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EVIDENCE REVIEW

Unhappy triad of the knee: What are the current concepts and opinions?

Amir Human Hoveidaei, Reza Sattarpour, Haleh Dadgostar, Saeed Razi, Mohammad Razi

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Abstract

The association between injuries to the anterior cruciate ligament, medial collateral ligament, and medial meniscus (MM) has been known to orthopedic surgeons since 1936; O'Donoghue first used the term "unhappy triad" of the knee to describe this condition in 1950. Later studies revealed that involvement of the lateral meniscus is more common than MM in these cases, leading to a change in the definition. Recent studies have revealed that this triad may be primarily linked to knee anterolateral complex injuries. Although there is not a definite management protocol for this triad, we try to mention the most recent concepts about it in addition to expert opinions.

Key Words: Anterior cruciate ligament; Lateral meniscus; Anterolateral complex; Medial collateral ligament; Medial meniscus

Core Tip: Traditionally, the anterior cruciate ligament (ACL), medial collateral ligament (MCL), and medial meniscus (MM) were thought to be the unhappy triad of the knee; however, lateral meniscus injuries are thought to be more common in association with ACL and MCL tears. Clinicians, radiologists, and orthopedic surgeons should be aware of the unhappy triad of the knee, while performing physical examinations, radiologic assessments, or knee arthroscopy. MCL spontaneous healing is possible in some cases with lower grades of tear; however, consideration of patient knee alignment and accuracy in MCL size for non-operative treatment decision-making is critical.

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INTRODUCTION

Overview: Medial meniscus or lateral meniscus, triad or tetrad?

Campbell first described a "combination" knee injury in 1936[1], which included injury to the anterior cruciate ligament (ACL), medial collateral ligament (MCL), and medial meniscus (MM), but the term "unhappy triad" was not used until O'Donoghue (1950) reported that about a quarter of all acute athletic knee injuries involve damage to the ACL, MCL, and MM. The MM was initially suspected as the main site of injury compared with lateral meniscal (LM) tears, and O'Donoghue found that only 3% of his sample of 33 patients had LM injuries[2,3]. However, arthroscopy studies showing the higher prevalence of LM tears shifted this dominance[4-6]. The definition of "medial meniscus injury" might have been misunderstood. Perhaps what O'Donoghue considered a MM injury was actually a capsular injury[7].

Extreme reflectoric muscle contractions brought on by rotational stress may result in chondromalacic lesions in the femoro-patellar joint, expanding the "unhappy triad" syndrome into the "unhappy tetrad [8]. According to Müller *et al*[9], the fourth component of this tetrad is antero-lateral femoro-tibial ligament lesions. These are the distal posterior portions of the iliotibial tract that pass from the linea aspra to Gerdy's tubercle[10]. The jerk test, a type of pivot-shift test, can be used to assess anterolateral rotatory instability[11], and magnetic resonance imaging (MRI) has been shown to be useful[12]. According to some studies, anterolateral ligament abnormalities can increase the risk of a complete ACL tear and collateral ligament injuries[13,14]. Nonetheless, the MM is intact in these patients[15].

The injury pattern in the lateral compartment is usually stretching and hemorrhage of the antero-lateral capsule; Segond's fracture is less reported[10]. Ferretti *et al*[16] reported anterolateral capsule and ligament injuries in isolated ACL injuries. They also announced a new classification for this type of injury: Type I (stretching and bleeding in the anterolateral capsule alone), type II (stretching and bleeding from the front to the back), type III (complete tear of the anterolateral ligament [ALL]), and type IV (bone avulsion and Segond's fracture).

Recent studies have focused on the anterolateral femur-tibial ligament as a stabilizer of the knee's internal rotation and pivotal shift[17-19]. So, repairing these ligament injuries could help people who are getting their ACLs reconstructed.

Grading of MCL injuries is based on joint space widening by applying a valgus force on a 0-30° flexed knee[11,20,21]. Seventy-eight percent of MCL grade III injuries are associated with ACL injuries[22]. Shebourne and Posch proposed that parallel meniscus injuries have a relatively protective effect for higher-grade injuries[20,21].

In general, we can conclude that this triad should be defined as concomitant ACL, MCL, and MM/LM injuries, mostly associated with the anterolateral complex of the knee (Figure 1).

EPIDEMIOLOGY, MECHANISM OF INJURY, AND TYPE OF SPORTS

O'Donoghue reported an incidence as high as 25% of the "unhappy triad" in acute athletic knee injuries, and in a study of 22 patients with combined ACL and MCL injuries, it was found that 17 (or 77%) of them had an associated MM tear. However, later studies showed more dominant LM injuries. Shelbourne *et al*[23] found a 32-71% prevalence of LM injury while finding significantly lower rates of MM injury, even 0% in one of their study groups. The mechanism of injury in the unhappy knee triad is sudden valgus impact with external or internal rotation[16]. However, it is controversial whether the MCL or ACL is injured first[24,25].

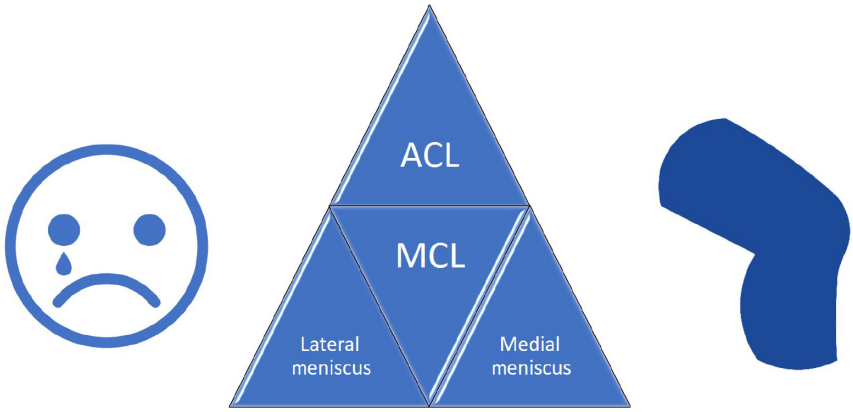

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Figure 1 Unhappy triad of the knee. ACL: Anterior cruciate ligament; MCL: Medial collateral ligament.

This triad often occurs in contact and non-contact sports such as netball, basketball, soccer, skiing, and rugby[26,27]. A recent study, for example, discovered that the ACL was involved in all skiers' knee injuries[21], contrary to the popular belief about the MCL's dominance[28].

CLINICAL PRESENTATIONS

Immediately after trauma, the "unhappy triad" is observed. Swelling, hemorrhage, and serous effusion form after hours and accompany the meniscal and ligament injuries. However, in disrupted capsular injuries, effusion can be negated[29]. There is pain, impaired muscle control, edema, and reflex muscle inhibition in the acute phase. Through an accurate history and physical examination, we can determine injured structures. When rotating on a fixed knee, the majority of patients reported hearing a snapping click noise. Physical examinations, usually the Lachman test, pivot shift test, anterior drawer test, and valgus stress test, are positive, and patients have localized tenderness through the MCL[10,30]. Some patients have patellar instability because of a concomitant injury to the medial patellofemoral ligament and a superficial part of the MCL[27].

DIAGNOSTIC IMAGING TOOLS

X-ray images are not used often because of their low input except for insertion site bone avulsions and lower limb alignment. Using valgus stress X-ray, we can classify injuries into complete medial side tears and isolated high-grade MCL injuries by measuring the opening of medial tears[31]. Valgus stress X-ray results depend on patients' pain and muscular relaxation and could not be accurate in patients with higher degrees of immobility[32]. MRI and arthroscopy are considered accurate diagnostic tools for ACL injuries (around 90% sensitivity), but a blind arthroscopic approach could result in inappropriate treatment for 35% of patients[33,34]. We can use MRI to detect medial side and meniscus injuries, as well as cartilage injuries. As said, lateral side bruises and MRI findings can indicate a higher grade of injury in the medial compartment[27].

MANAGEMENT

Most cases require surgery and a recovery period of 6 to 9 mo. Reconstruction and repair of the ALL lesions should be considered to improve the control of rotational stability and future knee kinematics scores provided by ACL reconstruction. For high-risk patients, a combined ACL and ALL reconstruction improves rotational control and reduces the rate of re-rupture without increasing postoperative complication rates compared to an ACL-only reconstruction[35-39]. However, it needs further investigation for different degrees of injury[39,40]. Another important aspect of surgery is determining whether we can choose a conservative approach for MCL injuries in patients with an unhappy triad (tetrad). Treatment of MCL injuries evolved from an aggressive surgical approach[5,41] around 1960 to non-operative MCL treatment and early range of motion regarding the extra-articular healing ability of the MCL[42,43]. This healing potential is because of the enriched blood supply of the medial compartment of the knee. The Hughston grading system can be used to classify MCL injuries: Applying valgus stress opening in MCL tears between 1 and 5 mm is considered grade I; between 5 and

10 mm is considered grade II; and more than 10 mm is considered grade III[44]. In the original Hughston grading system, grades I and II injuries are named after incomplete MCL injuries, which are not present in the unhappy triad (tetrad). Several studies have highlighted that non-operative and operative managements of MCL injuries have similar satisfactory results, but these patients only had ACL injuries parallel to the MCL[27,45-47]. Patients with the unhappy knee triad (tetrad) with grades I and II MCL injuries can be treated conservatively (using injections and physiotherapy) with a delay in ACL reconstruction, allowing the MCL to heal by itself[48]. It is essential to note that early range of motion is recommended because of better collagen organization and healing outcomes[49]. Grade III injuries and competitive athletes are better treated surgically because of the risk of future ACL reconstruction failure, knee osteoarthritis, which has an increasing burden, and valgus knee instability [50,51]. The reason may be the disruption of menisco-tibial and menisco-femoral attachments during injuries involving deeper layers of the medial compartment (deep MCL). Even so, some studies show satisfactory outcomes in the non-operative management of isolated MCL grade III injuries, but confounding factors such as parallel ACL and meniscal injuries are not considered[52,53]. Meniscus repair is the other consideration that surgeons need to address. The MM is usually repaired because of its role in knee stability and protective effect on osteoarthritis[54].

PROGNOSIS

The unhappy triad can cause osteoarthritis in 50% of patients in 10-20 years due to intra-articular processes initiated by injury. Also, MCL injuries can cause long-term knee instability and increase susceptibility to meniscus injuries[26,55]. The osteoarthritis risk is not covered by anyone, with its pain and function impairment playing a major role in these patients, but the most important question is its rate in these patients and treatment outcomes. In Lundberg's study, 13% of patients with MCL injuries treated non-operatively showed radiographic signs of osteoarthritis[56]. Ochiai *et al*[57] found that in patients with injuries to the ACL, MCL, and LM, reconstruction of the ACL with or without the MCL and LM significantly improved the outcome. However, scores were higher in the group with a conservative approach to MCL. Physiotherapy, early range of motion, and limited weight bearing after reconstruction can improve knee mobility[58]. Using knee braces in high-grade injuries can help keep the knee in correct healing alignment, but it needs further study for long-term outcomes[59].

CONCLUSION

Even with recent studies, choosing between the conservative and operative approaches remains controversial among clinicians. In some cases, spontaneous healing of the MCL occurs without a surgical intervention[60]. Using some expert recommendations, we propose that patients with the unhappy triad of the knee who have varus alignment in the physical examination could undergo a conservative approach, meaning MCL non-operative treatment and ACL reconstruction surgery. These patients should be observed for complications like patellofemoral subluxation and pain. Although some previous studies have mentioned that low grade MCL tearing may not require surgical intervention, considering the fact that MCL tear size estimation without performing arthroscopy may not be accurate, we recommend operative treatment in patients with valgus and normal alignments.

FOOTNOTES

Author contributions: Hoveidaei AH and Sattarpour R contributed equally to the work. All authors contributed to the conception and design of the study; Hoveidaei AH, Sattarpour R, and Razi S drafted the article; Dadgostar H and Razi M made critical revisions related to the important intellectual content of the manuscript; all authors approved the final version of the article to be published.

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REVIEW

Tuberculosis of the spine

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Abstract

Pott's spine, commonly known as spinal tuberculosis (TB), is an extrapulmonary form of TB caused by Mycobacterium TB. Pott's paraplegia occurs when the spine is involved. Spinal TB is usually caused by the hematogenous spread of infection from a central focus, which can be in the lungs or another location. Spinal TB is distinguished by intervertebral disc involvement caused by the same segmental arterial supply, which can result in severe morbidity even after years of approved therapy. Neurological impairments and spine deformities are caused by progressive damage to the anterior vertebral body. The clinical, radiographic, microbiological, and histological data are used to make the diagnosis of spinal TB. In Pott's spine, combination multidrug antitubercular therapy is the basis of treatment. The recent appearance of multidrug-resistant/extremely drug-resistant TB and the growth of human immunodeficiency virus infection have presented significant challenges in the battle against TB infection. Patients who come with significant kyphosis or neurological impairments are the only ones who require surgical care. Debride-ment, fusion stabilization, and correction of spinal deformity are the cornerstones of surgical treatment. Clinical results for the treatment of spinal TB are generally quite good with adequate and prompt care.

