroid activity is well known to be associated with impaired cognitive function. Moreover, a recent 10-year longitudinal prospective study found that elevated PTH concentrations are associated with a five-year cognitive decline in a general aged population, although this was found to be independent of calcium concentrations[35]. Further investigation would be required to establish a common role for calcium as a contributing factor to both osteoporosis and cognitive decline.

Thyroid disease

Overt thyroid disease is well known to be a reversible cause of cognitive impairment and altered bone metabolism[36]. Subclinical thyroid disease - whereby normal levels of thyroxine (T4) and tri-iodothyronine (T3) are coupled with a deranged level of thyroid stimulating hormone (TSH) - is being increasingly recognised as a cause of significant morbidity and mortality within the elderly population[37].

Subclinical hyperthyroidism: Subclinical hyper-

thyroidism (levels of T3 and T4 that are towards the top of the reference range coupled with reduced TSH, without symptoms of thyrotoxicosis) has been associated with various pathologies, and affects both bone mineral density and cognition[38]. This may be due to exogenous causes, *i.e.*, excessive replacement with levothyroxine in hypothyroid patients; or endogenous causes such as Grave's disease[37].

There is considerable debate as to whether it is the level of TSH or of T4 itself that results in the physiological effects of thyroid hormone excess. A prospective study in Rotterdam found that individuals with subclinical hyperthyroidism had a greater than threefold increase in risk of developing dementia; with higher levels of T4 conferring greater risk. It is worth noting that none of these patients had a T4 level above the reference range[36]. This finding is supported by a further retrospective study, which also demonstrated an association between elevated thyroid hormone levels and dementia, not related to the concentration of TSH. It therefore seems likely that the level of T4 is the important determinant[39]. Furthermore, in a prospective cohort study of 665 Japanese-American men, followed-up for development of dementia after thyroid function was recorded, subsequent autopsy of one fifth of the cohort-including both healthy and demented patients-demonstrated that at higher levels of T4, more numerous intracerebral tangles and plaques are seen, as well as clinical dementia[40].

Data regarding any association between osteoporosis and subclinical hyperthyroidism is unclear. Some studies show low levels of TSH appear to result in slightly reduced bone mineral density in men and post-menopausal women, but the protective effect of oestrogens means this does not generally apply in pre-menopausal women[41]. The fifth Tromso population study in Norway, conducted in 2001, compared bone mineral density levels of TSH whilst adjusting for possible confounding factors such as weight and smoking. It discovered that, if TSH was normal, there was no relationship to bone mineral density; however, low TSH was seen in subjects with lower bone mineral density[42]. T4 levels that are within the normal range are correlated with a lower level of bone mineral density at both the higher and lower ends of the spectrum - that is, in the region of subclinical thyroid disease[36,43]. These hormone derangements are also associated with increased risk of fracture[44].

Subclinical hypothyroidism: Subclinical hypothyroidism is a significant problem within the elderly population, and is more common than overt hypothyroidism[45]. Despite the above discussion relating subclinical hyperthyroidism to cognitive impairment and dementia, patients with subclinical hypothyroidism have also been shown to be more likely to develop such attributes[46]. This may be due to the effect of T4 itself, or reduced hormone concentration within the brain, resulting in slower information processing and increased susceptibility to cognitive dysfunction[47]. It is also worth noting that treatment with levothyroxine has been shown to reduce cognitive impairment and improve mood in patients with mild hypothyroidism[48]. Currently, although there is evidence that both states can cause cognitive decline, subclinical hyperthyroidism appears to have a stronger association with the development of dementia. A small scale study of 59 patients with multi-diagnosis dementia found a slight increase in TSH serum levels patients with AD compared to other diagnosis dementia patients and with healthy controls, along with a decrease in cerebrospinal fluid (CSF) total T4 levels in both patients with AD and those with other diagnoses compared to healthy controls[49]. The CSF total T4 levels correlated positively with MMSE test scores and negatively with markers of axonal damage, which the authors hypothesized may mean that central levels of T4 are functionally important in AD[49].

Despite the association between subclinical hypothyroidism and cognitive impairment, osteoporosis has not specifically been linked to subclinical hypothyroidism. Overtreatment of these patients with thyroxine has in fact been shown to lead to reduced bone mineral density and an increased rate of osteoporosis[50,51]. This represents an important clinical disadvantage, and clinicians should exert caution in deciding whether or not to treat subclinical hypothyroidism[51]. Subclinical thyroid disease is common in the elderly population, and has been shown to be associated with a number of co-morbidities including osteoporosis and dementia in the case of subclinical hyperthyroidism. Additional work is required to establish if age-related changes in thyroid hormone concentrations represent a common factor in the aetiology of both conditions. Furthermore, investigating the treatment of subclinical disease, and whether or not it results in a lower rate of dementia and osteoporosis in the elderly, represents an exciting avenue for research in the future.

Alcohol

Excessive alcohol use is well known to result in low bone mineral density and increased risk of fracture[52]. This has been thought to be due to a direct deleterious effect on osteoblast activity and subsequently a decrease in bone formation[53], however this mechanism is not likely to be related to the development of dementia. Recently it has been suggested that lower levels of vitamin D in chronic alcoholics may be related to hepatic insufficiency and subsequently impaired metabolism of the substance[54]. This could in turn affect bone formation. It must be remembered that low to moderate levels of alcohol intake does not reduce bone density; however, there has been no protective effect demonstrated either.

Whilst chronic excessive alcohol use leads to unique forms of dementia (*i.e.*, Korsakoff's syndrome) this is secondary to vitamin deficiencies, especially thiamine. Ethanol toxicity has been shown in rats to cause hippocampal and cortical cell loss, as well as loss of proteins required for neuronal survival[55]. However, at low to moderate levels of intake there appears to be a protective effect against developing dementia[56,57]. Interestingly, there was no protective effect seen in individuals with the

APOE4 gene[56]. The reasons for this protective effect are currently unclear.

It is difficult to assess whether alcohol intake is related to an increased risk of osteoporosis and dementia, especially given the likely protective effect of a moderate alcohol intake against dementia. The multiple comorbidities often experienced by chronic alcoholics (most notably nutrient deficiency) means studies are affected by a number of confounding factors. Varying patterns in form and frequency of alcohol abuse also make analysis difficult. Any link that were to be demonstrated would possibly be due to a secondary impact on another aspect of physiology (such as vitamin D deficiency), as opposed to an innate property of ethanol itself.

Statins

Statins (HMG CoA reductase inhibitors) are currently the target of a large volume of research given their supposed pleiotropic effects. As well as treating dyslipidaemia, statins have been proposed as being effective against malignancy, nephropathy, cataract formation and macular degeneration as well as against osteoporosis and dementia[58].

The role of statins in reducing the risk of dementia was classically thought to be due to their role in reducing plaque formation, hence reducing vascular insults to the brain and the risk of ischaemic neuronal loss[59]. Newer studies have proposed a systemic reduction in the inflammatory response, as evidenced by the ability of statins to reduce levels of C-reactive protein[60]. Statins act on the mevalonate pathway, inhibiting conversion of HMG-CoA to mevalonate[61]. Mevalonate is a precursor of the interleukin-6 group of cytokines which are implicated in systemic inflammation[60]. It is possible that a reduction in systemic inflammation by inhibiting this pathway may help to prevent the development of dementia[62].

Given the interest in the proposed mechanisms, Cochrane reviews have been held into randomised controlled trials of both the prevention and treatment of dementia by statins. They have found that despite marked reductions in serum low density cholesterol levels, statin use neither improves cognitive function in those with dementia nor does it reduce the incidence. The reviews conclude that there is insufficient evidence to recommend statins as either a prophylactic against, or treatment for, dementia[63,64].

New theories on the development of osteoporosis hold that the mechanism is similar to that whereby lipids are oxidised[65]. If statins were shown to act directly on this mechanism then a beneficial effect in osteoporosis would also be likely. *In vitro* studies investigating mechanisms by which statins stimulate osteoblast differentiation have demonstrated that they exert their effects *via* the SMAD and the bone morphogenetic protein-2 (BMP-2) signalling pathways[66]. A recent review of *in vitro* and *in vivo* data suggests that statins also act *via* the RANKL pathway, which has been implicated in both adipogenesis and in changing osteoclastic activity, leading to osteoporosis[67].

Whilst there are theoretical benefits of statins in both dementia and osteoporosis, they have yet to be demonstrated in clinical studies. A large meta-analysis of hip bone mineral density showed a small but statistically significant benefit in patients taking statins[68]. However, this advantage does not translate into a decreased risk of fracture, according to a systematic review of studies observing fracture incidence in patients taking statins[69]. A recent RCT has also failed to demonstrate the benefit of specific statins in decreasing fracture risk[70]. Further evidence is required before routine statin use can be recommended for the prevention or treatment of either condition.

Androgens and oestrogens

Sex steroids play important roles in reproductive function, and in recent years receptors for these hormones have been identified in a range of body tissues, including bone and the nervous system[71]. The relationship between ageing, falling levels of sex steroids, and the subsequent reduction in bone mineral density is well described and a cause of much morbidity in the elderly population. Reduction in oestrogen levels in women is known to result in increased osteoclast activity and bone resorption[72]. The androgens are also known to be important in maintaining bone mineral density, both through intrinsic activity and as a result of aromatization to oestrogens[73]. Androgen activity gradually reduces in later male life, hence the resulting increase in rates of osteoporosis in older men. Whilst administration of endogenous sex steroids in the form of hormone replacement therapy in post-menopausal women does reduce the risk of fracture, it is no longer recommended for the prevention of osteoporosis due to cardiovascular side-effects[74]. Newer theories propose that oxidative stress holds an important role in the development of osteoporosis, and that sex steroids are important in protecting against this[65]. This would represent a possible therapeutic target with statin agents, if such a mechanism is proven.