Key Words: Tuberculosis; Pott's disease; Spinal tuberculosis; Kyphosis; Medical treatment of spinal tuberculosis; Surgical treatment of spinal tuberculosis; Drugs resistance

Core Tip: Pott's spine is a type of spinal tuberculosis (TB) characterized by hematogenous dissemination of mycobacterium from a primary lesion. It accounts for roughly half of all skeletal TB patients. The most frequent type of spinal TB is para-discal TB. Untreated infections can result in consequences such as a cold abscess, paraplegia, and deformity, all of which may necessitate surgical intervention. Rapid molecular approaches have aided in the detection of spinal TB and drug resistance, but it remains difficult due to sample collection issues and the paucibacillary nature of spinal TB. The presence of human immunodeficiency virus, which is endemic in some areas, increases the burden and complexity of care. Moreover, the emergence of multidrug-resistant TB and extremely drug-resistant TB has posed a big challenge in the management.

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INTRODUCTION

Tuberculosis (TB) is a disease characterized by poverty, economic distress, vulnerability, stigma, and discrimination[1-3]. TB affects roughly one-quarter of the world's population. In 2021, 10.6 million people were infected with TB, equating to 134 cases per 100000 people. Human immunodeficiency virus (HIV)-positive individuals accounted for 6.7% of all TB cases. Geographically, the WHO areas of South-East Asia (45%), Africa (23%), and the Western Pacific (18%) had the highest percentages of TB cases in 2021, while the Eastern Mediterranean (8.1%), the Americas (2.9%), and Europe (2.2%) had the lowest percentages[4]. Despite being a disease that may be prevented and treated, TB is still not completely under control on a worldwide scale. This is caused by a variety of factors, such as rising HIV infection rates, drug misuse, an increase in the population of developing nations, and the migration of people to developed countries. Involvement of the skeletal system has been documented in 1%-2% of all TB patients and 10% of extrapulmonary TB cases[5,6]. More than half of all skeletal TB patients are caused by spinal TB, which commonly affects the productive age group and is costly to the family and the nation. It is more common in developing countries, where many people continue to live in poverty, have poor nutrition, are overcrowded, and lack proper hygiene. There is no difference in susceptibility to TB depending on gender. Because of longer life expectancies, diabetes, cancer therapy, HIV, and greater use of immunosuppressive drugs, spinal TB is becoming more common among the elderly[7,8].

The clinical presentations of spinal TB are often mild. Patients may show up with typical symptoms including weight loss, evening fever, lack of appetite, and back pain that doesn't go away with physiotherapy, or they may show up with no symptoms at all. The importance of taking a detailed history and completing a thorough examination of the spine and other joints cannot be overemphasized. A TB family history, interactions with a patient with active TB, habits, and socioeconomic situations might all be indicators of an early diagnosis. After the clinical examination, one should be able to recognize the pathology and any new issues that may require further testing and treatment.

SIGNS AND SYMPTOMS

According to several retrospective studies, the lower thoracic and upper lumbar vertebrae account for 90% of individuals with spinal TB. Overall, the thoracolumbar junction is most frequently affected, followed by the lumbar, and cervical areas. The biomechanical change from an inflexible thoracic spine to a dynamic lumbar spine makes the thoracolumbar area susceptible to microtrauma, which may facilitate the seeding of TB bacteria. This region is commonly affected. TB bacteria often migrate from a primary location, such as the lungs or genitourinary system, to the vertebral body *via* a hematogenous pathway[9-13]. Each vertebra has a rich vascular plexus in the subchondral region, which makes it easier for TB bacteria to spread to the paradisiacal area. Two neighboring vertebrae are supplied by the same segmental artery, so often both are affected. A valveless system known as Batson's venous plexus connects the spine to the intra-abdominal and intra-thoracic chambers. Whereas TB bacilli propagating through the Batson's plexus generate core lesions in the vertebral body as well as involvement of non-contiguous vertebrae, dissemination through the anterior or posterior longitudinal ligaments leads in the involvement of numerous contiguous vertebrae[14,15]. The proportion of non-contiguous spinal involvement in skeletal TB was 63.6%, according to a published case series using FDG-PET SCAN to assess therapy response[16].

The clinical presentation is generally determined by a number of parameters, such as age, location of the lesions, duration, and so on. Immunological conditions, co-morbidities, and the emergence of issues such as a cold abscess, deformity, secondary infection, and neurological sequelae further complicate the neurological picture. The most common symptom is chronic low back pain, which is subtle at first, gradually worsening, dull and aching in nature, and typically non-radiating. There may be a link between constitutional symptoms such as malaise, lack of appetite, and weight loss. There may have been previously healed cases of pulmonary TB, cases in other places, or contact with a patient who had the disease[17,18]. Nighttime discomfort is a hallmark of this condition. If it's there, it wakes the sufferer. The absence of a protective muscle spasm, which indicates the spine's instability, is associated with the abrupt, excruciating pain. Night discomfort in the supine position is also connected to swelling and venous engorgement. Back pain in skeletal TB is particularly resistant to conservative treatment. When a root is squeezed owing to abscess development or a bone fragment, radicular pain might be a presenting symptom. Radicular discomfort directed to the belly might be mistaken for cholecystitis, pancreatitis, appendicitis, and renal disorders, leading to a delay in diagnosis and, in some cases, inappropriate examinations and operations[19]. There is muscular spasm on examination, which might manifest as prominent paraspinal muscles in the thoracolumbar spine and sciatic pain due to a unilateral spasm. Local sensitivity for the affected area might be evoked. Patients move with extreme caution while supporting the afflicted portion. The "Tripod Sign" with thoracolumbar spine involvement is one of the symptoms of skeletal TB[20,21].

Neurological deficit

Neurology is involved in 23% to 76% of cases of spinal TB. As the spinal cord terminates at L1 and the canal is somewhat large here, paraparesis is more common in the thoracic and cervical spines than below L1. Neurological symptoms might range from minor gait problems to total bladder and bowel incontinence. Patients in impoverished regions typically present after experiencing weakness. Patients first walk awkwardly and slowly as a result of their discomfort and weakness. Weakness in all four limbs is a sign of cervical cord compression. Whereas lumbar spine involvement is defined by lower motor neuron symptoms, thoracic cord compression is characterized by paralysis in both lower limbs, including or excluding bladder and bowel involvement[22]. When a disease is actively spreading or the body is healed slowly, paresis might develop. The active state is produced by either direct compression from an abscess, inflammatory tissue, sequestrum, or instability, or intrinsic causes such inflammation, meningitis, infective thrombi, or vascular damage brought on by endarteritis. Paraplegia is caused by the spinal cord expanding over the internal gibs, bony ridges, scarring, or disease recurrence in cured diseases.

With a spinal cord compression, motor function frequently deteriorates first, followed by sensory and autonomic impairments. Compression frequently starts anteriorly in an anterior lesion and progresses posteriorly. Spasticity may first develop without the patient being aware of it. During a clinical examination, it can be identified by brisk deep tendon reflexes and an extensor plantar response. The anterior columns gradually get implicated as a result of increased compression, which results in a loss of motor function. Further compression results in involvement of the lateral spinothalamic pathways, which results in a loss of pain, warmth, and rough touch. Complete loss of feeling happens when the posterior columns are involved, and by then, bladder and bowel irregularities have developed. When compression is applied for a long time, flaccidity and flexor spasms take the place of spasticity. Lesions at the conus medullaris or cauda equina may present mixed symptoms of upper motor neuron and lower motor neuron lesions with asymmetrical loss of feeling when bladder and bowel function is impaired early. It is possible to categorize neurological abnormalities in spinal TB using the Frankel and ASIA ratings, which were initially developed to identify neurological deficits in acute spinal injuries [23]. The most appropriate categorization of Pott paraplegia with spinal cord involvement is the modified Tuli classification[24]. Pott paraplegia was classified into five stages (Table 1). Despite the fact that the majority of neurologic abnormalities would fit into this category, neurological impairments in intraspinal granulomas, cauda equina syndromes, conus medullaris syndromes, or TB of other uncommon sites may not correlate to any of the phases described above.

Cold abscess

In at least half of cases with spinal TB, paravertebral abscesses are seen. As the name suggests, a cold abscess lacks signs of inflammation, including redness, dolor, and rubor, yet its existence indicates an active infection. Most cold abscesses can evoke a fluctuation, and they typically have a well-defined boundary with smooth, uniform borders. The skin above an abscess is typically swollen and glossy if it is large. Subcutaneous and dermal tissue are steadily destroyed by superficial abscesses, leading to a sinus that discharges. The abscess's pus is often light yellow or white. It contains caseous material with detritus and sequestered bone and has no unpleasant odor indicative of a pyogenic or fungal infection. When the underlying disease process is under control, tubercular sinuses gradually heal with a thin scar after a protracted period of time. Common symptoms of inflammation brought on by secondary infection might heal with an unsightly fibrotic scar that is anchored to the underlying tissue. According to culture, the presence of pyogenic organisms in the pus does not rule out TB. Paravertebral abscesses have a tendency to migrate along the path of least resistance after inflicting damage to the surrounding

Table 1 Classification of paraplegia in tuberculosis of the spine[24]

Stage	Complaints	Motor	Sensory	Autonomic
I	Nil	Plantar extensor/ankle clonus; ASIA motor score−100	Nil	Nil
II	Able to walk with support	ASIA motor score; Tetra paresis (60–100); Paraparesis (80–100)	Lateral column; Involvement	Nil
III	Confined to bed; Can move limbs	ASIA motor score; Tetra paresis (0–30); Paraparesis (50–80)	Lateral column; Involvement	May be present
IV	No limb movement	ASIA motor score; Tetra paresis (0); Paraparesis (50)	Both lateral and posterior column involvement	May be present
V	Flexor spasms	Flaccid paralysis	Complete loss	Complete loss of bladder and bowel control

areolar tissue, including the muscular, subpleural, sub-peritoneal, perivascular, perineural, and fascial planes, and may manifest as a superficial abscess far from the initial focus[25-27].

Swellings in the axilla, subscapular region, or anterior or posterior triangles of the neck might be signs of retropharyngeal abscesses in the cervical spine. The usual pharyngo-vertebral crepitus, which is felt when the larynx is gently pressed from side to side against the vertebral column, is absent in cases with retropharyngeal abscesses. Together with stridor, hoarseness, and dysphagia, it can also present as a potentially lethal condition. An abscess in the arm or forearm might occur if the infection spreads through the brachial plexus. A cold abscess is identified as a fusiform paravertebral swelling in the thoracic area. It may occasionally adhere to the arcuate ligament or the diaphragm aperture. It can also travel *via* the intercostal arteries and cause a protrusion in the chest wall. A lumbar spine cold abscess is generally detected in the Petit's triangle or groin. It has the potential to migrate down the psoas muscle and cause a hip pseudo-flexion deformity. It can occasionally appear as a tumor in the Scarpa's triangle or a gluteal abscess and follow the femoral or gluteal arteries. If the obturator vessels are followed, the abscess will show up in the adductor region. The abscess may develop in the gluteal area, the posterior thigh, or, on rare occasions, even the popliteal fossa if the sciatic nerve is suspected. Understanding the distribution of the pus is crucial since it can take the examiner away from the source of the TB focus. Although involvement of the thoracic spine may diffuse into the lumbar region through the diaphragmatic orifice, the emphasis on the cervical spine may present as an abscess in the mediastinum or elbow. A lumbar spine abscess might appear in the thigh, calf, or even the ankle[28,29].

Spine deformity

Patients may appear to have deformities during either the active or healed stages. After a surgical debridement, deformities may appear right away, or it may take years for older patients whose skeletal architecture has been weakened by osteoporosis to develop. TB first affects the anterior column, and increasing deterioration causes kyphotic deformity and, eventually, instability. If therapy is started at this point, the lesion heals without significant deformity when the intervertebral disc is destroyed and the cancellous bones come into contact with one another. Further degradation occurs if therapy is delayed, resulting in increased deformity. The clinical presentation is determined by the number of vertebrae affected. Further collapse will result in vertebral body retropulsion, resulting in cord compression and neurological impairment. Regular follow-up is critical in the development of children until they reach adulthood. Children who have facet damage during an active illness are more likely to suffer severe deformities later in life. Severe abnormalities can impair quality of life, impede cardiac function, and cause cerebral deficits. Kyphosis is less problematic in the cervical and lumbar spines than it is in the thoracic and thoracolumbar spines because of natural lordosis[30,31].

Pediatric spinal TB

Despite the fact that there may not be any discernible trends today, children are more influenced than adults. Due to their juvenile skeletons, flexibility, and levels of activity, it is crucial to have a high level of suspicion when a child complains of back discomfort at the spine clinic. Children's vertebral bodies contain more cartilage, which is quickly damaged by active diseases and mechanical stress. A neurological sequela can result from asymmetric loading of the ring apophysis, which causes the formation of new deformities or the advancement of previously existing deformities. Even after being pronounced cured, children should continue to get frequent clinical and radiological checks until they reach skeletal maturity, since residual deformity might worsen due to a developing spine and physical activity. More than two of the four spine-at-risk indicators were present in one-third of the kids, which is an undesirable development. Children under the age of seven, people with more than three vertebral bodies sick, and people with conditions affecting the lower thoracic or thoracolumbar junction are more likely to progress[32-34]. There are four symptoms of "spine at risk" in children: (1) Retropulsion of the affected vertebra; (2) Facet subluxation; (3) Lateral translation of vertebrae; and (4) Toppling of one

vertebra over the other.

Children who exhibit two or more of these symptoms may have posterior facet dislocation and necessitate surgical treatment, according to Rajasekaran[35,36]. Additionally, he proposed three categories for how the deformity progresses in children: Type 1 curves (curvature increases until growth stops or skeletal maturity is reached, at which point surgical intervention is necessary); type 2 curves (the deformity lessened as the child grew); and type 3 curves (there was minimal change in the deformity either during the active or healed phases of the disease).