Androgens and oestrogens have been suggested as being protective against AD, given that cognitive impairment is associated with a decrease in testosterone levels[75]. Animal studies have shown increased neuronal activity when testosterone supplements are administered, but the data from clinical trials is disappointingly inconclusive[75]. Additionally, the role of oestrogen in both preventing cognitive decline in intellectually normal women, and in maintaining cognitive function in patients with AD, has been the subject of a number of systematic reviews. Insufficient evidence for any beneficial effect was found for oestrogen administration in all studies reviewed[76,77]. Moreover, one review of long-term hormone replacement therapy found that in healthy women aged over 65 there was an increased incidence of dementia[74], although this is unlikely to be due to a direct effect of hormone replacement, and may simply be a result of an increase in frequency of cardiovascular events, a known independent risk factor for developing dementia.

There has been recent animal work looking at the effects of sex steroid analogues, so called selective androgen receptor agonists (SARMs) and selective estrogen receptor agonists, which are thought to allow for the beneficial effects of the sex steroids in protecting against neurodegenerative disorders whilst avoiding detrimental cardiovascular tissue effects which may also contribute to development of dementia[78]. Such analogues are thought to interfere in the progression of AD by aiding clearance of amyloid beta peptides from neurological tissue[78]. In the treated mice there were decreased levels of amyloid beta, along with increased levels of amyloid beta clearing enzymes and improved long term memory[78].

The evidence surrounding changes in sex steroid levels and dementia is inconclusive. There is no firm evidence for a beneficial effect of androgen administration, and the increase in frequency of cardiovascular events causes significant morbidity and may increase the prevalence of dementia itself. This may be due to the significant increase in cholesterol levels associated with falling androgen levels[79]. Additionally, the low levels of androgens demonstrated in some men with dementia may be unrelated or may be secondary to the disease itself.

DISCUSSION

Despite various possible mechanisms for a link between the two pathologies, it is also quite possible that these associations are coincidental and not related to a common aetiological factor. Only one such investigation into common aetiologies exists in a 2014 study which found raised amyloid beta peptide levels in osteoporotic bone tissue compared to age matched controls in female patients[80]. The level of amyloid beta expression negatively correlated with bone density levels in this study[80]. Amyloid beta was found to also have an impact on osteoclast differentiation and activation, implying it may play a role in the pathological processes of osteoporosis[80]. Authors hypothesized amyloid beta disorders to be systemic disorders resulting in differing tissue manifestations[80], yet robust evidence remains to be produced regarding this link and regarding the exact aetiology of amyloid beta in AD.

People with dementia are more prone to falls and fractures due to cognitive and behavioural disorders, visual and motor problems, gait and balance disturbances, malnutrition, and the adverse effects of medication[81]. Thus there may be a higher pick-up rate for osteoporosis amongst this group. However, a population-based study of more than 2600 elderly people found that those with dementia received less preventative treatment for osteoporosis compared to people without dementia[82]. In patients who have received the appropriate prescription, efficacy may be diminished in patients with dementia due to factors such as medical comorbidities, polypharmacy, lack of adherence, substance abuse, delirium and inadequate social support[83].

Nevertheless, we hypothesise that dementia and osteoporosis have common aetiologies as significant counterevidence exists in recent literature. There remains a significant increased prevalence of osteoporosis in AD sufferers in large scale observational studies compared to the general population, with an odds ratio for femoral fracture amongst a French female population the same as that of other severe systemic illnesses (OR = 4, $P < 0.0001$). The mortality and morbidity associated with such fractures in elderly populations prompts continued interest in this area of research[84]. Furthermore, following femoral neck fracture treatment and subsequent inpatient stays, this subsection of the population has been found to have poor return to previous functional states as measured by residential status, along with poor 30-d mortality compared to patients without dementia[85]. Other very large scale observational studies have had compelling results in favour of a potential link, with Chang *et al*[86] finding a 1.46-fold and 1.39-fold higher risk of dementia (95%CI: 1.37-1.56) and AD (95%CI: 0.95-2.02) in osteoporosis patients studied, whilst adjusting for potential confounders such as comorbid disease. This Taiwanese cohort also demonstrated a negative correlation between treatment for osteoporosis (such as bisphosphonates) and the risk of dementia, with the most marked negative correlation found in those taking bisphosphonates and oestrogens[86]. However, patients with dementia have repeatedly been found to be least likely to be prescribed osteoporosis treatments which may have such protective effects both in terms of fracture risk and cognitive health[87]. Despite these recent findings, the same limitations to such large scale retrospective studies apply and further RCTs would be required to provide higher quality evidence of such links despite the varied evidence explored in this paper.

The most compelling evidence for a common aetiology is the APOE4 allele, a major cholesterol carrier, and a well-established genetic risk factor for AD *via* its binding to Amyloid beta peptide and its potential role in deposition of senile plaques[3]. APOE4 has also been found to be associated with fracture, independent of dementia and falling[27]. The mechanism behind this effect on fracture risk is postulated to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele, which binds vitamin K in the plasma and promotes its uptake into the liver more rapidly than other APOE variants. Women who express this allele have a higher risk of osteoporotic fractures than other APOE genotypes found in the general population[1]. This may be multifactorial in its effect and augmented by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. In particular, vitamins D and K are known to play a role in the both bone matrix stability and neuronal protection in the CNS. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies.

Robust evidence of an underlying pathophysiological link between osteoporosis and dementia would potentially transform the care of the older adult. Research to date has tended to be fragmented and of a relatively weak

nature with multiple confounding factors reflecting the difficulties of *in vivo* experimentation in the population of interest. A suggestion for future work would include randomised controlled trials of vitamin supplementation *vs* placebo, stratified for APOE4 and hormone status. As our understanding of the molecular basis of osteoporosis and dementia improves, new therapeutic targets should become apparent.

COMMENTS

Background

Dementia and osteoporosis are diseases processes with similar epidemiology and increasing prevalence in the elderly, where the two coexist in a subsection of the population especially amongst females. The burden of elderly care continues to be a significant challenge to healthcare systems globally. Alzheimer's disease (AD) is the leading cause of loss of independence and autonomy in the elderly and osteoporotic fractures have a huge impact in this patient population in terms of morbidity and mortality. An odds ratio of 6.9 for fracture prevalence between people with and without AD has been reported. In current understanding of the disease aetiologies no pathological overlap has been identified but a common link has been postulated to exist. The pathogenesis of AD is currently understood to involve development of amyloid plaques causing neuronal death and subsequent phosphorylation of Tau proteins, which ultimately cause further neuronal degeneration and the localisation of these two abnormal proteins in the synapses causes post-synaptic neuronal death *via* calcium influx. Despite extensive research into AD and its multifactorial pathophysiology, current treatments are limited by cost and efficacy and their action lies in palliation of symptoms. Osteoporosis in contrast is a progressive skeletal disease characterised by reduced bone density and micro-architectural bone destruction leading to increased susceptibility to fracture. Both diseases have multifactorial pathophysiology and have been associated with other metabolic disturbances including decreased vitamin D levels and elevated parathyroid hormone. Other genetic variants such as the APOE4 allele have also been postulated to link their pathophysiology.

Research frontiers

Both osteoporosis and AD form part of frailty syndrome, a collection of signs and symptoms associated with significant disability in the elderly population and increased public expenditure in healthcare and social care systems. This paper hypothesizes that both diseases share a common predisposing aetiology, which may be multifactorial and involve genetic, metabolic, endocrine and environmental factors.

Innovations and breakthroughs

Many studies have been conducted in the last 60 years exploring various aspects of the pathophysiology of both osteoporosis and dementia as both diseases represent significant burdens upon the affected populations. However very few have been higher tier research designs such as randomised control trials or specifically examined an aetiological link as addressed by the research question of this paper. The authors' key findings were that the most compelling evidence of a common yet independent aetiology lies in the APOE4 allele, which is a well-established risk for AD but also carries an independent association with fracture risk and so osteoporosis. The mechanism behind this is thought to be the reduced plasma vitamin K levels in individuals exhibiting the APOE4 allele which may be amplified by the nutritional deficiencies associated with dementia, which are known to include vitamins K and D. The vitamin theory postulates that malnutrition and reduced exposure to sunlight in patients with AD leads to vitamin deficiencies which are then well associated with increased risk of fracture.

Applications

Discovery of a common aetiological link between the two may prove key in development of novel treatments for these complex medical and social problems. This study found that research to date on this topic has tended to be fragmented and of a relatively weak nature with multiple confounding factors, which may reflect inherent difficulties of *in vivo* experimentation in the population of interest. Despite many theoretical links between the two diseases, there is a lack of systematic high level evidence and as such the link between the two remains theoretical. This study may help direct design of future large scale studies or RCTs in the affected population groups.

Peer-review

This is an interesting study, and what is reviewed is well done.

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SYSTEMATIC REVIEWS

Surgery for calcifying tendinitis of the shoulder: A systematic review

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Abstract

AIM

To systematically search literature and determine a preferable surgical procedure in patients with failed conservative treatment of calcifying tendinitis of the shoulder.