Spinal TB in elderly

As people live longer, more and more older people are being identified as having spinal TB. Compromised health, co-morbidities, and medication interactions are specific issues that older people face. The elderly population has a threefold increased chance of experiencing drug reactions, a sixfold increased risk of mortality, and a twentyfold increased risk of receiving an incorrect diagnosis. Malignancy, diabetes, poor nutrition, immunosuppression, prolonged hospitalization, and other variables are risk factors for an increased incidence of spinal TB. When assessing an elderly person, look for signs of TB meningitis, disseminated TB, or other system involvement. Elderly low back discomfort is frequently disregarded in terms of degenerative conditions[37-39].

Atypical presentations

Intervertebral disc prolapses, isolated abscesses without skeletal involvement, and pure intraspinal granulomas are a few examples of unusual clinical presentations. Atypical radiographic appearances include circumferential vertebral involvement, solitary vertebral involvement, isolated meningeal, neural, or perineural involvement without any vertebral destruction, concentric vertebral collapse, isolated posterior arch involvement, and multifocal osseous lesions[40-43].

LABORATORY DIAGNOSIS

Spinal TB is diagnosed based on clinical and radiographic cues, as well as microbiological and histological markers. Diagnosis is challenging, even when there is a strong clinical suspicion of spinal TB. Clinical symptoms lack specificity, and testing for TB infection may yield conflicting results. Spinal TB is usually paucibacillary, and the sites of infection may be difficult to collect specimens adequate for molecular testing, histology, culture, or microscopy. Despite this, mycobacterium isolation from clinical samples is critical for both diagnostic confirmation and drug susceptibility testing. Diagnostic delays are prevalent due to the subtle clinical features of spinal TB[44,45]. It should be underlined that early identification of TB spine is crucial in minimizing deformity and neurological damage and improving patient outcomes from this illness. If discovered early, TB of the spine may typically be treated with antitubercular medication without the need for surgery. Despite technological developments, the diagnosis is still predicated on a strong clinical index of suspicion based on the history and examination results, which are complemented with biochemical and radiographic evidence[46,47].

Microscopy

Because of the high lipid content in their cell walls, mycobacteria are also known as acid fast bacilli (AFB). When exposed to acid alcohol, this binds to the fuchsin dye, preventing it from escaping from the cells. Early diagnosis is aided by the presence of AFB on microscopy, as well as a history of constitutional TB symptoms and evidence of pulmonary lesions on chest X-rays. Acid fast smears, in addition to supporting diagnosis, can aid in monitoring therapeutic response. The main limitation of smears is that they require a minimum of 10000 AFB per ml of material to be recognized, which is typically not the case with paucibacillary diseases like spinal TB[48,49]. Acid fast staining procedures include:

Carbol fuchsin stains: A fuchsin and phenol (carbolic acid) combination.

Ziehl–Neelsen (ZN, hot stain): Mycobacteria are stained red in this smear, whereas the backgrounds are bright blue. It is called "hot staining" because heat is used to help carbol fuchsin penetrate the bacilli. The smear is then decolored with 20% H_2SO_4 before being counterstained with methylene blue. Tubercular bacilli are acid fast because they resist decolorization by H_2SO_4 due to their high lipid content in the cell wall. Ziehl-Neelsen staining has the benefit of being a dependable, repeatable, and inexpensive process that may also be used to evaluate antitubercular treatment response. The limitations of this technology are that it has poor sensitivity and cannot distinguish between various species of Mycobacteria[17].

Kinyoun (cold stain): When compared to ZN staining, this procedure uses a higher quantity of phenol, removing the requirement for heat to penetrate carbol fuchsin. Mycobacteria look red on a pale blue background, similar to ZN staining.

Fluorochrome stains: rhodamine, a second fluorochrome, with or without auramine O. Compared to ZN staining, fluorochrome staining has the benefit of being able to scan a substantially broader region of the smear. This leads to greater sensitivity to detect bacteria as well as a reduction in the time necessary to scan the smear[50].

Culture

Culture methods identify substantially fewer tubercle bacilli (10-100/mL of specimen) than microscopy. Furthermore, the isolated bacilli can be utilized to identify the species as well as for drug susceptibility tests. As a result, the presence of TB bacilli in culture is regarded as the "gold standard" for TB diagnosis. The limitation of traditional culture procedures is the length of time required to detect noticeable growth, which can range from 4 to 8 wk. The various cultural mediums used to grow Mycobacterium TB are classified as follows:

Solid medias

Egg-based: Whole eggs or egg yolks, potato flour, salts, and glycerol that have been stiffened by inspissation are among the ingredients. They have a long shelf life and promote the growth of the majority of mycobacteria. The Lowenstein-Jensen (LJ) medium is the most often used egg-based medium.

Agar-based: Compared to egg-based media, this medium has a higher chemical definition. Colonies may therefore appear considerably sooner than in egg-based media (10-12 d).

Selective media: Due to the usage of antibacterial medications that prevent contaminating germs, this medium is more selective, allowing the development of Mycobacteria alone. It is therefore frequently used in conjunction with a non-selective egg or agar medium. Both the Gruft modification, which enhances LJ media with nalidixic acid and penicillin, and the Mitchison selective 7H11 medium, which enhances LJ media with carbenicillin, polymyxin B, trimethoprim, and amphotericin B, are examples of selective media.

Liquid medias

Mycobacteria growth indicator tube (MGIT): To help identify tubercle bacilli development in modified Middlebrook 7H9 culture, the MGIT includes a fluorescence-quenching-based oxygen sensor (silicon rubber impregnated with ruthenium pentahydrate).

BACTEC 460 TB system: A method that is semi-automated and uses palmitic acid that has been 14C-labeled as the carbon source for the medium. The apparatus detects $^{14}CO_2$, which is produced as a result of this being digested in the presence of bacteria. Bacilli in a smear-positive specimen for TB often take 9 to 14 d to be found. The drawbacks of this approach are the inability to monitor colony shape, difficulties detecting mixed cultures, contamination overgrowth, expense, and radioactive disposal.

Automated continuous monitoring systems: Similar to the MGIT system, the BACTEC 9000 MB system uses a fluorescence quenching-based oxygen sensor to identify growth. The MB/BacT ALERT 3D system monitors the presence and generation of CO_2 dissolved in growth media using a colorimetric CO_2 sensor in each bottle and reflected light. When the bacilli grow, CO_2 is produced. This gas diffuses to the sensor across the membrane, dissolves in water, and builds up as hydrogen ions. The amount of CO_2 generated is proportional to the development of microorganisms in the medium, leading to the accumulation of hydrogen ions and a decrease in the sensor's pH. As a result, the color shifts from dark to bright green or yellow[51].

Serological tests

IgM levels are known to be a predictor of TB activity and have been proven to decrease during a three-month period after starting medication. IgG levels, on the other hand, show an increasing trend over the same time period and are therefore non-diagnostic but suggestive of chronic or cured disorders. Interferon (IFN) gamma, a cytokine produced by the body as part of its cell-mediated inflammatory response to tubercular antigen, is detected by the Interferon Gamma Release Assay, an ELISA test. One such test is QuantiFERON-TB Gold, which can detect IFN gamma in patients with spinal TB and vertebral body collapse with a sensitivity of 84% and specificity of 95%. While ELISA has improved the detection of these antibodies, it cannot tell the difference between current and latent infections or pulmonary and extrapulmonary TB[52,53].

Molecular testing methods

Nucleic ACID probes: Ribosomal RNA (rRNA), which is abundant in cells and culture, serves as a genetic target in this approach. Stable DNA-RNA complexes are produced when single-stranded radiolabeled (acridine ester) DNA probes hybridize with rRNA. An instrument that is proportional to the amount of probe present measures the light an unhybridized probe produces after it is deactivated.

To assess positivity, a specified threshold is applied. It takes two hours to complete this technique[54].

In situ hybridization: This technique uses an oligonucleotide probe that has been fluorescein-labeled, and interpretation is done by direct fluorescence microscopy viewing. The phrase "fluorescence in situ hybridization" (FISH) is a popular one[54].

Nucleic acid amplification (NAA) methods: Nowadays, the PCR technique is often used in research and diagnostic applications. This technique works by amplifying certain DNA sequences into several copies that may be distinguished using gel electrophoresis separation. Synthetic oligonucleotide primers that are complementary to a certain DNA sequence are used to achieve amplification. The target DNA is amplified a million times as a result of this technique. The most often amplified target is the IS 6110 repetitive element, which is present in many copies in the majority of *M. tuberculosis* strains. The precision and expertise of the technician performing the assay determine the efficacy of PCR for TB. Using real-time PCR, the amount of *M. tuberculosis* in a clinical sample may be quantified while the detection time is sped up. In a closed system, the entire amplification and detection process takes place in a single reaction vessel. The risk of amplicon contamination in the lab is thereby diminished. There is no need for electrophoresis or post-amplification processing because this process is entirely automated.

Xpert MTB/rifampicin (RIF) test: An automated PCR test called the Xpert MTB/RIF Test (Cepheid, Sunnyvale, California) may detect rifampicin resistance and TB in less than two hours. To conduct the test, lysis reagent and tissue samples acquired during a biopsy are combined, and a mixture is then swiftly oscillated between the two. Two mL of the mixture are removed and put through the GeneXpert machine after being allowed to stand. After around 90 minutes, the results will be available[55,56]. Rapid results, a fully automated system, simultaneous detection of rifampicin resistance, the ability to detect very low amounts of TB bacilli, and the ability to differentiate between typical and atypical mycobacteria are all advantages of this system. The Xpert MTB/RIF test has the disadvantage of detecting non-viable pathogens, missing mono drug resistance, and having a single gene target.

Multiplex PCR: Instead of amplifying just one *M. tuberculosis* gene, the multiplex PCR aims to do so. Under these circumstances, it has been demonstrated that multiplex PCR, which amplifies both the IS6110 and MPB 64 genes identified in mycobacterium, has higher sensitivity and specificity. It has been established that both genes may be amplified from a single tissue sample to lower the expense of this inquiry[57,58].

Nanotechnology

Despite improvements in the field of TB diagnosis, there is still no point-of-care test for *M. tuberculosis* that is accurate in detecting children, extrapulmonary TB, or HIV-associated TB. This gap will be filled by nanotechnology, which will provide a point-of-care diagnosis that is rapid, effective, and affordable and uses particles with a size range of 1-100 nm. The possibility of using different physiological fluids, such as blood, sputum, or urine samples from patients, in nano-diagnostic methods to get reliable and quick results using affordable and portable tools, seems to be promising in the detection of infectious diseases like TB[59-61].

Among the nano-diagnostic techniques being explored for TB are:

Gold nanoparticle (NP)-based TB diagnostic techniques: For colorimetric detection of *M. tuberculosis*, gold NPs are combined with DNA probes. If complementary DNA is present, the nanoprobe solution remains pink at a wavelength of 526 nm, when complementary DNA is missing from the samples, the solution becomes purple.

Dipstick with gold NPs: Alkanethiol derivatives were used to coat colloidal gold NPs with the *M. tuberculosis* antigen; this coating produced a pronounced red color when mixed with serum containing antibodies.

Detection based on silica NPs: Indirect immunofluorescence microscopy has been created to detect *M. tuberculosis* using NPs linked with fluorescent dye.

Detection system based on quantum dots: In this approach, one probe accurately binds to the mycobacterium's *23S rRNA* gene, and when the mycobacterium is treated with sulfuric acid and chromium quantum dots, a second probe accurately identifies the IS900 conserved sequence. As a consequence of hybridization with target gene sequences of mycobacterium DNA isolated from probable TB patient samples, a sandwich is produced. The conjugates of quantum dots and magnetic beads are then exposed to ultraviolet light, which causes red fluorescence that can be seen with the unaided eye.

Biosensors detection: Based on finding short nucleotide sequences of *M. tuberculosis* DNA, this is done. Sensors are classified as mass/piezoelectric, biological, electrical, or optical.

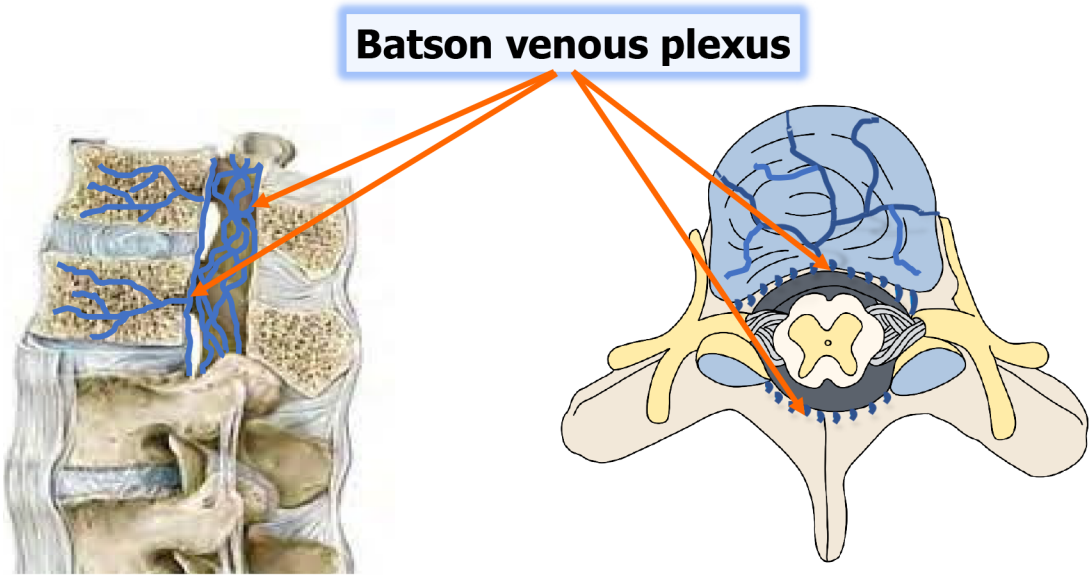

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Figure 1 The Batson venous plexus is a network of valveless veins that connects the deep pelvic veins and thoracic veins (which drain the inferior end of the urine bladder, breast, and prostate) to the internal vertebral venous plexuses in the human body.