METHODS

The electronic online databases MEDLINE (through PubMed), EMBASE (through OVID), CINAHL (through EBSCO), Web of Science and Cochrane Central Register of Controlled Trials were systematically searched in May 2016. Eligible for inclusion were all available studies with level Ⅱ and level Ⅲ evidence (LoE). Data was assessed and extracted by two independent review authors using a specifically for this study designed data extraction form.

RESULTS

Six studies (294 surgically treated shoulders) were included in this review. No significant differences between the three available treatment options (acromioplasty with the removal of the calcific deposits, acromioplasty or solely the removal of the calcific deposits) were detected regarding the functional and clinical outcome. The follow-up ranged from 12 mo to 5 years. Complication rates were low. No reoperations were necessary and the only reported complication was adhesive capsulitis, which in all cases could be treated conservatively with full recovery.

CONCLUSION

We found that all three available treatment options show good functional and clinical outcomes in the short and midterm. However, a favorable procedure is difficult to determine due to the lack of high-quality comparing studies.

Key words: Calcifying tendinitis; Surgery; Systematic review; Acromioplasty; Debridement

Core tip: All three available surgical treatment options (acromioplasty with the removal of the calcific deposits, acromioplasty or solely the removal of the calcific deposits) show good functional and clinical results and low complication rates. However, more high-quality comparative research is needed to appoint a preferential procedure.

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INTRODUCTION

Calcifying tendinitis (CT) of the shoulder is a common disease. It is one the most frequent causes of non-traumatic shoulder pain and has a high disease burden. In a healthy population the incidence of subacromial calcific deposits is 2.7%[1]. In patients with shoulder complaints this number rises to 6.8%. CT mainly affects individuals between 30 and 60 years of age. Males and females are equally affected[1-3]. The calcific deposits are most frequently (80%) seen in the supraspinatus tendon, at a typical location of 1.5 to 2.0 cm of its insertion on the major tuberculum. CT is primarily treated conservatively, though in about 10% of the cases this fails. Then often surgery is a last resort. The etiology of CT remains unclear and is still a matter of dispute. Some authors state that CT is not related to subacromial impingement[2]. This is supported by the histological finding in the study of Uhthoff *et al*[4]. In this study only minimal signs of inflammation in the rotator cuff of patients with CT were seen. Conversely, other authors observed that there was neovascularization and influx of phagocytes around the calcific deposits. As they state this could lead to subsequent edema of the rotator cuff and an increase of the intratendinous pressure. This theoretically can lead to secondary subacromial impingement as the thickened and calcified tendon decreases the subacromial space. Others state that impingement causes rotator cuff tendinitis, which when chronically apparent leads to CT, due to decreased local oxygen tension or hypoxia[1,2,5,6].

There are several surgical procedures available, mostly in accordance with the above-mentioned theories. In the current orthopedic literature three major surgical strategies have been postulated. The first is an acromioplasty in combination with removal of the calcific deposits, the second is an acromioplasty without removing the calcific deposits and the third surgical procedure is to solely debride the calcific deposits and leave the acromion untouched. However, there is still some debate what is the most preferable procedure. It remains unclear whether the calcific deposits need to be, completely or partially, removed and if an additional acromioplasty is beneficial.

Therefore, the objective of this study is to determine if there is a preferable surgical procedure in patients with conservative treatment resistant CT. We performed a systematic review with two clear research questions: (1) Is there a difference in functional and clinical outcomes after debridement of the calcifications in comparison with debridement and additional acromioplasty on the short- and mid-term; and (2) Is there a difference in the functional and clinical outcomes after acromioplasty compared to acromioplasty with debridement of the calcifications on the short- and mid-term?

MATERIALS AND METHODS

This review was performed and written down following the principles of the PRISMA statement[7]. Five relevant electronical databases (MEDLINE through PubMed, EMBASE through OVID, CINAHL through EBSCO, Web of Science and Cochrane Central Register of Controlled Trials) were systematically searched by one review author (FV) in May 2016 for studies in English, German and Dutch. Furthermore, the reference lists of the included articles and available reviews were crosschecked for possible relevant studies. The search was set up using a PICO format [patient (or disease), intervention (drug or treatment), comparison (another drug of treatment) and outcome], from which search terms were deduced, as can be seen in Table 1. Studies eligible for inclusion were Level of Evidence (LoE) Ⅱ (randomized controlled trials) and LoE Ⅲ (comparative cohort studies) that compared different surgical procedures for CT of the shoulder. From the selected articles, the authors, their institutions and the journal name were masked, a few weeks before data assessment took place.

Data assessment and management

Risk of bias and the quality of the included studies were assessed independently by two authors (FV, EF). The included RCTs and quasi-RCTs were assessed using the 12 quality criteria of Furlan *et al* (2008). High-Quality was defined as a "yes" score in ⩾ 50% of all items[8]. The non-randomized studies were assessed using the Newcastle-Ottawa assessment scale[9]. Disagreements were resolved by consensus, or when necessary a third review author (JWM) was consulted. Data was independently extracted by two reviewers (FV, EF) and crosschecked for accuracy. The reviewers were blinded to the authors of the included articles, their institutions, and the journals in which they were published. Data from each individual study was extracted in a standardized way using a specifically designed extraction form (appendix 1 in supplemental material). Discrepancies were resolved by scrutinizing the original article until a consensus was reached. Extracted data included information such as inclusion and exclusion

Table 1 PICO search strategy

Population	Patients with radiographically confirmed symptomatic tendinitis calcarea of the shoulder (search terms: Shoulder joint, rotator cuff, shoulder, supraspinatus, infraspinatus, subscapular or teres, impingement syndrome, tendinopathy, tendonitis or tendinitis, tendinosis, calcinosis, calcifying, calcification, calcified, calcific, calcarea)
Intervention	Surgery (search terms: Surgery, surgical, orthopaedic surgery, shoulder surgery, acromioplasty, debridement, bursectomy, arthroscopic, Neer)
Comparison	Surgery (search terms: Surgery, surgical, orthopaedic surgery, shoulder surgery, acromioplasty, debridement, bursectomy, arthroscopic, Neer)
Outcome	Functional and clinical outcome
Limits	Language: English, German, Dutch Publication year: 1996-2016 Human

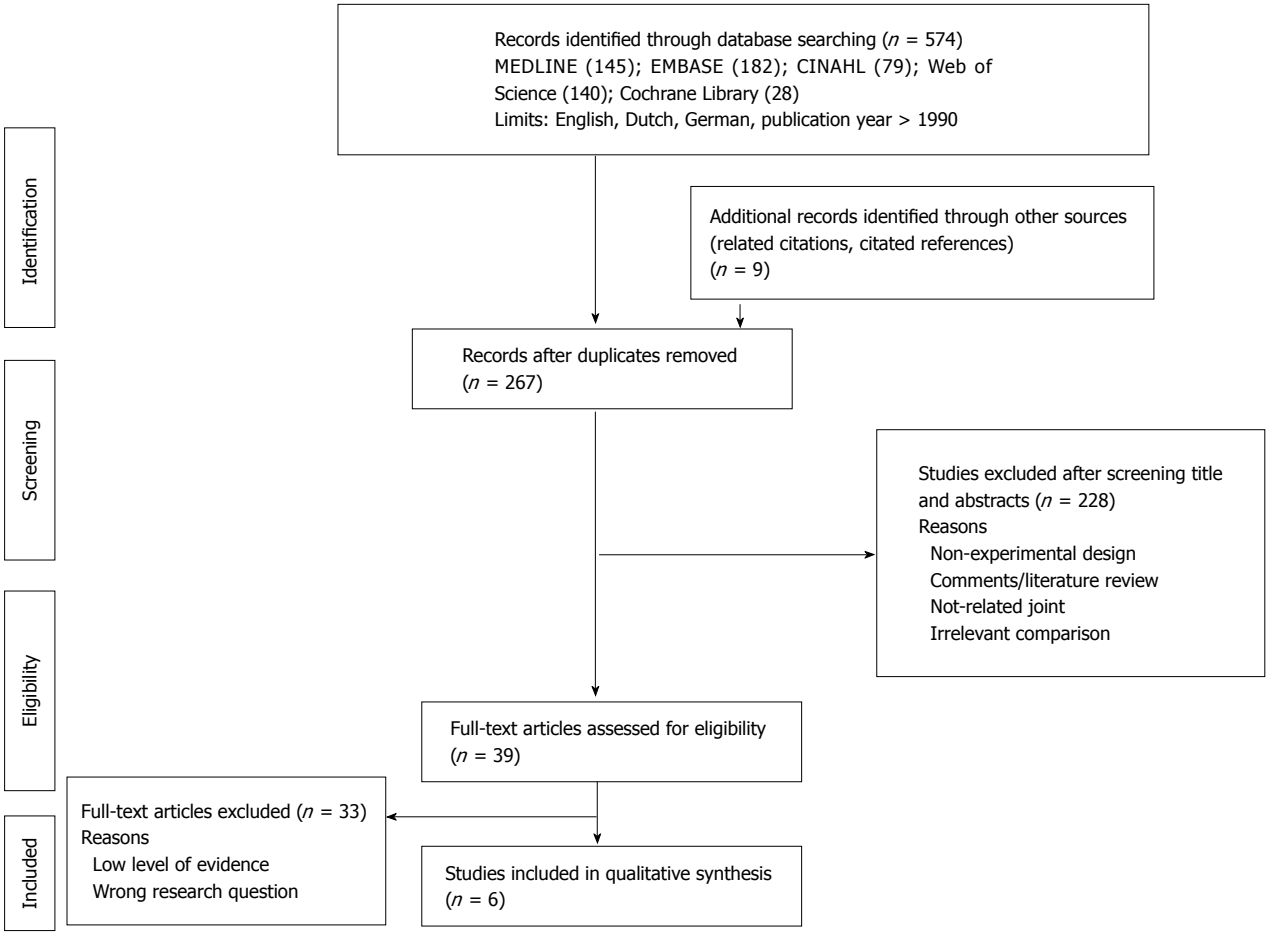

Figure 1 PRISMA flow diagram.

criteria, inclusion period, method of randomization, specific characteristics of the patient groups, specific surgical information, primary and secondary outcomes, baseline characteristics, statistics used, results and complications (appendix 2 in supplemental material). In case of missing information, we tried to contact the authors of the identified studies.