Erythrocyte sedimentation rate and C-reactive protein

In spinal TB, the erythrocyte sedimentation rate (ESR) is often greater than 20 mm/hour (60%-90% sensitivity) and decreases with treatment response. It is, however, not a particularly sensitive test. C-reactive protein (CRP) has a higher specificity (71% sensitivity) than ESR[62,63].

IMAGING MODALITIES

Plain radiographs

In the early stages of illness, plain radiographs may be normal. Before the lesions become radiographically visible, a 30% mineral loss must occur. Various publications have reported an average of 3.4 to 3.8 degrees of vertebral involvement over the years. Immunocompromised patients, diabetics, and people with hemoglobinopathies may have extensive spinal involvement. A "skipped lesion" occurs in 7% of patients when two non-contiguous vertebrae are implicated without the involvement of neighboring vertebral bodies and intervertebral discs; the mechanism is assumed to be infection transmission through the Batson's plexus of veins[64,65] (Figure 1). The thoracic spine is the most commonly involved area, followed by the lumbar region. The posterior arch is more commonly impacted than the vertebral body. There are four radiographic forms of spinal involvement: para-discal, anterior, central, neural arch, or appendiceal (pedicles, laminae, spinous processes, or transverse processes).

Para-discal type

It is the most typical type of vertebral involvement, in which two contiguous vertebrae close to the disc space are involved at the same time. This points to a shared blood supply in this area. On radiographs, it appears as a decrease in intervertebral disc space associated with endplate irregularities in the adjacent vertebrae. Plain radiographs show tuberculous granulation tissue and abscess development in the paravertebral area as soft tissue shadows next to the spine. It is best apparent on a lateral radiograph in the cervical area as an enhanced prevertebral soft tissue shadow. Abscesses below the T4 spinal level have a distinctive fusiform shape (like a bird's nest), but bigger abscesses may have a broad posterior mediastinal shadow. A globular-shaped shadow might form when an abscess is under strain. The psoas shadow in the lumbar region enlarges as an indication of an abscess tracking down the muscle. In cases of long-standing destruction of adjacent para-discal vertebral bodies, the spine may angle, and one or both bodies may show posterior convexity with wedge collapse. The most frequent spinal deformity is kyphotic deformity, which is caused by involvement of the thoracic vertebrae. Multiple involvement of neighboring vertebrae may result in a significant kyphotic deformity[66].

Central type

When the infection starts in the center of the vertebral body and spreads *via* Batson's venous plexus or the branches of the posterior vertebral artery, the pattern of involvement described above occurs. Later,

with axial stress, the diseased vertebral body collapses due to trabecular bone loss. Because the loss of disc space and paravertebral shadow is minor in comparison to the para-discal type, it is sometimes mistaken for having neoplastic origins. However, with a longer follow-up, there may be a reduction in the nearby disc area[45].

Anterior type

When the disease process begins just below the anterior longitudinal ligament and periosteum, this pattern is observed. This results in erosions of the vertebral body's anterior aspect, which may be detected on lateral radiographs as uneven cortical borders. Multiple adjacent vertebrae may be involved if the infection spreads beneath the anterior or posterior longitudinal ligaments. Vertebral body collapse with loss of neighboring disc space is generally minor and appears later[41,42].

Appendiceal type

This involves either isolated or mixed involvement of the neural arch (pedicles and laminae), transverse processes, and spinous processes. When there are indirect symptoms of involvement, such as paravertebral shadows or erosive alterations with an undamaged disc, these lesions may be suspected radiographically. Routine radiography makes it difficult to see the involvement of the posterior spinal joints. Posterior spinal articulations may also be affected, resulting in lateral translation, an uncommon malformation. The fundamental drawback of radiography is that it is insensitive in the early stages of illness. The craniovertebral and cervicodorsal junctions are two spinal locations that are difficult to identify on X-ray. Plain X-rays make it difficult to assess spinal cord alterations, soft tissue involvement, and the exact location and extent of abscesses. So, the appearance of any of the radiographic signs may be a sign that the disease process has progressed to a fair degree[67,68].

COMPUTED TOMOGRAPHY

Computed tomography (CT) reveals findings significantly earlier than normal radiography because it shows more detail of bone irregularity, disruption, sclerosis, and disc collapse. Fragmentary, osteolytic, sclerotic, and subperiosteal bone disintegration patterns have all been documented. Aside from bony detail, paraspinal abscesses are assessed better than plain radiography. It's essential for detecting calcification within an abscess or bone pieces within epidural lesions. It is quite useful for providing direction for percutaneous diagnostic sampling, particularly in inaccessible locations. The main drawback is that magnetic resonance imaging (MRI)scores higher than CT when evaluating the effect of the disease on brain structures. In spinal TB, radiological evidence of healing lags behind clinical and laboratory results. Several months after the start of combination therapy, many patients may not exhibit any signs of improvement on X-rays or CT scans, which should not be construed as a sign that the treatment is failing. Nevertheless, if the pictures are repeated more than 6 months after the commencement of the treatment and do not demonstrate improvement, the possibility of an extra lesion or a condition that is therapeutically resistant should be taken into account[69,70].

MAGNETIC RESONANCE IMAGING

Because of its improved soft tissue contrast and capacity to spot and classify anomalies in the spinal cord, bone marrow, and intervertebral disc, MRI outperforms other imaging modalities. For the entire examination of the tuberculous spine, MRI is the modality of choice. The craniovertebral junction, cervicodorsal junction, neural arch components, vertebral appendages, sacroiliac joint region, sacrum, and coccyx are just a few tough places where it is very helpful in diagnosing disorders. Standard MRI procedures include fat-suppressed T1W, T2W, and short tau inversion recovery sequences in the axial, sagittal, and coronal planes, as well as contrast-enhanced T1W sequences after gadolinium contrast injection. An abnormal marrow signal intensity that appears hypointense on T1W sequences and hyperintense on T2W sequences, showing heterogeneous enhancement and a lack of cortical definition, is indicative of the vertebral body being involved. Contiguous vertebral body disease with disc degeneration is common. Loss of normal internuclear cleft with increased signal on T2W images, as well as post-contrast enhancement, are indications of disc involvement. Because mycobacterium lacks proteolytic enzymes, disc involvement occurs later than in pyogenic spondylitis. The "floating disc sign" may arise infrequently if there is severe spinal damage with disc sparing. In children, the disc is highly hydrated and more susceptible to infection.

The intercostal space, mediastinum, pleural cavity, or even the intercostal arteries themselves may get enclosed by the paraspinal collection as it just barely breaches the anterior longitudinal ligament in the thoracic region. When the psoas muscle is involved in the lumbar area, there is a loss of typical muscle shape, increased muscular size, and uniform signal intensity on T1W imaging. In T2W imaging, the psoas abscess appears as a high-signal fluid with dense peripheral post-contrast enhancement.

Although posterior element involvement is less likely in TB than in a pyogenic infection, it is nonetheless more common. The disease's involvement manifests as an aberrant signal and in the homogeneous amplification of the afflicted spot. The posterior elements can be afflicted alone, although they are most typically encountered in conjunction with anterior element abnormalities. Composite lesions, or panvertebral lesions, are defined as involving both the posterior and anterior components. The epidural/subdural space or the spinal cord may be involved in addition to granulomatous lesions inside the spinal canal. Around 61% of afflicted vertebrae have epidural extension that may be seen on an MRI. When the spinal cord is squeezed from the front or the rear, compression myelopathy can happen[71-73].

MEDICAL MANAGEMENT

Multidrug antitubercular therapy

Unlike other infections, TB needs multidrug treatment for a variety of microbiological reasons, as mentioned below: Mycobacteria exist in four types in the human body: (1) Extracellular fast dividing; (2) Extracellular slowly dividing; (3) Intracellular intermittently dividing; and (4) Dormant bacilli. As a result, it needs the use of many medications that are effective against various bacterial types. Rifampicin destroys slowly growing bacteria, ethambutol kills intracellular bacteria inside macrophages, and streptomycin kills rapidly multiplying bacteria. In contrast, isoniazid, ethambutol, and streptomycin all kill rapidly multiplying bacteria[74].

Mycobacteria's modest growth rate is both a blessing and a curse. While the illness progresses slowly, medications that work on quick multipliers become ineffective, limiting therapy choices. As a result, it is necessary to use medications for a longer period of time.

The drug permeability is minimal due to the restricted permeability of mycobacterial cell walls and intra-macrophage bacilli. As a result, specialized medications that penetrate macrophages and thick bacterial cell walls are required for therapy[75].

Mycobacteria are well-known for rapidly acquiring antibiotic resistance to monotherapy. Isoniazid resistance mutations occur at a rate of 1 in 10^6, while rifampicin resistance mutations occur at a rate of 1 in 10^8. Resistance to both can be found in 1 in 10^{14} people. As a result, a minimum of two medications are administered in combination to prevent the development of resistance[76].

Most anti-tubercular medications, with the exception of thioacetazone, have a protracted period of action known as the "lag-effect." This quality made it possible to take medications on an intermittent schedule, which was essential for the success of directly observed therapy[77].

FIRST-LINE DRUGS

Despite decades of extensive study, only a few medications have been shown to be effective. Since the current anti-tubercular treatments consist of the five first-line drugs isoniazid (INH), RIF, ethambutol (EMB), pyrazinamide (PZA), and streptomycin, which are the most efficient and least toxic, it is advised to use these drugs with caution and a focus on compliance in order to prevent the emergence of resistance. Prolonged use of numerous medicines may increase the risk of a variety of side effects and problems. To achieve a safe and effective therapy, a detailed understanding of pharmacokinetics, medication interactions, and side effect profiles is required, as well as monthly monitoring.

INH

Isoniazid is an important drug in the treatment and prevention of TB. INH is a prodrug that, when activated by the catalase-peroxidase KatG, creates a variety of radicals. The bonding of the radicals with nicotinamide adenine dinucleotide (NAD) causes an INH-NAD adduct, which inhibits the enoyl-ACP reductase *Inh*A of the fatty acid synthase type II (FASII) pathway, ultimately leading to cell death. INH is especially effective against rapidly developing mycobacteria. It can pass the blood-brain barrier and act on both intracellular and extracellular bacteria. Only dividing bacteria are killed when INH penetrates the bacterial cell; mycobacteria in the stationary phase are unaffected. INH is bacteriostatic for the first 1-4 days, thereafter, it becomes bactericidal, which coincides with its lack of acid fastness. Multiple genes in different pathways are involved in INH resistance. A mutation in the *katG* gene is the most prevalent source of resistance, followed by mutations in other genes such as *inhA*, *ahpC*, *kasA*, and *ndh*. Adults should take 5 mg/kg, while children should take 10 mg/kg. Peripheral neuropathy, lethargy, hepatitis, and, in rare cases, convulsions, insanity, and a lupus-like condition are among the side effects. Pyridoxine (10-25 mg/d) is also indicated to help reduce the risk of peripheral neuropathy. INH is a cytochrome P450 inhibitor that has been shown to raise the plasma concentrations of anticonvulsants, benzodiazepines, acetaminophen, and oral anticoagulants[78,79].

RIF

Rifampicin, a rifamycin derivative, inhibits messenger RNA elongation by binding to the β-subunit of the RNA polymerase. Both intracellularly and extracellularly, it is effective against bacteria that quickly proliferate and slowly metabolize. This impact on bacteria with irregular metabolism provides a "sterilizing effect". Adults should take 10 mg/kg, while children should take 15-20 mg/kg. High dosages can cause hepatotoxicity; hence, the maximum daily dose shouldn't exceed 600 mg. Additional adverse effects include hemolytic anemia, gastrointestinal distress, purpura, and orange-red urine stains. Rifampicin is a cytochrome P450 inducer, which necessitates dose changes for other medications that are processed in the liver, such as oral hypoglycemics, anticonvulsants, antifungals, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, cardiac therapies, and so on. Rifampicin resistance is most frequently caused by a mutation in the 81-bp *rpo*B gene (codons 507–533), which codes for the β-subunit of RNA polymerase[80,81].

PZA

An amidase enzyme produced by the *pnc*A gene transforms the prodrug PZA into its active form, pyrazinoic acid. PZA is thought to hinder membrane transport, trans-translation, and coenzyme A production, all of which are required for bacteria to thrive. The primary characteristic of PZA is its ability to combat non-replicating persisters in an inflammatory, acidic environment. The first two months of treatment, when acute inflammatory changes are still apparent, are when it works best. It has a great "sterilizing effect" and is critical in decreasing the length of chemotherapy. Adults should take 25 mg/kg, while children should take 35 mg/kg. The recognized side effects are hepatotoxicity, hyperuricemic arthralgia, exanthema, and pruritis. Cyclosporine and gout patients need dosage adjustments. *Pnc*A mutations in the 561 bp open reading frame or an 82 bp putative promoter region are the main causes of PZA resistance in *M. tuberculosis*[82,83].