Data analysis

Whenever possible data was pooled. When pooling was not possible, due to clinical heterogeneity of the included studies based on the included intervention and/or study population, data is presented in a quality synthesis.

RESULTS

Using the above-mentioned search strategy (appendix 3 in supplemental material) 574 potential relevant studies were identified (Figure 1); of which 267 remained after removing the duplicates. After screening of the titles and abstracts 228 studies were excluded. The main reasons for exclusion were that the studies did not concern the shoulder, were non-experimental studies, or made an irrelevant comparison. The full-texts were read in 39 studies. Finally, 6 studies were included in

Table 2 Characteristics of the included studies

Ref.	Study design (LoE)	Population	Mean age (range)	Duration of symptoms in months (range)	Interventions	Outcome measures	Findings	
							Baseline	Follow-up
Rubenthaler *et al*[10]	RCT (Ⅱ)	38	51.1 (-)	-	Arthroscopic debridement + acromioplasty *vs* Open debridement + acromioplasty	Patte score, VAS, CMS	No significant baseline differences	16 mo: CMS: 86.0 *vs* 85.3 (NS) VAS: 1.4 *vs* 1.8 (NS) Patte score: 84.4 *vs* 84.6 (NS)
Clement *et al*[11]	RCT (Ⅱ)	80	49 (32-75)	6.2 (-)	Arthroscopic debridement + acromioplasty *vs* arthroscopic debridement	VAS, DASH, CMS, SF-12	No significant baseline differences	6 wk: CMS: 62.2 *vs* 64.1 (NS) DASH: 24.5 *vs* 24.0 (NS) VAS: 4.4 *vs* 4.5 (NS) SF-12: 45.7 *vs* 44.3 (NS) 12 mo: CMS: 82.4 *vs* 77.5 (NS) DASH: 14.5 *vs* 14.0 (NS) VAS: 1.6 *vs* 2.5 (NS) SF-12: 43.0 *vs* 42.5 (NS)
Hofstee *et al*[12]	Quasi-RCT (Ⅲ)	40	52.3 (41-62	14.5 (6-36)	Arthroscopic debridement + acromioplasty *vs* arthroscopic debridement	DASH, VAS, satisfaction, ROM	No significant baseline differences	36 mo: DASH: 3.14 *vs* 3.04 (NS) VAS: 4.3 *vs* 4.2 satisfied, yes: 80% *vs* 75%
Marder *et al*[13]	Retrospective case-control study (Ⅲ)	50	44 (27-67)	13 (-)	Arthroscopic debridement *vs* arthroscopic debridement + acromioplasty	QuickDASH, RTW, UCLA	No significant baseline differences	6 wk: RTW: 60% *vs* 20% (P = 0.004) 5 yr: QuickDASH: 6.3 *vs* 11.1 (NS) VAS: not well recorded UCLA: 32.0 *vs* 32.4 (NS)
Tillander *et al*[14]	Matched pair analysis (Ⅲ)	50	50 (40-67)	66 (12-216)	Arthroscopic acromioplasty in patients with *vs* without CT	CMS, satisfaction, radiological	No significant baseline differences	24 mo: CMS: 78 *vs* 79 (NS) Satisfaction, yes: 72% *vs* 80% (NS)
Maier *et al*[15]	Comparative cohort study (Ⅲ)	36	48.9 (29-70)	35.2 (9-84)	Open debridement *vs* open debridement + acromioplasty	CMS	No significant baseline differences	34 mo: CMS: 74.9 *vs* 73.4 (NS)

RCT: Randomized controlled trial; CMS: Constant-Murley score; DASH: Disabilities of Arm, Shoulder and Hand score; VAS: Visual Analog Scale for pain; UCLA: University of California-Los Angeles score; RTW: Return to work; -: No information available in included study; NS: Not significant.

this review, concerning 294 surgically treated shoulders with CT.

Characteristics

Study characteristics of the included studies are summarized in Table 2. Of these 6 studies there were two were RCTs (118 participants), one quasi-RCT (40 participants) and three comparative cohort studies (136 participants). The data could not be pooled because of the incompleteness of the extracted data and owing to the diversity in timing of the outcome moments (range, 6 wk-5 years).

Data assessment

The risk of bias was assessed by two independent review authors (FV, EF). Three studies were evaluated with the 12 criteria of Furlan *et al*[8], and three studies were evaluated with the Newcastle-Ottawa scale[9]. Two RCTs were assessed as high-quality RCTs (Table 3), whereas in the non-randomized group one study received the maximum score and the other two studies had a near to maximum score (Table 4). Results of the functional outcome are presented using different outcome measures, namely the Constant-Murley score (CMS), Patte score and the University of California-Los Angeles score (UCLA). The results of the clinical outcome are presented with various outcomes measures, including the Disabilities of Arm, Shoulder and Hand score (DASH) and return to work, as can be seen in Table 2.

Debridement vs debridement with additional acromioplasty

The studies of Rubenthaler *et al*[10], Clement *et al*[11], Marder *et al*[12] and Maier *et al*[13] aided in answering the

Table 3 Methodological quality scores of the individual included randomized controlled trial's and qausi-randomized controlled trial

Ref.	Adequate randomization?	Allocation concealment?	Blinding patients?	Blinding caregiver?	Blinding outcome assessors?	Incomplete outcome data addressed? dropouts	Incomplete outcome data? ITT-analysis?	No selective outcome reporting?
Rubenthaler *et al*[10]	+	+	+	-	?	+	-	+
Clement *et al*[11]	+	+	+	-	+	+	-	+
Hofstee *et al*[12]	-	-	?	-	?	+	-	+

12 quality criteria of Furlan *et al*[8]. +: Yes = 1 point; -: No = 0 points; ?: Unclear/unsure = 0 points. High-quality ⩾ 50%, Low-quality ⩽ 50%.

Table 4 Methodological quality scores of the individual included comparative cohort studies

Ref.	Selection (max = ****)	Comparability (max = **)	Exposure (max = ***)
Marder *et al*[13]	***	**	***
Tillander *et al*[14]	****	**	***
Maier *et al*[15]	***	**	***

Newcastle-Ottawa Scale[9].

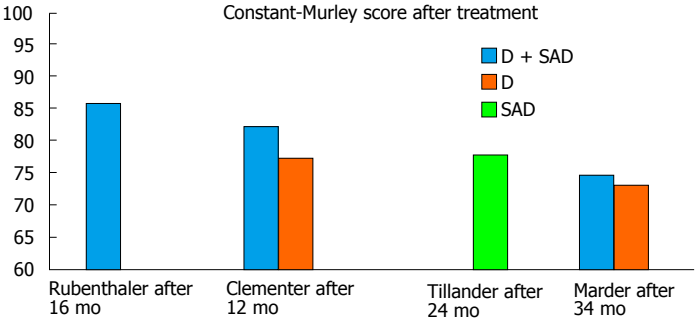

Figure 2 Constant-Murley score after treatment. D: Debridement; SAD: Subacromial decompression.

first research question (Figure 2).

Functional outcome: For the comparison of the functional outcome on the short and midterm only the RCT of Clement *et al*[11] reported data 6 wk and 12 mo after debridement *vs* debridement with acromioplasty. They reported no significant difference after 6 wk (mean CMS 62.2 *vs* 64.1) and 12 mo (mean CMS 82.4 *vs* 77.5). Rubenthaler *et al*[10] reported the results after debridement with acromioplasty in an open *vs* arthroscopic procedure (mean CMS 86.0 *vs* 85.3). Marder *et al*[13] and Maier *et al*[15] reported data of debridement *vs* debridement with acromioplasty after 5 years and 34 mo, respectively. The mean UCLA of 32.0 *vs* 32.4 after 5 years did not differ significantly and the mean CMS of 74.9 *vs* 73.4 after 34 mo did not differ either.

Clinical outcome: The clinical outcome was reported by Clement *et al*[11] and Marder *et al*[13] using the DASH score and QuickDASH score. The clinical outcome did not differ significantly in the short and midterm (6 wk: mean DASH 24.5 *vs* 24.0 and 12 mo: mean DASH 14.5 *vs* 14.0). After 5 years the mean QuickDASH did not differ significantly either (6.3 *vs* 11.1).

Acromioplasty vs acromioplasty with additional debridement

The studies of Hofstee *et al*[12] and Tillander *et al*[14] were helpful in answering the second research question. There was no information available for the comparison of the results in the short term.

Functional outcome: Tillander *et al*[14] reported results of the functional outcome after 24 mo after solitary acromioplasty in patients with and without CT. The mean CMS was 78.0 and 79.0, respectively. As an indication of the functional outcome Hofstee *et al*[12] reported the ROM after 36 mo. In all six planes the ROM did not differ significantly between patients after acromioplasty in comparison with patients after acromioplasty with debridement.

Clinical outcome: Hofstee *et al*[12] reported a DASH score of 3.1 *vs* 3.0 after 36 mo of surgery which was not significantly different.

Complications

Four of the included six studies reported information about adverse events or complications[10,11,13,15]. There were no intraoperative complications reported, none of the included patients required reoperation. The only complication reported was adhesive capsulitis. In the studies of Clement *et al*[11] and Marder *et al*[13], one patient (1.3%) and three patients (6%) showed signs of adhesive capsulitis. These patients could all could be treated conservatively and showed full recovery at the

end of the follow-up.

DISCUSSION

CT is often a self-limiting disease which in the majority of the patients can be managed with conservative measures, such as physical therapy, subacromial infiltrations, shock wave therapy or needling. However, in some patients these conservative measures fail and surgery is needed. Based on the results of this systematic review of LoE Ⅱ and Ⅲ evidence, we found that all three available treatment options show good functional and clinical outcomes in the short and midterm. However, a favored procedure is difficult to determine due to the lack of high-quality comparing studies.

Regarding the first research question four studies aided in answering this "question"[10,11,13,15]. The functional and clinical outcome did not differ after debridement *vs* debridement with an additional acromioplasty. It could be postulated that CT is not correlated with subacromial impingement and an acromioplasty does not seem to be beneficial. This supports the aforementioned theory of Gärtner *et al*[2]. Of the other outcomes extracted from the included studies, only in the study of Marder *et al*[13] did significantly more patients return to work after six weeks (Table 2). In the included RCT[11] an additional acromioplasty was not found to be beneficial. Though, in this study the (patho)anatomy (*e.g.*, classification of Bigliani[16]) of the acromion was not considered. It has been postulated that if there are any radiological or intraoperative signs of impingement an acromioplasty can be performed[16,17].

The studies of Hofstee *et al*[12] and Tillander *et al*[14] aided in answering the second research question. They found good functional and clinical results 24 and 36 mo after an acromioplasty and an acromioplasty with an additional debridement of the calcifications. They found no significant differences. Short term results were not available. Other variables (VAS and satisfaction) also did not differ significantly. These results support the correlation between CT and subacromial impingement. Whereas, this suggests that the complete or partial debridement of the calcific deposits is not necessary.

All three available treatment options are safe; the complication rates are low and the reported complications were treated conservatively and showed full recovery. In the included studies the percentage of adhesive capsulitis was low, comparing to the current literature where rates as high as 18% are reported[18-20]. In the included studies in which a debridement was performed the rotator cuff defect was not sutured afterwards, even though no rotator cuff tears were seen in our entire study population.

Some limitations apply to this systematic review. The main limitation is the lack of high-quality, preferably randomized, comparing trials between the different treatment options. Two high-quality RCTs were included of which one did not make the exact comparison we were interested in. The other one was valuable, however the follow-up was rather short (one year). Therefore, there is a need for more research on this topic. The data could not be pooled due to heterogeneity of the included studies and therefore no quantitative analysis could be made. We analyzed the causes of this heterogeneity. But, we could not improve this sufficiently; therefore data is presented in a narrative fashion. On the other hand, we were able to detect all relevant LoE Ⅱ and Ⅲ evidence regarding the surgical treatment options of CT and describe their results in this concise review.

All three available surgical treatment options for patient with conservative therapy resistant CT of the shoulder show good functional and clinical outcome and are safe procedures. Based on this systematic review a preferable treatment option could not be appointed and therefore recommendations cannot be made. Future research should be aimed at comparing all three available options. This is preferably done in a randomized fashion including a short, mid and long term follow-up.

COMMENTS

Background

There still is no consensus on what is the best surgical treatment of therapy resistant calcifying tendinitis of the shoulder. Different authors opt different surgical procedures. The authors tried to identify the surgical treatment with the best functional and clinical outcome.

Research frontiers

Calcifying tendinitis was probably first diagnosed by Plenk *et al* in 1953. Up till to today the exact etiology is still unclear. In the majority of the cases the disease resolves spontaneously or with conservative measures. However, sometimes surgery is necessary. Several authors have pointed out the beneficial effect of an additional acromioplasty with the debridement of the calcific deposits.

Innovations and breakthroughs

Although this disease is extensively studied the exact surgical management has not been clarified yet. There were several comparative studies available but Clement *et al* were in 2015 the first to publish a randomized study on this particular subject. They stated that an additional acromioplasty was not beneficial.

Applications

This review suggests that all three available surgical options are safe and effective. However, a preferable could not be appointed.

Terminology

SAD is a subacromial decompression which is the resection of the anterolateral part of acromion and release of the coracoacromial ligament.

Peer-review

This is a very interesting and well planned study.

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SYSTEMATIC REVIEWS

Effect of lengthening along the anatomical axis of the femur and its clinical impact

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Abstract

AIM

To review and study the effect of lengthening along the anatomical axis of long bones and its relation to the mechanical axis deviation.

METHODS

We try in this review to calculate and discuss the exact clinical impact of lengthening along the anatomical axis of the femur on affecting the limb alignment. Also we used a trigonometric formula to predict the change of the femoral distal anatomical mechanical angle (AMA) after lengthening along the anatomical axis.

RESULTS

Lengthening along the anatomical axis of the femur by 10% of its original length results in reduction in the distal femoral AMA by 0.57 degrees. There is no objective experimental scientific data to prove that the Mechanical axis is passing *via* the center of the hip to the center of the knee. There is wide variation in normal anatomical axis for different populations. In deformity correction, surgeons try to reproduce the normal usual bone shape to regain normal function, which is mainly anatomical axis.

CONCLUSION

Lengthening of the femur along its anatomical axis results in mild reduction of the distal femoral AMA. This may partially compensate for the expected mechanical axis lateralisation and hence justify its minimal clinical impact.

Key words: Bone lengthening; Deformity; Femoral lengthening; External fixation; Intramedullary nail; Axis deviation

Core tip: In deformity correction the aim is to reproduce

the normal anatomical shape of the bone to regain normal function. There is no experimental data to prove the passage of the imaginary mechanical axis and load distribution of the body *via* the center of the hip to the center of the knee. Lengthening along anatomical axis of the bone is expected to cause minimal or no clinical effect on mechanical axis and load distribution on joints.

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INTRODUCTION

The goal of recent advances in the field of limb lengthening is to increase the patient acceptance and comfort and avoid the common complications of the classic external fixators. One important achievement is the use of totally implantable intramedullary distracting nails for tibia and femur. Among them, the Albizzia nail (DePuy, Villeurbanne, France), Fitbone (Wittenstein, Igersheim, Germany), Intramedullary Skeletal Kinetic Distractor (ISKD, OrthofixInc., McKinney, TX, United States) and Precise nail (Ellipse Technologies Inc., Irvine, California) were used successfully[1,2]. These are self-lengthening telescopic intramedullary rods, which could be fully motorized or un-motorized and depend on external apparatus or limb movement to make them extend[1]. Intramedullary lengthening utilizes the anatomical axis of the bone, in contrast to lengthening with external fixators which occurs along the mechanical axis. In the tibia, no difference would be detected after either ways of lengthening since the anatomical and mechanical axes of the tibia are almost the same[3]. However, in normal femora, the mechanical and anatomic femoral axes diverge by approximately 5°-9°. This angle is known as the anatomic-mechanical angle (AMA)[2-4]. When using intramedullary lengthening in femora, lateralization of the overall limb alignment has been observed both theoretically and radiologically[2-7]. The amount of mechanical axis lateralization has been documented by Burghardt *et al*[2], who concluded that each 1 cm lengthening of the femur results in about 1 mm lateralization of the mechanical axis radiologically. However, the exact clinical outcome of such mechanical axis lateralization has not been presented clearly in literature. The purpose of this study is to review the exact effect of lengthening along the anatomical axis on disturbing the normal mechanical alignment of the limb and hence distribution of load along the joint surface. We have reviewed the trigonometric formula to predict the change of the femoral AMA after lengthening along the anatomical axis, and reflected the results on the clinical outcome of mechanical axis deviation.

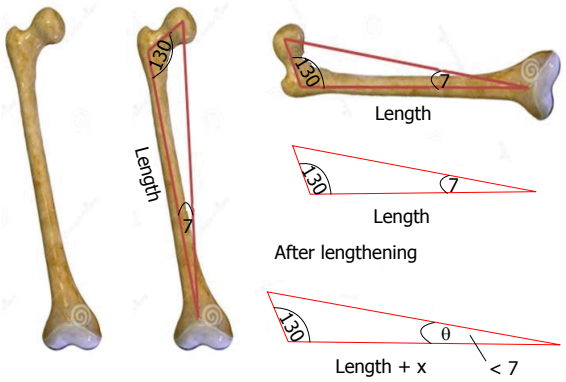

Figure 1 Femoral lengthening along the anatomical axis (length) affects the femoral anatomical mechanical angle (assumed to be 7 degrees). Increasing the femoral length along the anatomical axis would cause degrease in the anatomical mechanical angle (θ).

MATERIALS AND METHODS

Trigonometry was used to calculate the change in the angle between the femoral mechanical and anatomical axes resulting from lengthening along the anatomical axis. The original angle is assumed to be 7°, where "θ" is the angle after lengthening the femur a distance of "x" cm (Figure 1).