EMB

Ethambutol is only effective against growing bacteria (bacteriostatic), where it prevents mycobacterial arabinogalactan biosynthesis by inhibiting the enzyme arabinosyltransferases. Other pathways include glycerol metabolism and RNA synthesis disruption. Adults should take 15 mg/kg, while youngsters should take 15-25 mg/kg. Dose-dependent retrobulbar neuritis is the most significant side effect. The central fibers are frequently compromised, leading to loss of visual acuity, scotomas, and the inability to discern between green and red colors. The effects are reversible if recognized early and the medicine is stopped. Abdominal discomfort, eosinophilia, peripheral neuritis, myocarditis, and hypersensitivity are some of the other side effects. The drug is not recommended for children due to the difficulties in evaluating visual acuity consistently. Dosage adjustments are necessary for patients with low creatinine clearance (30 mL/min). The *emb*B gene, which codes for arabinosyltransferases, has codon 306, which is the most often occurring mutation for EMB resistance[84,85].

Streptomycin

Streptomycin is a *Streptomyces griseus* aminocyclitol glycoside. It is highly effective against actively proliferating bacilli found in cavities when administered intramuscularly. The ribosomal proteins S12 and 16S rRNA, which are encoded by the genes *rps*L and *rrs*, respectively, are not translated as a result of their action. The fact that it is active at an alkaline pH is significant. Adults should take 15 mg/kg of streptomycin, whereas children should take 15-25 mg/kg. Ototoxicity, vestibulotoxicity, nephrotoxicity, rashes, eosinophilia, and fever are among the side effects. The most prevalent mutation giving streptomycin resistance is a lysine to arginine change in codon 43 of *rpsL*. Streptomycin can cross the placenta and cause fetal ototoxicity and nephrotoxicity; hence, it is not recommended for use during pregnancy. All other first-line medications are safe to use while pregnant. Children's pharmacokinetics differ from those of adults. Children metabolize medicines quicker than adults, and their blood concentrations are substantially lower, necessitating a greater body weight dosage[86,87].

The first-line anti-tubercular medications' dose, pharmacological activities, and side effects are summarized in Table 2.

SECOND-LINE DRUGS

The emergence of first-line antibiotic resistance has required the frequent use of second-line treatments. Second-line medications are less effective, have more toxicity, and are more expensive than first-line treatments. The most often used second-line medications include fluoroquinolones, injectable aminoglycosides, ethionamide, and cycloserine.

Fluoroquinolones

Fluoroquinolones (FQs) are antibiotics with broad spectrum action against *M. tuberculosis in vitro* and *in vivo*. They are bactericidal, with the mechanism of action being DNA synthesis inhibition.

Table 2 The first-line anti-tubercular medications' dose, pharmacological activities, and side effects[85]

Anti-tuberculosis drugs	Dose (mg/kg)	Pharmacological activities	Side effects
Isoniazid	5	-Inhibits the enoyl-ACP reductase *Inh*A of the fatty acid synthase type II (FASII) pathway	-Peripheral neuropathy, lethargy, hepatitis, insanity, convulsions, and a lupus-like condition
Rifampicin	10	-Inhibits messenger RNA elongation by binding to the β-subunit of the RNA polymerase	-Hemolytic anemia, gastrointestinal distress, purpura, and orange-red urine stains
Ethambutol	15	-Inhibits enzyme arabinosyltransferases, glycerol metabolism, and RNA synthesis	-Abdominal discomfort, eosinophilia, peripheral neuritis, myocarditis, and hypersensitivity
Pyrazinamide	25	-Disrupts membrane energetics and inhibits membrane transport function	-Hepatotoxicity, pruritis, hyperuricemic arthralgia, and exanthema
Streptomycin	15	-Binds to the small 16S rRNA of the 30S ribosomal subunit irreversibly, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit	-Ototoxicity, rashes, fever, nephrotoxicity, eosinophilia, and vestibulotoxicity

Fluoroquinolones that are routinely utilized include ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin. The suggested daily dose is 400-600 mg. Adverse effects such as headache, gastric discomfort, rashes, and dizziness are uncommon. A mutation in DNA gyrase, the biological target for FQs, is the most prevalent route for drug resistance[88,89].

Aminoglycosides

Amikacin (AMK), kanamycin (KAN), and capreomycin (CAP) are injectable aminoglycosides that are crucial to the treatment of multidrug-resistant (MDR) TB. They are made from Streptomyces and are bactericidal. AMK and KAN work by inhibiting protein translation, but capreomycin works by inhibiting mRNA-tRNA translocation by attaching to the 70S ribosome. All three drugs are administered in a single dose of 15 mg/kg per day. Due to the adverse effects, which include renal toxicity, ototoxicity, and electrolyte abnormalities, frequent monitoring of hearing and renal function is required. Resistance to AMK and KAN is associated with changes in the 16S rRNA, and cross-resistance between both drugs is frequent. Capreomycin resistance is linked to a *Tly*A mutation and is more likely to result in treatment failure and death[90,91].

Cycloserine

Cycloserine is a bacteriostatic drug derived from *Streptomyces orchidaceus*. It prevents the formation of mycobacterial cell walls. Moreover, cycloserine could successfully permeate bone and reach quantities that were equivalent to those in plasma, which supports its use in the treatment of osteoarticular TB [92]. The recommended daily dosage is 1 g, taken as a single dose. Those with psychiatric disorders and renal insufficiency should avoid using the medication since it might cause seizures, headaches, and psychosis. Because of its high stomach tolerance and low drug-drug interactions, it may be used to treat MDR and extremely drug-resistant (XDR) TB[93].

Ethionamide/prothionamide

Iso-nicotinic acid is used to make the bacteriostatics ethionamide and protionamide. The mechanism of action is similar to that of INH in that it inhibits *Inh*A of mycolic acid production. The medication is administered in a single daily dosage of 1 g. Severe gastrointestinal intolerance, hepatitis, peripheral neuropathy, hypothyroidism, and depression are among the adverse effects. There is a lot of cross-resistance between the two medications[94,95].

Para-aminosalicylic acid

Para-aminosalicylic acid was one of the first anti-tubercular medications to be developed. However, due to quick resistance and gastrointestinal intolerance, it was replaced. Hypothyroidism, hepatic dysfunction, and hypersensitivity are some of the other side effects. A single or two split dosages of 12 g are advised[96].

NOVEL DRUGS

In view of rising treatment failure in *M. tuberculosis*, there is an unmet need for innovative medicines that act on novel targets and have higher effectiveness while requiring fewer drug interactions and having a lower toxicity profile.

Delamanid

Delamanid is a prodrug (dihydro-nitroimidazo-oxazole derivative) that inhibits the formation of mycobacterial cell wall components when activated by the enzyme deazaflavin-dependent nitroreductase (Rv3547). Headache, nausea, dizziness, and QT prolongation are all side effects. The safety profile is good, with the least amount of toxicity and no major drug interactions with other anti-TB drugs. Given the inconsistent findings of effectiveness trials, WHO recommends using the medicine only in a more protracted MDR regimen if no viable alternative can be discovered[97,98].

Bedaquiline

Bedaquiline is a new anti-tubercular drug that was released in 2012. It targets the mycobacterial ATP synthase and binds to one of its components to prevent it from functioning. Like other second-line medications, it is advised for use in MDR and XDR-TB patients. Its distinct mode of action makes it less likely than other anti-TB medications to produce cross-resistance. Among the side effects that have been seen are nausea, arthralgia, headaches, hemoptysis, chest pain, anorexia, rashes, and an increase in hepatic transaminases[99]. The most significant side effect is QT prolongation; hence, it should not be used with other QT-prolonging medications. Mutations in the *rv0678* gene, which encodes the MmpL5 efflux pump repressor, have been linked to low-level bedaquline resistance and cross-resistance to clofazimine.

SURGICAL MANAGEMENT

Chemotherapy is the primary treatment for spinal TB. Long-term antitubercular chemotherapy is a crucial component of the treatment of spinal TB. Surgery for TB of the spine is a contentious subject, with no clear consensus on the indications for surgical therapy. To prevent and cure complications of spinal TB, such as cold abscess, deformity, and neurological deficiency, surgical intervention may be necessary. Excisional treatment and antitubercular therapy were shown to be equivalent in studies. In fact, excisional treatment alone causes anterior column deficiency, deformity, and delayed neurological damage[100].

According to Mak *et al*[100] the following circumstances warrant surgical intervention:

Progressive neurological deficit: Early surgical decompression contributes to the resolution of the deficiency, which lowers morbidity and improves quality of life.

Progressive spinal deformity: More kyphosis in the thoracic spine may be tolerated if the lumbar spine compensates, but an excessive loss of lordosis in the lumbar spine is not acceptable. Kyphosis of sixty degrees should be surgically corrected since it can cause paraplegia and cardiovascular impairment.

Failure of conservative treatment: Following 3-4 wk of chemotherapy with or without a brace or bed rest, any increase in discomfort or neurological deficit should be treated surgically as a therapeutic failure.

Uncertain diagnosis: Making a diagnosis or determining medication sensitivity might be challenging when there isn't a surface abscess or when percutaneous biopsy samples are either insufficient or impossible to acquire. In these circumstances, surgery should be done to collect enough tissue samples.

END POINT OF CHEMOTHERAPY

The major issue with spinal TB is that there are no clear standards for determining "healed status." Therefore, it is difficult to determine when to discontinue using anti-tubercular medications. In order to determine the end point of treatment for spinal TB, the "gold standard" in pulmonary TB—repeated tissue biopsy and culture conversion—is not used because, the paucibacillary nature of the TB spine makes it an invasive, time-consuming, and consequently impractical method with a very poor yield. Additionally, there is no established method for estimating the total body burden of *M. tuberculosis* or forecasting clinical results. Therefore, the trifecta of clinical improvement, laboratory markers, and radiographic evaluation continues to be used as corroborated indicators of healing status.

Clinical improvement

Pain: Although the majority of spinal TB patients who are recovering report lessening of their pain, this cannot be taken as an absolute criterion because there can be several different causes of back pain, and more importantly, healing can take place without a strong bony fusion, which can result in persistent pain from spinal instability despite the disease's recovery. In addition, there is currently no accurate metric for measuring the degree of pain.

Deformity: The same is true for spinal deformity, which in most individuals either worsens or remains as the illness progresses and collapses.

Neurology: Although the patient's neurology improves when the diseased soft tissue crushing the neural components is reduced, in a small number of cases, neurologic dysfunction may continue despite the illness healing due to chronic bony compression.

Laboratory improvement

ESR: In most situations, ESR is increased. It is used to track how well patients respond to therapy. Failure to normalize following therapy should raise concerns about primary drug resistance or alternate causation.

CRP: CRP levels have been shown to be up to 75% higher in patients with spinal TB. It is more targeted toward viral and inflammatory lesions. It takes around 2 wk to detect a change, whereas ESR takes about 4 wk and hence has more relevance in monitoring therapy response.

Imging improvement

MRI: There are numerous well-known criteria for determining spinal TB healing.

Even after the infection has been completely eradicated, an MRI may still reveal soft tissues and even sterile abscesses.

MRI often lags behind clinical recovery by up to 3 mo.

MRI may be too sensitive when utilized as a sole source of information to assess the degree of a current infection, inflammatory edema, or active disease pus.

Poor disease management is indicated by the development of new lesions while receiving treatment, the worsening of existing lesions, marrow edema, and new bone damage or abscesses, particularly when these symptoms are coupled with clinical deterioration[101,102].

PROGNOSIS

Younger age and earlier diagnosis have been reported to be favorable prognostic factors. The severity of the disease (number of damaged vertebrae) and the extent of spinal deterioration (instability, deformity, abnormalities) influence the clinical outcome. The existence of paraplegic symptoms at the time of the initial diagnosis is considered a bad prognosis. Immunodeficiency (HIV, drug addiction, and alcoholism), malnutrition, and poverty are additional risk factors[103,104].

CONCLUSION

Early identification and prompt treatment enhance the prognosis for spinal TB. Even in the absence of neurological symptoms and indications, individuals who appear to have persistent back pain must be viewed with a high degree of clinical suspicion. Medical treatment is generally effective. However, MDR/XDR TB is increasing and should be identified early by using molecular methods to diagnose spinal TB and drug resistance. Advanced instances with significant bone involvement, abscess development, or paraplegia require surgical intervention. Young individuals are susceptible to spinal TB; thus, measures should be taken for effective prevention. The only strategy to avoid spinal TB is to stop the spread of the disease.

FOOTNOTES

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MINIREVIEWS

Implications of obesity in patients with foot and ankle pathology

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Abstract

Obesity is a growing problem defined as a body mass index of greater than 30 kg/m^2. It is predicted that by 2030, 48.9% of adults will be classified as obese which expands surgical risk factors to a broad population while increasing healthcare costs at the same time in different socioeconomic groups. This specific population has been widely studied in multiple surgical fields and published studies have shown the implications in each of these fields. The impact of obesity on orthopedic surgical outcomes has been previously reported in several total hip and knee arthroscopy studies, with evidence indicating that obesity is strongly associated with an increased risk of post operative complications together with higher revision rates. In line with increasing interest on the impact of obesity in orthopedics, there has been a similar output of publications in the foot and ankle literature. This review article evaluates several foot and ankle pathologies, their risk factors associated with obesity and subsequent management. It provides an updated, comprehensive analysis of the effects of obesity on foot and ankle surgical outcomes, with the ultimate aim of educating both surgeons and allied health professionals about the risks, benefits, and modifiable factors of operating on obese patients.