The angle θ was calculated for different original bone lengths and different lengthening distances. Original bone lengths used in our calculations are average lengths that vary from 21 cm for a 3 years old, up to 44 cm for an adult female and 47 cm for an adult male[6]. Femur lengths were considered for different ages with a step of 3 years of age, and so 3, 6, 9, 12, 15 years old, adults' femurs were considered. Lengthening distances that were considered to vary from 3 to 18 cm, adding 3 cm each step (3, 6, 9, 12, 15, and 18) (Figure 2).

RESULTS

Results of the change of the femoral AMA after lengthening were expressed in Table 1. From the calculations, it was deduced that increasing the bone length by 10% its original length results in reduction of the angle between the mechanical and anatomic axes by 0.57°, and increasing the length by 20% reduces the angle by 1.05° approximately.

DISCUSSION

Our hypothesis was that the femoral lengthening along the anatomical axis with a telescopic intramedullary nail induces reduction of the femoral anatomical mechanical angle (AMA) which is normally around 7°. This may compensate for the limb mechanical axis that lateralization that was proven both theoretically and radiologically[2-4,6], and hence could partially justify the minimal clinical impact of such mechanical angle lateralization after intramedullary lengthening.

A shift of the mechanical axis of the limb has been

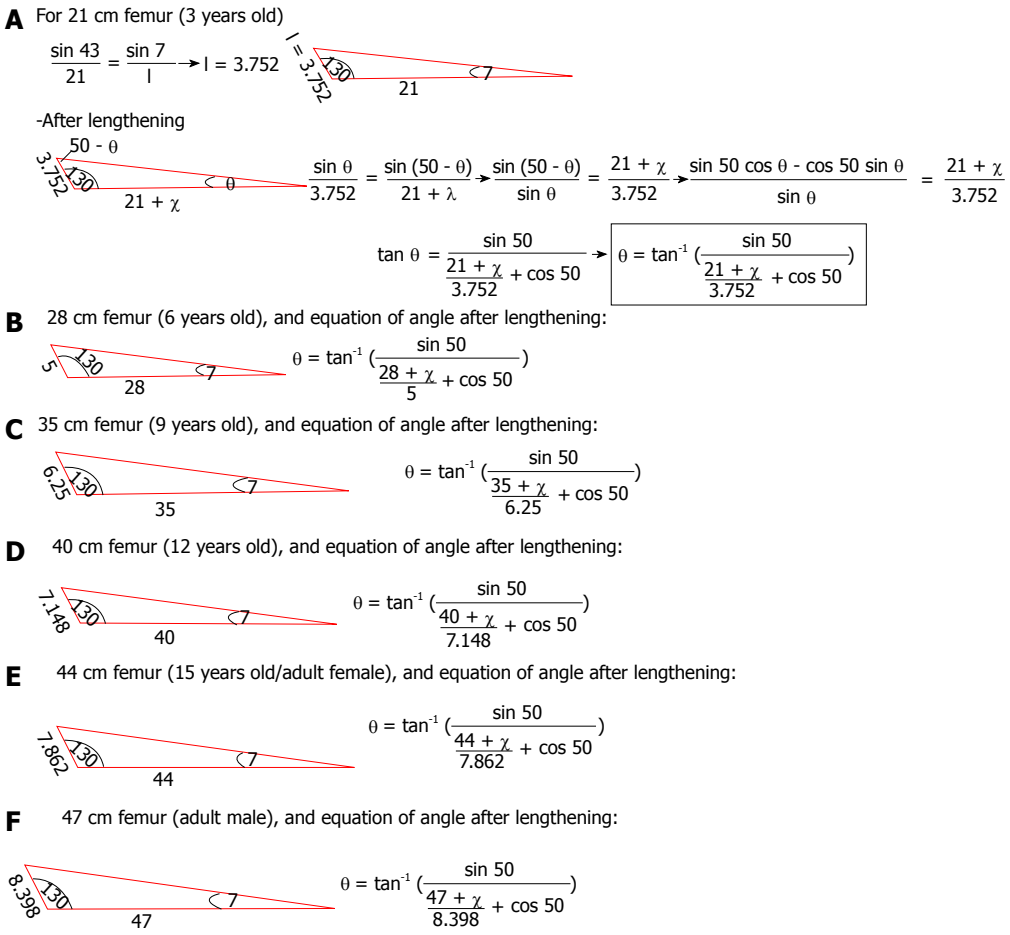

Figure 2 Calculation of the changes in the θ angle after lengthening of different sizes of femora using Law of Sines (A-F).

reported differently in studies about lengthening with a telescopic intramedullary nails[2,8-11]. Theoretically, Burghardt *et al*[4] found lateralization of the limb mechanical axis after lengthening along the anatomical axis using trigonometry. Radiologically, Bughdart *et al*[2] found that 26 of 27 limbs which had intramedullary lengthening with the Precise nail, had a lateral shift of the mechanical axis, and concluded that lengthening of the femur by 1 cm causes lateral shift of the limb mechanical axis by 1 mm. In a similar study about femoral lengthening with the Albizzia nail, Guichet *et al*[12] found that a lateral shift of the mechanical axis of the limb was seen in all the study cases, with a mean increase in the genu valgum angle by 1.04 degrees, however they could not find a constant correlation between the amount of mechanical axis deviation and the gain in femoral length. Similarly, Baumgart *et al*[8] found a maximal mechanical axis deviation of 2 mm after using fully motorized intramedullary nails in femoral lengthening, and hence they recommended shifting the distal fragment laterally before reaming, in order to achieve normal mechanical alignment. Other similar studies about intramedullary femoral lengthening either have not commented on the mechanical axis deviation[9], noticed very rare occurrence of mechanical axis deviation[5,10] or did not find any mechanical axis alteration nor angular deformities after lengthening[11].

On the other hand, all the studies which found a radiological mechanical axis deviation after femoral lengthening with intramedullary nails did not comment on the isolated femoral axes relation changes, which in our case represented by the distal femoral AMA. Clinically, all these studies have described that mechanical axis lateral shift to be inconsequent or clinically insignificant[2,5,7,9-12]. This might support our hypothesis, that such mechanical axis shift could be partially compensated by reduction in the distal femoral AMA concluded in our study, and hence no clinical consequences could be observed. Also this might be attributed due to the wide variation of the mechanical limb alignment in (normal) individuals. In the study of Ekhoff *et al*[13], only 2% of normal limbs included in the study have a neutral mechanical axis, and as many as 76% deviate from neutral by > 3° varus when measured using CT. Also, Bellemans *et al*[14] found that limb alignment differs between males and females as studied by using full-length lower limb radiographs. In this study, 32% of male and 17.2% female knees were in > 3° of constitutional varus. Similarly, Yaniv *et al*[15] found that varus knee axis deviation is normally present in football players older than 13 years old.

The mechanical axis is supposed to be the line of body weight loading the joints to the ground, and since

Table 1 Changes in the anatomical mechanical angle after lengthening

Femur length (cm)	X	P	θ	Δθ
21	3	14	6.21	0.79
	6	28	5.58	1.42
	9	42	5.06	1.94
	12	57	4.64	2.36
	15	71	4.28	2.72
	18	85	3.97	3.03
28	3	10	6.38	0.62
	6	21	5.87	1.13
	9	32	5.44	1.56
	12	42	5.06	1.94
	15	53	4.73	2.27
	18	64	4.45	2.55
35	3	8	6.5	0.5
	6	17	6.07	0.93
	9	25	5.69	1.31
	12	34	5.36	1.64
	15	42	5.06	1.94
	18	51	4.8	2.2
40	3	7	6.56	0.44
	6	15	6.17	0.83
	9	22	5.83	1.17
	12	30	5.52	1.48
	15	37	5.25	1.75
	18	45	5	2
44	3	7	6.6	0.4
	6	13	6.24	0.76
	9	20	5.92	1.08
	12	27	5.63	1.37
	15	34	5.37	1.63
	18	41	5.13	1.87
47	3	6	6.62	0.38
	6	12	6.28	0.72
	9	19	5.98	1.02
	12	25	5.7	1.3
	15	32	5.45	1.55
	18	38	5.22	1.78

X: Distance lengthened (cm); P: Percentage lengthened distance of the original bone length (%), θ: Angle between mechanical and anatomical axes after lengthening (degree); Δθ: Change in the angle between mechanical and anatomical axes due to lengthening (degree).

the body centre of gravity could be affected greatly by postural abnormalities that may be present in different patients, marked differences in the limb mechanical axes could be seen in different individuals. The situation is further complicated by differences in the alignment of the limb when measured in a lying position (which is non-weight bearing) and in a weight-bearing standing position[16]. In a study by Deep *et al*[17], they found the limb alignment to be dynamic process that differs according to different postures, and also varies between males and females in normal knees. Deep *et al*[17] found also a greater tendency into varus malalignment in the study group with normal non-arthritic knees, that go into more varus when changing the position from supine to standing. Walcox *et al*[16] found similar changes in arthritic knees. Again, the presence of nutritional abnormalities in Calcium and vitamin D metabolism could lead high prevalence of mechanical axes varus malalignment in normally looking adolescents[18]. Again, in general population and different races, there is a range of varus and valgus deformation that has no clinical effect, and there is no fixed number for the normal anatomical shape of human bone. Some mild change during lengthening can stay in most of the cases within this range. The assumption of fixed normal passage of mechanical loading on the limb is not exactly compatible with reality due to the different positions the normal human body use along the day in normal life. Also there is no objective Empirical data to prove where is the normal passage of mechanical axis in relation to the human joints. Since the aim of deformity correction surgery is to reproduce the near normal anatomical shape of bones to improve function, anatomical axis should be the main guide for surgeons in deformity correction and limb reconstruction.

All these data, beside the fact that even the documented amount of mechanical axis lateralization, 1 mm for each 1 cm lengthening, remains very little, this may further justify that the actual implementation of the mechanical axis deviation on the clinical outcome could be very mild or even non significant.

In conclusion, although mechanical axis lateralization after lengthening along the anatomical axis was documented theoretically and radiologically in literature, we found that lengthening of the femur along the anatomical axis theoretically reduce the distal femur AMA by around 0.57 degrees approximately for lengthening by 10% of the original bone length. This change, along with the high variation of population mechanical limb alignment could justify the minimal clinical effect seen with of such mechanical axis deviation after femoral lengthening along the anatomical axis.

COMMENTS

Background

Bone lengthening and deformity correction surgery consider the mechanical and anatomical axes during the surgical planning and treatment. This review article aim to stimulate critical thinking to some fixed ideas in the community of orthopaedic surgeons, specially pediatric orthopedics and limb reconstruction.

Research frontiers

There are objective data about anatomical shape of bone and the range of normal variation but there is no sufficient data regarding the normal mechanical axis and its variation between normal population.

Innovations and breakthroughs

The authors recommend considering anatomical axis as the main guide for lengthening, and not to over emphasize on mechanical axis, and mild variations in anatomical axis during lengthening.

Applications

Lengthening along anatomical axis is safe and effective.

Terminology

Anatomical and mechanical axis are terms used in deformity correction and bone lengthening.

Peer-review

The authors present a review article about the effects of lengthening along the anatomical axis, using a trigonometric approach. They refer to the topic of

mechanical axis lateralisation in intramedullary limb lengthening and check the clinical relevance.

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CASE REPORT

Chest pain caused by multiple exostoses of the ribs: A case report and a review of literature

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Abstract

The aim of this paper is to report an exceptional case of multiple internal exostoses of the ribs in a young patient affected by multiple hereditary exostoses (MHE) coming to our observation for chest pain as the only symptom of an intra-thoracic localization. A 16 years old patient with familiar history of MHE came to our observation complaining a left-sided chest pain. This pain had increased in the last months with no correlation to a traumatic event. The computed tomography (CT) scan revealed the presence of three exostoses located on the left third, fourth and sixth ribs, all protruding into the thoracic cavity, directly in contact with visceral pleura. Moreover, the apex of the one located on the sixth rib revealed to be only 12 mm away from pericardium. Patient underwent video-assisted thoracoscopy with an additional 4-cm mini toracotomy approach. At the last 1-year follow-up, patient was very satisfied and no signs of recurrence or major complication had occured. In conclusion, chest pain could be the only symptom of an intra-thoracic exostoses localization, possibly leading to serious complications. Thoracic localization in MHE must be suspected when patients complain chest pain. A chest CT scan is indicated to confirm exostoses and to clarify relationship with surrounding structures. Video-assisted thoracoscopic surgery can be considered a valuable option for exostoses removal, alone or in addiction to a mini-thoracotomy approach, in order to reduce thoracotomy morbidity.

Key words: Multiple hereditary exostoses; Thoracoscopy; Ribs exostoses; Chest exostoses; Chest pain

Core tip: This is a report of an exceptional case of multiple internal exostoses of the ribs in a young patient affected by Multiple hereditary exostoses observed for chest pain as symptom of an intra-thoracic localization. Chest pain could be the only symptom of an intra-thoracic

localization, possibly leading to serious complications. Thoracic localization must be suspected when patients complain chest pain. Computed tomography scan in indicated to confirm exostoses and to clarify relationship with surrounding structures. Video-assisted thoracoscopy surgery can be considered a valuable option for exostoses removal, alone or in addiction to a mini-thoracotomy approach, in order to reduce thoracotomy morbidity.

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INTRODUCTION

The aim of this paper is to report an exceptional case of multiple internal exostoses of the ribs in a young patient affected by multiple hereditary exostoses (MHE), who came to our observation complaining chest pain as the only symptom of an intra-thoracic localization. MHE is also known as diaphyseal aclasia, Osteochondromatosis or multiple osteochondroma. It is an autosomal dominant disorder with growth plate-like exostoses next to long bones and other skeletal elements.

Usually, all affected individuals are diagnosed by age 12 years, but the median age of diagnosis is three years. The risk for malignant degeneration to osteochondrosarcoma increases with age[1].

The diagnosis of MHE is based on clinical-radiographic results of multiple exostoses in members of a family. The two genes involved are known to cause MHE are EXT1 and EXT2. Mutations in both EXT1 and EXT2 are detected in 70%-95% of affected individuals[2]. Exostoses of the rib are extremely rare, contributing to approximately 1% of all exostoses in MHE[3-5]. We report the case of a patient, complaining only chest pain, affected by MHE with three exostoses protruding directly into the thoracic cavity.

CASE REPORT

A 16 years old patient with familiar history of MHE, came to our observation for a right sided knee-pain caused by an exostoses of the distal femur irritating the surrounding aponeurotic structures. The patient had undergone several surgical procedures for exostoses removal on both femur, tibia and fibula, left radius and fourth finger of the right hand, all performed by our Unit. During physical examination, patient reported even having a left-sided chest pain. This pain had increased in the last months with no correlation to a traumatic event and was exacerbated by physical activity and cough. Palpation didn't reveal any subcutaneous swelling. There was no sign of coughing, sputum, nausea, tremor or fever and his laboratory values were all normal. The chest x-ray revealed the presence of three exostoses located on the right second and twelfth and on the tenth left ribs, not related to the pain complained by the patient. We therefore performed a computed tomography (CT) (Figure 1) of the chest with 3-dimension reconstruction which even showed the presence of three exostoses on the left third, fourth and sixth ribs. All the three exostoses protruded into the thoracic cavity, directly in contact with visceral pleura. Moreover, the apex of the one located on the sixth rib revealed to be only 12 mm away from pericardium. Because of symptoms complained by the patient and the particular location of exostoses with potential serious complication, we therefore decided for surgical intervention.

Surgical technique

The patient received general anesthesia. Unilateral ventilation with a tidal volume of 300 mL was obtained using a double-lumen endotracheal tube.

A lateral decubitus position was used and a 4-cm long mini-thoracotomy incision was performed at the fifth intercostal space in addition to a standard thoracoscopic portal at the eighth intercostal space in order to completely resect exostoses avoiding recurrence and organ injury.

The surgeon identified by thoracoscopy three significant exostoses originating from the ribs within the left side of the chest (Figure 2); one of them hurt the pericardium during cardiac pulsations, as visualized under unilateral right ventilation after exclusion of the left lung. This scratching caused a thickening of the adjacent pericardium and visceral. Each exostoses were completely resected using a chisel and the specimens obtained were sent to the pathologist. In the apex of the chest cavity a single thoracotomy tube was inserted and positioned.

The incisions were closed and the lung was re-expanded to evaluate correct ventilation. The postoperative course was ordinary, and the patient was discharged on the seventh postoperative day. Pathological examination of the specimens obtained were consistent for exostoses, measuring 2 cm in length and 1 cm in width in the third rib, in the fourth one 2 cm in length and 0.5 cm in width and in the sixth one 2.5 cm in length and 1.5 cm in width (Figure 3). At the last 1-year follow-up, patient was very satisfied and no signs of recurrence or major complication had occurred.

DISCUSSION

The most common localization of exostoses is distal femur, proximal tibia, fibula and humerus, bones that develop from cartilage. Angular deformities, leg-length inequalities and pain resulting from inflammation of skin, tendons or nerves often require surgery.

The flat bones like iliac and scapula are less frequently involved. Rarely ribs, spine, metatarsals, meta-

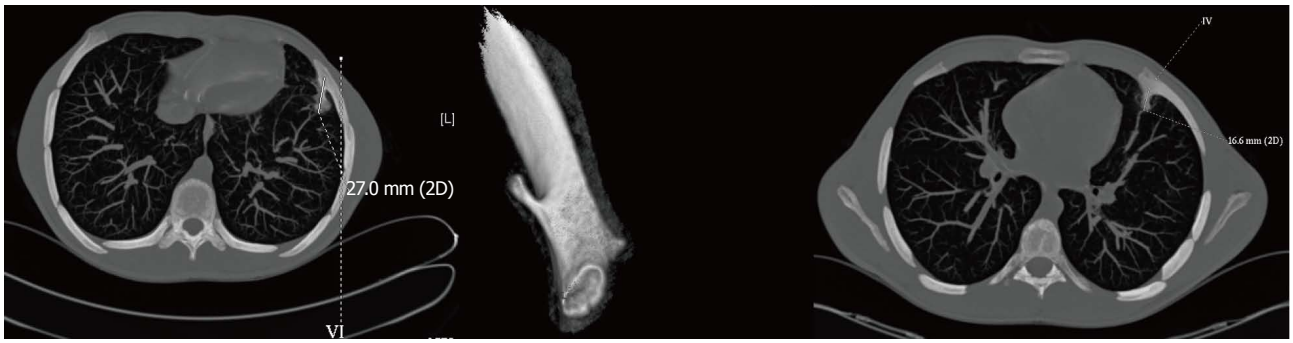

Figure 1 Thoracoscopic findings. Exostosis originating from the costochondral junction of the ribs, with the tip adjacent to the pericardium. The thickening of the pericardium and pleura was caused by scratching with the exostosis during respiratory movements and cardiac pulsations.