Key Words: Obesity; Foot and ankle surgery; Ankle fracture; Total ankle replacement; Achilles tendinopathy; Hallux valgus

Core Tip: Obesity is a growing population. The impact of this is also reflected in fields such as Orthopedic Surgery including foot and ankle. Mobility is determinant in every aspect of life and in the obese population it reflects a greater challenge when addressing pathologies affecting the foot and ankle. Multiple factors can affect the outcomes of surgical treatments in this population and we believe that a greater understanding is needed to be prepared to treat these patients while trying to reduce the further complications that they face.

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INTRODUCTION

Obesity is a growing problem; it is predicted that by 2030, 48.9% of adults in the United States will be classified as obese[1] (Table 1). Causes of obesity are multifactorial, ranging from increasingly sedentary lifestyles, lower socioeconomic groups, as well as several genetic factors[1]. Obesity also contributes to healthcare costs, with an estimated $150 billion spent on direct impact costs per year in the United States [2]. Obese individuals have been found to have medical costs that are approximately 30% greater than their normal weight peers[3]. Worldwide costs of obesity continue to increase with an estimated two trillion dollars per year, or approximately 2.5% of the global Gross Domestic Product in 2014, spent solely on obesity related costs[4].

Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2[1]. The importance of this lies in the physiologic changes of obesity presented by patients, both metabolic and biomechanical. Metabolically, hypertrophic adipocytes and adipose tissue-resident immune cells release increased levels of adipokines and lipokines, creating a chronic inflammatory state that exacerbates cardiovascular disease and insulin resistance, both of which adversely affect bone metabolism[5]. It has been shown that obese subjects who have one or two additional risk factors, like smoking and sedentarism, their risk of developing diabetes increases by nine times[5].

Bone mineral density is compromised in obese people by two mechanisms[6]. Firstly, increased levels of chemerin, an adipokine, correlates with an increased osteoporotic fracture risk[7]. Secondly, increased receptor activator of nuclear factor-kB (RANK)/RANK Ligand activity results in increased bone resorption by inducing increased osteoclast activity[8].

Forward progression forces are essential for normal gait. In obese subjects, energy usages tend to be lower in the anteroposterior plane and higher in the mediolateral plane indicating lower energy efficiency[9,10]. Other factors associated with abnormal gait include quadriceps weakening, knee osteoarthritis, poor balance, increased risk of falls, and skin irritation from poor shoe fit secondary to increased foot width and acquired flatfoot deformity[11-13]. Tibiotalar joints experience forces up to 5 times the body weight during the stance phase which is greater in an obese person[14,15]. With this knowledge in mind, it is no coincidence that there is an increased incidence of foot pain and higher rates of tendinitis, plantar fasciitis, and osteoarthritis in obese individuals[16-19].

Pre-operative weight loss seems the obvious solution for improving surgical outcomes. However, weight loss is difficult to achieve and to maintain[20,21]. Patients with foot and ankle pathologies often report pain as a limiting factor for successful weight loss. These patients have a higher risk of unsuccessful conservative treatment in conditions including Achilles' tendinopathy, plantar fasciitis and posterior tibial tendon dysfunction[22]. This leads to the belief that surgery will eliminate pain and finally allow them to lose weight as reported by MacMahon *et al*[23] where > 66% of obese patients had higher expectations than their surgeons, prior to surgical intervention[23].

The impact of obesity in orthopedic surgical outcomes has been extensively reported in total hip and knee arthroplasty studies, with strong evidence that obesity is highly associated with increased perioperative complications and higher revision rates[22,24-26]. A frequent complication present in this type of patients are wound complications which occur 3 times more often in obese individuals as shown in the literature[24]. In recent years, there has been more literature evaluating the implications of obesity in foot and ankle surgery[27]. This review will provide an updated, comprehensive analysis of the effects of obesity on foot and ankle surgical outcomes, provide insight into outcomes obese patients may expect from their surgeries, and highlight risks, benefits, and modifiable factors when operating on this cohort.

Table 1 Summary of foot and ankle surgical implications in obese patients

No.	Key points
1	By 2030, 48.9% of adults will be classified as obese, expanding surgical risk factors to a broad population
2	A chronic pro-inflammatory state faced by these patients, adversely affects bone metabolism
3	Factors associated with abnormal gait include quadriceps weakening, knee osteoarthritis, poor balance and an increased risk of falls
4	In obese subjects who have one or two additional risk factors like smoking and sedentary, their risk of developing diabetes increases by nine times
5	In Achilles tendon repairs, there is a significant increased rate of surgical site infection at the time of surgery if a comorbidity is present compared to those without a comorbidity
6	Patients with diabetes and vascular complications have the highest surgical site infection rate followed by obesity
7	Percutaneous hallux valgus procedures have found no difference in complication or re operation rates between normal weight and obese adults after surgery
8	There is an increased incidence of foot pain including higher rates of tendinitis, plantar fasciitis, and osteoarthritis in obese individuals
9	Compared with normal weight women, obese women have a three-fold increased risk of sustaining an ankle fracture after a fall
10	Obese patients have a greater proportion of chondral lesions when compared with normal weight subjects, 58% *vs* 30% respectively

IMPLICATIONS IN FOOT AND ANKLE SURGERY

Ankle fractures

A positive relationship between obesity and ankle fractures has been found in both men and women[28-31]. Compared with normal weight women, obese women have a three-fold increased risk of sustaining an ankle fracture after a fall[29].

Obesity has a direct correlation to ankle fractures in part due to altered gait changes as outlined above [32,33]. Mechanical loading is also affected in the obese population. Goodloe *et al*[34] found that after ankle fractures, obese patients have a significantly greater risk of needing repair of the syndesmosis[34]. They demonstrated an increased risk of 4.2% for each point increase in BMI for malleolar fractures, 3% for bi-malleolar fractures, and 3.4% for tri-malleolar fractures[29]. They proposed a biomechanical explanation where increased weight generates greater torque contributing to an increased risk of a more complex injury.

A greater risk of surgical site infections (SSIs) after open reduction internal fixation (ORIF) is a concern in obese patients. Specifically, Richardson *et al*[35] reported the greatest risk factors for SSIs were a BMI over 40 kg/m^2 [odds ratio (OR): 2.23, $P < 0.0001$] and the presence of peripheral vascular disease (OR: 2.16, $P < 0.0001$)[35]. Stavem *et al*[36] reported increasing BMI was associated with increased rates of venous thromboembolism (VTE) within 6 mo of ORIF for closed ankle fractures [OR: 1.15 per kg/m^2, 95% confidence interval (CI): 1.07-1.24, $P < 0.001$]. These complications arise from the fact that obese patients are at a constant inflammatory and immunosuppressed state[37,38].

Osteochondral lesions

Osteochondral lesions (OCLs) of the talus occur in approximately 70% of patients with an ankle sprain or fracture[37]. Frequently, a BMI greater than 25 kg/m^2 is associated with negative clinical outcomes [39].

Mardani-Kivi *et al*[14] performed a study of 26 obese patients and 10 nonobese patients evaluating the success of arthroscopic treatment of anterior ankle impingement in these groups. Patients underwent American Orthopaedic Foot and Ankle Society (AOFAS) scores at 6- and 12-mo follow-up demonstrating no difference in clinical outcomes. However obese patients were found to have a greater proportion of chondral lesions, when compared with normal weight subjects (58% *vs* 30% respectively) [40].

Ankle arthroscopy is more technically demanding in obese patients with significantly longer operative times[41]. This itself may be a risk factor for wound complications post-operatively, however further study is required.

Usuelli *et al*[42] studied arthroscopic autologous matrix-induced chondrogenesis for talar OCLs and found that overweight patients were more likely to have larger lesions based on preoperative magnetic resonance imaging scans. Despite this, they had similar clinical improvements and functional outcomes compared with normal weight patients. Koh *et al*[41] retrospectively evaluated 252 patients who underwent arthroscopic treatment for OCLs of the talus and found that a BMI > 25 kg/m^2 was not associated with worse post-operative and clinical outcomes when compared to non-overweight patients [43]. In contrast, a prospective study by Chuckpaiwong *et al*[44] investigating the relationship between lesion size and microfracture for OCLs found that higher BMI was a significant predictor of a negative outcome[44]. Younger patients with a shorter duration of symptoms and a lower BMI had better outcomes than older patients with a higher BMI and a more chronic symptomatic course[44].

Total ankle replacement

Total ankle replacement (TAR) surgery is increasingly performed for end stage arthritis to reduce pain and improve function and mobility to these patients. Obesity is important when considering TAR. These patients induce greater stress on prosthetic joints which may cause premature failure and subsequent surgery[45]. Werner *et al*[46] analyzed 5361 TAR procedures for end-stage arthritis and found obese patients had significantly more major and minor complications at 90 d post-surgery including infection and VET[46]. Comorbidity were more prevalent in the obese cohort compared to the nonobese cohort (P < 0.0001)[46]. While these may explain the higher complication rate and revision in obese patients following total ankle arthroplasty, multivariate regression analysis was not performed to determine if any of them were confounding variables.

Implant failure at mid and long-term follow up has been reported by Schipper *et al*[47]. Their study showed that a BMI 30 kg/m^2 was associated with a higher probability of implant failure (OR: 2.8, 95%CI: 1.04-7.53, P = 0.04), revision, and a significant decrease of 5-year survivorship when compared to nonobese patients (adjusted hazard ratio 3.73, 95%CI: 1.05-10.43, P = 0.04)[47].

Gross *et al*[48] carried out a prospective study of 455 primary TARs with a minimum follow-up of 2 years and reported no difference in complication, infection, or failure rates between obese and non-obese groups. While obese patients had high post-operative satisfaction and statistically significant improved clinical outcomes, they were all lower than their normal weight counterparts[48].

Ankle arthrodesis

Ankle arthrodesis remains the primary surgical approach in end-stage arthritis for many patients[49]. Using the United States Medicare database, Kamalapathy *et al*[50] evaluated the relationship between obesity, postoperative complications and hospital utilization following ankle arthrodesis[50]. They identified 5540 patients with normal BMI, 1108 patients who were obese and 1108 patients who were morbidly obese. Morbid obesity was associated with a statistically significant increased risk for acute kidney injury, urinary tract infection, VTE, readmission, and minor complications. Morbidly obese patients' length of stay was on average 2 d longer, and total hospital charge also correlated with increasing BMI, averaging $34335 more for morbidly obese and $28942 for obese patients compared to their normal weight counterparts[50].

Likewise, Werner *et al*[46] analyzed 17688 patients who underwent ankle arthrodesis and found that obesity was associated with a significant increase of thromboembolic events, infection and revision surgery[46]. Similar to TAR, complications can be related to additional medical comorbidities, intra operative factors and larger tissue envelopes[46].

Adult acquired flatfoot deformity

Obesity is a known risk factor for developing adult acquired flatfoot deformity (AAFD). The main stabilizer of the longitudinal medial arch is the posterior tibial tendon which, in obese patients, sustains greater axial load leading to insufficiency and finally collapse.

Soukup *et al*[51] performed a retrospective study comparing the outcomes of normal weight, overweight, and obese patients following AAFD reconstruction to treat stage II adult acquired flatfoot [51]. They identified 44 normal weight, 39 overweight and 44 obese patients with a mean follow up of 2.9 years. Obese patients reported more severe symptoms pre-operatively, but had similar clinical and radiological outcomes in the short-term when compared to the other two groups. They suggest that obese patients are still candidates for reconstruction with comparable short-term outcomes, but recognized that longer follow up and larger patient cohorts are needed to evaluate mid-term and long-term outcomes[51].

Fuhrmann *et al*[52] performed a retrospective analysis looking at clinical and radiological outcomes of hindfoot arthrodesis in patients with and without a flatfoot deformity showing that increased weight and BMI were predictors of recurrent deformity[52]. They suggested that when performing Stage 2 flatfoot deformity correction in obese patients, tissue reconstruction and corrective osteotomies should be augmented with a subtalar fusion, to enhance hindfoot stability[52].

Achilles tendinopathy

Achilles tendinopathy is a common condition associated with age greater than 50 years, male sex, increased BMI and lower extremity deformities[53]. Macchi *et al*[54] performed a meta-analysis of 22 studies comprising 18814 patients, 4010 of whom were obese (BMI ≥ 30 kg/m^2). They found that obese patients had increased rates of Achilles tendinopathy but not increased rates of rupture[54].

Some of the most common complications of Achilles tendon surgery are wound dehiscence and wound infection[53-55]. Dombrowski *et al*[55] identified that in a population of 24269 primary Achilles tendon repairs, there was a significantly increased rate of SSI if a medical comorbidity was present at the time of surgery compared to those without a comorbidity (17.96% *vs* 5.96%, P < 0.0001)[55]. Patients with diabetes and vascular complications had the highest SSI rate (OR: 7.85, 95%CI: 6.25-9.86, P < 0.001), followed by obesity (OR: 3.2, 95%CI: 2.9–3.6, P < 0.001)[55,56]. Bruggeman *et al*[53] also showed that patients with one or more risk factors had a greater rate of wound complications than patients without risk factors (P < 0.0001)[53].

Hallux surgery

Dufour *et al*[18] examined the association between obesity and foot problems in older adults and found that both men and women had an increased risk of morbidity with increasing BMI. Interestingly, severely obese women were less likely to develop hallux valgus (HV)[18]. Frey and Zamora[57] also identified that normal weight people had an increased likelihood of HV[57]. We suspect that shoe wear options in patients with large feet may have a wide toe-box and thus help prevent the development of HV.

Chen *et al*[58] found a 7-fold increase of re-operation in obese patients due to rates of non-union[58]. They proposed that fat-derived adipokines resulted in poor bone healing[58]. While obese patients had a poorer preoperative AOFAS Hallux Metatarsophalangeal-Interphalangeal scores, they were able to achieve functional outcome scores comparable to those of patients of normal weight, suggesting that obese patients can experience a greater improvement in function after HV surgery[58].

Percutaneous HV procedures have found no difference in complication or reoperation rates between normal weight and obese adults after surgery[59]. This may be due to the fact that surgeries on the forefoot are typically shorter, usually performed under regional anesthesia, and can allow for partial weight bearing operatively.

At present, it is unclear if BMI has an adverse effect in HV surgery. Although some studies suggest higher reoperation rates, and others state no correlation[60], most authors agree that while it is important to warn obese patients of the significantly higher risk of repeated surgery, these patients should not be excluded from undergoing HV surgery[58], and in most scenarios BMI should not influence prognosis[61].

LIMITATIONS

Obesity cannot be seen as an isolated risk factor for surgical procedures. Various clinical diseases arise from obesity and a better stratification of individuals should be contemplated when designing clinical studies to reach more significant clinical results according to each risk factor that englobes obesity. Large prospective studies are an urge in the field to identify associated risk factors and accurately stratify patients. This would enable choosing management adequately, including appropriate selection for surgery, in order to optimise the clinical outcomes.

CONCLUSION

Obesity significantly increases the risk of post-operative complications for many foot and ankle surgical procedures. However, these patients should not be excluded from undergoing surgery as improved functional outcomes can be achieved, relieving suffering for many patients. A multi-disciplinary pre-operative approach including different specialties should be considered to address the possible clinical implications such as wound infections, cardiovascular events and delayed functional recovery after these procedures. This way, risks can be reduced by preparing patients in the best way before a surgical procedure.

Future steps are necessary regarding better quality of evidence studies to examine how obesity and associated complications may contribute to unwanted surgical outcomes and how these risks can be managed.

FOOTNOTES

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MINIREVIEWS

Surgical strategy of the treatment of atypical femoral fractures

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Abstract

The atypical femoral fracture (AFF) has been attracting significant attention because of its increasing incidence; additionally, its treatment is challenging from biological and mechanical aspects. Although surgery is often required to manage complete AFFs, clear guidelines for the surgical treatment of AFFs are currently sparse. We reviewed and described the surgical treatment of AFFs and the surveillance of the contralateral femur. For complete AFFs, cephalomedullary intramedullary nailing spanning the entire length of the femur can be used. Various surgical techniques to overcome the femoral bowing common in AFFs include a lateral entry point, external rotation of the nail, and the use of a nail with a small radius of curvature, or a contralateral nail. In the case of a narrow medullary canal, severe femoral bowing, or pre-existing implants, plate fixation may be considered as an alternative. For incomplete AFFs, prophylactic fixation depends on several risk factors, such as a subtrochanteric location, presence of a radiolucent line, functional pain, and condition of the contralateral femur; the same surgical principles as those in complete AFFs can be applied. Finally, once AFF is diagnosed, clinicians should recognize the increased risk of contralateral AFFs, and close surveillance of the contralateral femur is recommended.

Key Words: Atypical femoral fracture; Surgical treatment; Surveillance; Contralateral femur; Femoral bowing

Core Tip: For complete atypical femoral fractures (AFFs), cephalomedullary intramedullary nailing spanning the entire femur and various surgical techniques to overcome femoral bowing should be considered. For incomplete AFFs, the recognition of impending complete fractures is important. For the contralateral femur, close surveillance is recommended because of the increased risk of contralateral AFF.

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INTRODUCTION

The atypical femoral fracture (AFF) has attracted significant attention since Odvina *et al*[1] first reported non-traumatic subtrochanteric fractures in the femur in nine patients with the prolonged use of bisphosphonate therapy (BP). The treatment of AFFs is challenging, even for skilled orthopedic surgeons. Biologically, long-term use of anti-resorptive agents is associated with reduction of bone turnover and altered biomechanics[2]. The inhibition of the bone remodeling process by reducing the activity of osteoclasts causes changes in the mineral and matrix properties of the bone, consequently increasing the thickness of the bone cortex. As a result, bone strength and stiffness increase, making the bone more brittle and susceptible to fragility fractures. Also, biomechanical analyses indicate that tensile stresses are high in the lateral femoral cortex and these can predispose the AFFs[3]. In addition, it affects primary and secondary bone healing[2-4], resulting in delayed union or non-union[5]. In addition, AFFs are often encountered in unfavorable mechanical environments, such as anterolateral bowing of the femur[6], and intramedullary nailing (IMN) may not fit the femur[7-9]. As the incidence of AFF is rising owing to an increase in the aging population[4] and is often associated with the potential risk of poor bone healing, the treatment of AFF has become a major issue in the medical community, leading to convening a task force by the American Society of Bone and Mineral Research[10,11].

In general, AFF often requires surgical treatment depending on the fracture pattern (complete or incomplete), location (subtrochanter or diaphysis), and presence of symptoms (thigh pain), which is considered the standard treatment for both complete and incomplete fractures. However, as there has been a lack of randomized controlled trials demonstrating the optimal treatment of AFFs, clear guidelines for surgical treatment are currently scarce[12,13], and treatment for AFF is being performed according to a lack of consensus based on expert opinions.

In the current study, we reviewed the current surgical treatment methods for complete and incomplete AFF and highlighted the specific considerations to be observed in unique situations, such as concurrent severe bowing and surveillance of the contralateral femur. Finally, we summarized the context by providing a management algorithm for AFFs based on contemporary evidence in the literature.

SURGICAL TREATMENT OF COMPLETE FRACTURES

AFFs can be classified into complete and incomplete fractures, and surgical treatment is inevitable for complete fractures[14]. Randomized clinical trials have not yet been conducted to determine the optimal surgical method for complete fractures; however, long cephalomedullary IMN spanning the full length of the femur has been recommended[6,10].

Biomechanical aspect should be considered for the surgical treatment of AFFs. Previous reports have suggested several reasons why IMN is preferred for plate fixation in AFFs. First, from a mechanical aspect, IMN has advantages, including a better load-sharing capacity and less bending moment owing to its more medial location compared to plate fixation[15,16]. Thus, devices with greater load sharing have an advantage in AFFs in terms of early ambulation in elderly patients. Second, because of decreased bone remodeling and the subsequent poor bone quality, the stress concentration around the end of implants may induce peri-implant stress fractures[17]. While it is difficult to span the full length of the femur with open plating, IMN has the advantage of spanning the whole femur, and therefore, stabile fixation can be achieved without imbalance between tensile force and compressive force of the fracture site and it may be better than plating in reducing subsequent fatigue fractures[18]. Biologically, osteoclastic activity is suppressed by previous anti-resorptive medication in AFF patients, thereby rendering bone remodeling and subsequent direct bone healing difficult[1-4]. Although direct bone healing is important in plate fixation, IMN may induce indirect bone healing by endochondral ossification, and decreased osteoclastic function may affect the fracture healing process lesser compared to other methods[19]. Also, Basically, biological damage can be minimized by avoiding incision and

direct manipulation of the fracture site. In addition, Although intramedullary nailing can have detrimental effect on the cortical and the endosteal blood flow, it has important effect for bone healing with increased extraosseous circulation and the bone grafting effect from marrow reaming during IMN may enhance osteosynthesis in AFF patients with reduced fracture healing potential[20,21]. Finally, AFFs often accompany anterolateral bowing of the femur; however, contouring the plate to fit the three-dimensional (3D) curvature of the bowed femur during surgery requires additional time and a large incision for open plating itself in elderly patients[9]. Therefore, IMN has theoretical advantages over plating in terms of mechanical, biological, and practical aspects.

Systematic reviews have shown that a greater proportion of complete AFFs treated with plate fixation required reoperation compared to those individuals treated with IMN[11,22]. Egol *et al*[23] reported favorable functional outcomes with IMN in the treatment of AFFs. Shkolnikova *et al*[24] demonstrated that extramedullary fixation, such as plate fixation, resulted in a functional decline in the majority of patients with AFFs. Thus far, studies have shown that IMN provides better radiographic and functional outcomes when compared to plate fixation[11,22].

The selection of an IMN implant design is important for AFFs. The largest possible nail should be used to avoid distal perforation and iatrogenic fractures caused by IMN[25]. If accompanied by femoral bowing, it is recommended to use a nail with a small radius of curvature (ROC)[7,25]. The conventional standard IMN involves the oblique transverse orientation of the proximal interlocking screws across the proximal femur. However, because these interlocking screws do not cover the femoral neck, there is a potential risk of stress fractures around this unprotected area[26]. As cephalomedullary IMN incorporates one or two large proximal locking screws into the nail and places them in the direction of the femoral head, this method may protect the femoral neck from subsequent fragility fractures. A recent study showed that cephalomedullary IMN reduces the incidence of delayed peri-implant fragility fractures, newly developed AFFs, and non-unions in patients with AFF[27].

AFFs have been reported to have high complication rates with operative fixation because of their unique properties, including anterolateral bowing of the femur[4,28,29]. Although IMN follows the standard surgical technique for subtrochanteric or shaft fractures, meticulous surgical techniques may be necessary to treat complete AFFs. In AFFs, the lateral cortex of the femur at the fracture site is often thickened, which makes nail passage difficult. To overcome this, the medullary canal can be over-reamed by 2.5 mm to ensure good nail passage, stimulate fracture site healing, and reduce iatrogenic fractures[30]. The quality of fracture reduction is important for determining the healing of AFFs, and mal-alignment is strongly correlated with the healing time and failure rate[31,32]. Moreover, if the IMN straightens the curved femur, this not only affects the healing time but also induces limb length discrepancy (LLD)[9]. A previous study analyzed the factors affecting healing in complete AFFs and reported that IMN without cortical breakage around the fracture site and reduction of the fracture gaps anteriorly and laterally affected the healing of AFFs[33]. Since non-union may occur if there are residual fracture gaps anteriorly and laterally more than 2 mm, it is recommended to attempt narrowing of the gaps using the back-slapping method by applying the angular stable locking system (ASLS®, Synthes GmbH, Oberdorf, Switzerland) for distal interlocking. Another study reported that the quality of fracture reduction was the most important factor for achieving bone union; additionally, the cutoff points for the neck-shaft angle, differences in the neck-shaft angle, and sagittal angulation were 125.6, 4.4, and 5.5°, respectively[34]. If adequate alignment cannot be achieved with traction, particularly in subtrochanteric AFFs associated with strong muscle forces, percutaneous wiring or preliminary plating may be necessary[32,33]. The possible causes of failure include the position of the nail as well as the quality of reduction, and it is important to consider the respective starting points[35]. If loss of reduction occurs during nail passage, repositioning of the starting point should be considered.

IMN in AFF with severe anterolateral bowing is challenging, and various methods have been suggested to overcome this difficulty[8]. First, as mentioned above, if the bowing of the femur is severe, it is recommended to use a nail with as small ROC as possible[7,27]. Second, the entry point lateral to the greater trochanter or piriformis fossa can be used as a site of insertion (Figure 1)[36]. Third, an alternative method is to use the opposite side of the nail (Figure 2)[37]. Some femoral nails have an anterior curve as well as proximal lateral bending, and thus can be aligned with the anatomical axis of the femur with anterolateral bowing by rotating the zig 180° to the opposite side of the nail. The fourth method involves adjusting the alignment by externally rotating the nail. In this method, the anterior curvature of the nail is externally rotated to fit the anterolateral bowing of the femur, and the proximal lateral bending of the nail is matched to the anterior curvature of the femur[6]. However, this method requires the use of a standard nail with proximal screws in the transverse direction instead of the cephalomedullary nail in AFFs and demonstrates concerns related to femoral neck stress fractures. Finally, with the introduction of the minimally invasive plate osteosynthesis (MIPO) technique, which can facilitate indirect bone healing, plate fixation can be considered as an alternative to IMN in AFF with an extremely narrow canal, no nail match with severe femoral bowing, or pre-existing metal implants (Figure 3)[38]. When plate fixation is considered for AFF treatment, spanning the full length of the femur is recommended, and prophylactic screw fixation toward the femoral neck may be necessary to prevent peri-implant or femoral neck fractures (Figure 4)[18,39].