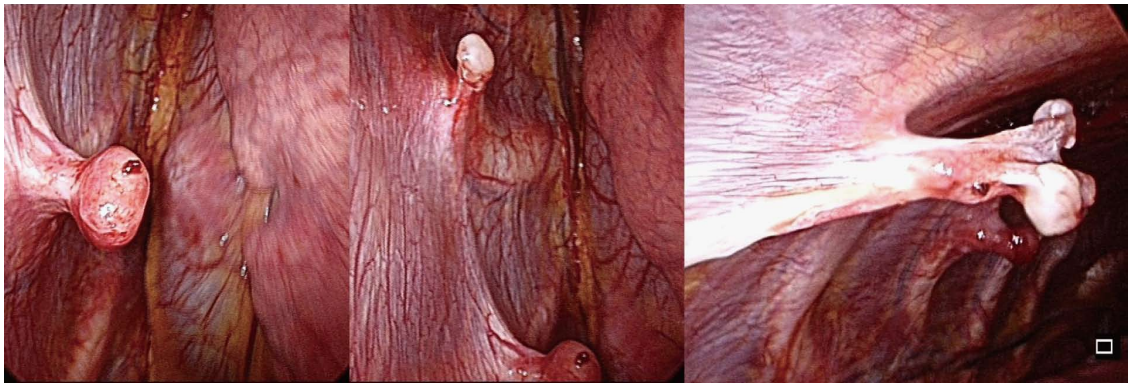

Figure 2 A chest computed tomography scan showing exostoses originating from the left third, fourth and sixth ribs, with a long bony spicule projecting inwards toward the lung.

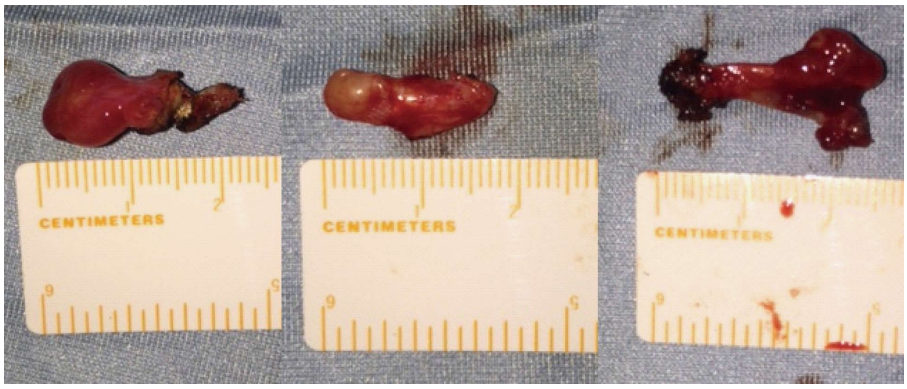

Figure 3 Macroscopic aspect of exostosis.

carpals, phalanges are involved[1]. Costal exostoses may be difficult to recognize on the chest using only X-ray and the chest CT scan is usually suitable[3-5]. Malignant transformation is seen in 0.5%-5% cases of MHE. Axial sites as ribs, spine, pelvic hips and shoulder are sites of increased risk of malignant transformation. Average age at malignant transformation in MHE is 25-30. It is rare before 20 years of age.

Generally, exostoses grow and gradually ossify during skeletal growth and stop growing with skeletal maturity. The proportion of individuals with MHE who have clinical symptoms rises from approximately 5% at birth to 96% at age 12 years[1].

MHE doesn't require therapy in the absence of clinical symptoms, but it should be recommended in selected patients. Despite several studies exist in literature regarding costal exostoses, only few Authors have reported surgical management and outcomes of intra-thoracic localization (Table 1).

Most of the cases described concern about a single exostoses, alone or associated to MHE, while very few papers report the management of multiple intra-thoracic exostoses[3,16,19,27,28]. The majority of cases were treated with a thoracotomy approach, with an increase of less

Table 1 Review of surgically treated intra-thoracic exostoses reports

Ref.	Year	Age	No. of exostoses	Procedure	Outcomes
[6]	1980	9	1	Thoracotomy	Good
[7]	1981	20	1	Thoracotomy	Good
[8]	1989	7	1	Thoracotomy	Good
[9]	1990	14	1	Thoracotomy	Good
[10]	1993	19	1	Thoracotomy	Good
[11]	1994	36	1	Thoracotomy	Good
[12]	1994	3	1	Thoracoscopy	Good
[13]	1997	19	1	Thoracotomy	Good
[14]	1998	15	1	Thoracotomy	Good
[15]	1997	17	1	Thoracoscopy	Good
[16]	2001	21	1	Thoracotomy	Good
[17]	2005	6	3	Thoracoscopy	Good
[4]	2005	15	1	Thoracotomy	Good
[18]	2005	11	1	Thoracotomy	Good
[19]	2006	14	1	Thoracotomy/ thoracoscopy	Good
[20]	2008	17	2	Thoracotomy	Good
		15	1	Thoracotomy	Good
		23	2	Thoracotomy	Good
		12	1	Thoracotomy	Good
		3	1	Thoracotomy	Good
[21]	2009	15	1	Thoracoscopy	Good
[22]	2009	16	1	Thoracoscopy	Good
[23]	2010	17	1	Thoracoscopy	Good
[3]	2011	14	2	Thoracotomy	Good
		6	2	Thoracotomy	Good
[24]	2012	25	1	Thoracotomy/ thoracoscopy	Good
[25]	2013	2	1	Thoracotomy	Good
[26]	2013	5	1	Thoracoscopy	Good
[27]	2012	21	1	Thoracotomy/ thoracoscopy	Good
[28]	2014	16	2	Thoracoscopy	Good
[29]	2014	15	1	Thoracotomy	Good
		5	Multiple intra/ extrathoracic	Thoracotomy	Good
[30]	2015	18	1	Thoracoscopy	Good

invasive surgery such as video-assisted thoracoscopy in the last two decades[12,15,17,21-23,26,28,30]. However, some Authors have underlined the needs of an additional mini-thoracotomy incision depending on the localization of rib involvement and the dimension of the exostoses[19,24,27]. Therefore, considering our case, we sought to completely resect exostoses avoiding recurrence and organ injury preferring a 4-cm mini-thoracotomy approach instead of an additional standard thoracoscopic portal.

The outcomes of surgical management were favorable in all previously reported cases with no significant complications, as in our case. Only Cowles *et al*[17] reported a persistent post-operative pneumothorax related to a malfunction of chest drainage system, resolved without consequence[17].

Interestingly, in most of the cases reported the diagnosis was made due to complication, potentially fatal, caused by interference with surrounding structures, as was the choice to surgically treat the exostoses. On the contrary, only two cases are described in literature with pain caused by intra-thoracic localization of exostoses as the only reason for exostoses removal[14,29], as in our case.

The patient described in this report revealed only chest pain, but localization and dimension of exostoses could have had a possible risk of dangerous thoracic organ damage or risk of haemothorax due to traumas or vascular wound directly caused by the tip of the exostoses, as widely reported in literature.

Chest pain could be the only symptom of an intra-thoracic exostoses localization, possibly leading to serious complications. Thoracic localization in MHE must be suspected when patients complain chest pain. A chest CT scan is indicated to confirm exostoses and to clarify relationship with surrounding structures. Video-assisted thoracoscopic surgery can be considered a valuable option for exostoses removal, alone or in addiction to a mini-thoracotomy approach, in order to reduce thoracotomy morbidity.

COMMENTS

Case characteristics

The patient, a 16 years old Caucasian male, reported having a left-sided chest pain, increased in the last months with no correlation to a traumatic event and was exacerbated by physical activity and cough.

Clinical diagnosis

Palpation don't showed evidence of any subcutaneous swelling and there was no sign of coughing, sputum, vomiting, palpitation or fever.

Differential diagnosis

Neuropathic pain, rib fracture, pneumothorax, haemothorax, pneumonia, pleuritis, chest or pleural or lung neoplastic process were excluded by the clinical and objective sign, laboratory tests and imaging.

Laboratory diagnosis

Hemoglobin level, hematocrit, electrolytes, liver enzymes and coagulation parameters were all normal.

Imaging diagnosis

The chest X-ray and computed tomography (CT) revealed the presence of three exostoses located on the right second and twelfth and on the tenth left ribs, not related to the pain complained and other of the three exostoses on the left third, fourth and sixth ribs.

Pathological diagnosis

The imaging suggested the diagnosis of multiple exostoses of the rib and it was confirmed after the surgical excision by the pathological examination of the speciments.

Treatment

All the exostoses were removed by a thoracoscopy approach with a chisel.

Related reports

Costal exostoses may be difficult to recognize on the chest X-ray. The chest CT scan is usually useful for diagnosis and malignant transformation is seen in 0.5%-5% cases of multiple hereditary exostoses (MHE).

Term explanation

MHE, also known as Multiple Osteochondroma, Osteochondromatosis and Diaphyseal Aclasia, is an autosomal dominant disorder characterized by formation of ectopic, cartilage-capped, growth plate-like exostoses next to long

bones and other skeletal elements.

Experiences and lessons

Thoracic localization in MHE can be suspected when patients complain chest pain and a chest CT scan is indicated to confirm exostoses and to clarify relationship with surrounding structures.

Peer-review

This is an interesting and well presented case report of a rare genetic disease.

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