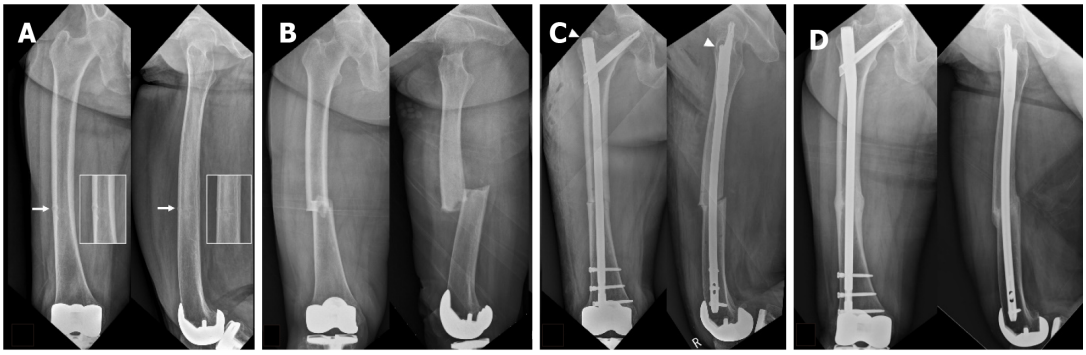

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Figure 1 Images of an 80-year-old woman. A: An 80-year-old woman was transferred from a spine clinic because of intractable right thigh pain for three months. Radiographs revealed a transverse radiolucent line (white arrows and insets) on the lateral and anterior cortex of the right femur with 10° of varus. The patient refused prophylactic surgery for incomplete atypical femoral fracture (AFF); however, medical treatment including a switch from bisphosphonate to teriparatide was initiated. According to a scoring system[11], the risk for impending complete AFF was scored as 10 points; B: Two months later, she visited the emergency department due to progression to a complete AFF; C: She underwent fixation with a long cephalomedullary nail (Trochanteric Fixation Nail-Advanced®, DePuy Synthes, Winterthur, Switzerland) spanning the whole length of the femur. It is to be noted that the entry point of the nail is lateral and anterior to the greater trochanter tip (arrowheads); D: Radiographs taken at 18 mo postoperatively showed healing of the fracture site.

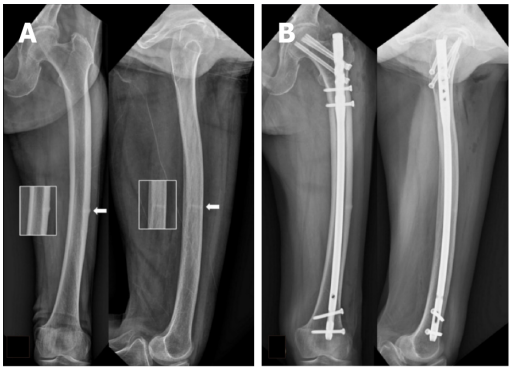

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Figure 2 Images of an 81-year-old woman who had taken bisphosphonate for two years. A: An 81-year-old woman who had taken bisphosphonate for two years visited the outpatient clinic complaining of left thigh pain for two months. Radiographs revealed a transverse beak and radiolucent line (white arrows) on the lateral and anterior cortex of the right femur with 10° of varus and 7° of anterior angulation. According to a scoring system[11], the risk for impending complete atypical femoral fracture was scored as 11 points; B: She underwent fixation with an opposite-side (right side) standard nail (Sirus Femoral Nail®, Zimmer, Warsaw, IN, USA). Prophylactic screw fixation toward the femoral neck on her left femur was performed to prevent potential femoral neck fracture around the nail.

Delayed union, non-union, or implant failure has been a common complication reported after the surgical treatment of AFFs[11,22,40]. Among them, non-union is the most frequent complication, followed by implant failure. According to a recent systemic review including 348 complete AFFs, reoperation was required in 6 out of 38 (15.7%) extramedullary fixation devices used for treating AFF, whereas revision was required in 20 out of 310 (6.45%) IMNs[22]. This finding is consistent with the results reported by Koh *et al*[11]; a greater proportion of complete AFFs treated with plate fixation (31.3%) required reoperation than those treated with IMN (12.9%) (P<0.01). With regard to the clinical outcomes, the patients who underwent IMN demonstrated better functional scores[40]. A previous study reported that IMN returned to the baseline function in 64% and pain-free status in 66% of patients at postoperative 12 mo[23], while another study with a follow-up duration of up to 46 mo demonstrated a functional decline in 64% of the patients, the majority of whom had extramedullary fixation devices [24]. Unlike the increased mortality associated with typical osteoporotic fractures of the femur, a previous study reported that the mortality rate after treating AFFs was lower than that after treating ordinary femoral fractures[41]. Therefore, although the treatment of AFFs is often challenging, orthopedic surgeons may obtain promising outcomes if they choose a proper treatment option according to the individual and pay attention to meticulous surgical techniques.

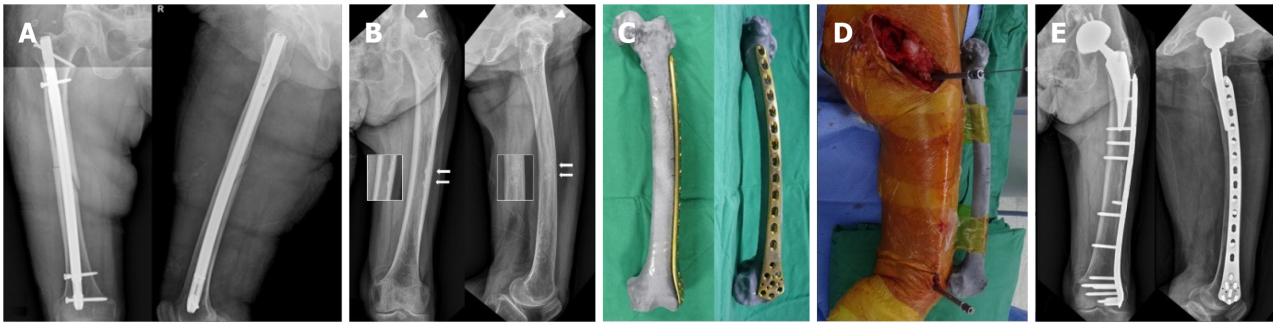

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Figure 3 Images of a 75-year-old woman underwent a fixation with a long standard nail. A: A 75-year-old woman underwent a fixation with a long standard nail due to a complete atypical femoral fracture (AFF) on her right femur two years ago at another hospital and kept taking bisphosphonate (BP) until she visited our clinic; B: She reported left groin and thigh pain for six months. Radiographs revealed arthritis on her left hip joint (arrowheads) and transverse beaks with radiolucent lines ("dreaded black line") on the lateral and anterior cortex of the left femur (white arrows and insets). According to a scoring system[11], the risk for impending complete AFF was scored as 8 points and BP medication was discontinued; C: Before total hip arthroplasty (THA) to treat hip arthritis, a locking compression plate was pre-contoured along the shape of the bone model with 3D printing rapid prototyping; D: During THA, the sterile 3D-printed model was placed in the same position as that of the femur and used as a surgical navigation. Fixation with the pre-contoured plate *via* minimally invasive plate osteosynthesis was performed to treat incomplete AFF; E: Radiographs taken three years postoperatively showed complete healing of the AFF without progression of femoral bowing or implant-related complications.

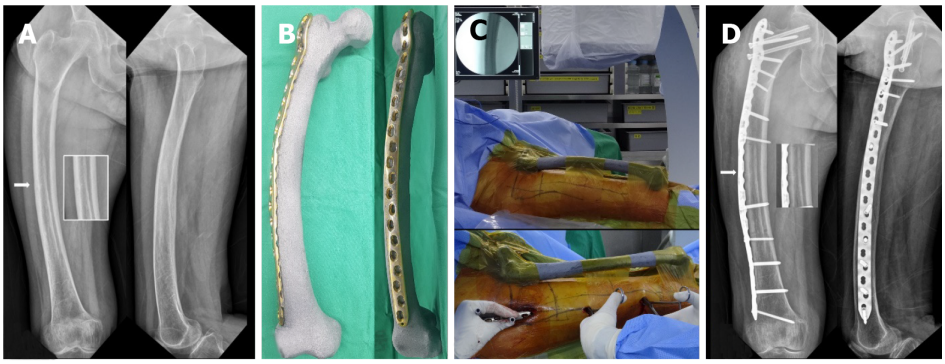

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Figure 4 Images of a 75-year-old woman who had taken bisphosphonate. A: A 75-year-old woman who had taken bisphosphonate for a period of four years visited our clinic with right thigh pain for three months. Radiographs showed a transverse radiolucent line (white arrow and inset) on the apex of the lateral cortex of the right femur with 7° of varus. According to a scoring system[11], the risk for impending complete atypical femoral fracture (AFF) was scored as 9 points; B: Before the surgery, a locking compression plate was pre-contoured along the shape of the bone model with 3D printing rapid prototyping; C: During the surgery, the sterile 3D-printed bone model was placed in the same position as that of the femur and used as a surgical navigation; D: Fixation with pre-contoured plate fixation for incomplete AFF (white arrow and inset) with severe bowing was performed *via* minimally invasive plate osteosynthesis. It is to be noted that additional prophylactic screw fixation toward the femoral neck was performed to prevent potential femoral neck fractures.

SURGICAL TREATMENT OF INCOMPLETE FRACTURES

The natural history of incomplete AFFs has not yet been determined; therefore, taking decisions regarding whether or when to perform surgery is difficult[42]. Incomplete AFFs are easily misdiagnosed or undiagnosed before the fracture becomes complete (Figure 1)[43]. Meanwhile, a previous study reported that 10 of 14 (71.4%) incomplete AFFs were eventually treated surgically because of their progression to complete fractures or intractable pain[14]. The purpose of prophylactic surgery in incomplete AFFs is not only to reduce pain, but also to prevent progression to complete fractures, thereby avoiding commonly developed complications after complete AFFs, such as delayed union, non-union, implant failure, and LLD, as described above[11,44]. Therefore, it is important to assess whether the optimal option for treating incomplete AFFs is to perform prophylactic surgery or close observation. Recently, a scoring system was introduced to identify impending fractures among incomplete AFFs according to the fracture location, nature of pain, the extent of the radiolucent line, and condition of the contralateral femur (Table 1)[12]. If the score is equal to or greater than eight points, prophylactic fixation is recommended. Contrastingly, patients with a score of seven or less may be treated conservatively, and the responsible physician should carefully evaluate the patient's symptoms and radiographic findings to identify the changes during follow-up. In addition, some authors have recommended prophylactic fixation for incomplete AFFs in cases with the "dreaded black line" on radiographs, varus femoral bowing, a history of contralateral AFF, or failure to improve after two or

Table 1 A scoring system for the surveillance of impending complete atypical femoral fracture in an incomplete state[11]

Variables	Score		
	1	2	3
Pain	None	Mild	Functional
Site	Others	Diaphyseal area	Subtrochanteric area
Contralateral femur	Complete fracture	Incomplete fracture	Intact
Radiolucent line	Focal changes	Less than 1/2	More than 1/2

three months of conservative management[38,45].

The same surgical principles as those for complete AFFs can be applied; thus, cephalomedullary IMN has been proposed as a standard prophylactic fixation for incomplete AFFs[46]. However, for those with severe femoral bowing, which is common in incomplete AFFs, care should be taken because IMN may lead to iatrogenic complete fractures and result in LLD, delayed- or non-union[11,46]. Recently, a report demonstrated that the use of a 3D printing technique could facilitate the reconstruction of severely bowed femurs with incomplete AFF, which were then fixed with a pre-contoured plate using an MIPO technique to match the shape of the femur (Figure 3 and 4)[9]. In this case, additional prophylactic screw fixation toward the femoral neck was required to prevent stress concentration and potential femoral neck fractures.

Although the indications or methods of prophylactic fixation for incomplete AFFs are still controversial, this approach has generally been associated with excellent results[23,47]. A previous study reported that incomplete AFFs treated with surgery showed radiographic healing in 100% and pain-free status in 81% of patients at a mean of 7.1 mo postoperatively[23]. In a systematic review of 109 incomplete AFFs treated with prophylactic fixation (78 fractures with IMN, 12 fractures with plate fixation, and the remaining by unspecified means), 106 fractures (97%) healed radiologically without any revision surgery at an average of 7 mo (range, 1.5–20 mo)[11].

SURVEILLANCE OF CONTRALATERAL FEMUR

Although the pathogenesis of AFFs remains unclear, patients with unilateral AFF have an increased risk of subsequent contralateral fractures[10]. Previous studies have reported that up to 62.9% of patients with AFFs had bilateral fractures or radiographic abnormalities in the contralateral femur[10,48]. However, as most patients with complete AFFs may have an asymptomatic contralateral femur at initial presentation, it is easy to underestimate the potential AFF in the contralateral femur until the fracture becomes complete (Figure 3)[49]. Several authors have investigated the natural course of the contralateral femur in patients with AFF and reported that up to 88.5% of contralateral femurs eventually progressed to an incomplete or complete fracture within a period of three years[50-52]. This is because reduced weight bearing in the fractured femur may propagate incipient stress fractures in the contralateral femur[9]. A recent report highlighted that the postoperative use of BP might influence the development of contralateral AFF[50]. Therefore, once AFF is diagnosed, a contralateral femur should be evaluated and appropriate medical treatment, including the discontinuation of BPs and initiation of calcium and vitamin D supplementation, must be initiated in addition to endocrine assessments, such as bone turnover markers[53]. When diagnosing a contralateral incomplete AFF, clinicians should decide whether to perform prophylactic surgery or conduct a close observation. As described in the surgical treatment of incomplete fractures, a history of contralateral AFF is a potential risk for an impending complete fracture; thus, the current consensus is that contralateral incomplete AFF may be considered an impending complete fracture[12,23,54].

In summary, orthopedic surgeons should be aware of the potential risk of contralateral AFF in patients with unilateral AFF and must evaluate the contralateral side. Although the validated guidelines to support the subsequent decision-making processes remain unclear, prophylactic fixation for contralateral incomplete AFF may be recommended in cases where the risk of impending complete AFF is increased (Figure 5)[55]. In the absence of such signs of incomplete AFF, close surveillance of the contralateral femur for at least two years may be required[50]. Once AFF is diagnosed, clinicians should discontinue BPs and provide calcium and vitamin D supplements. The use of bone-forming agents may promote healing and reduce the potential risk of complete AFF on the contralateral side[10].

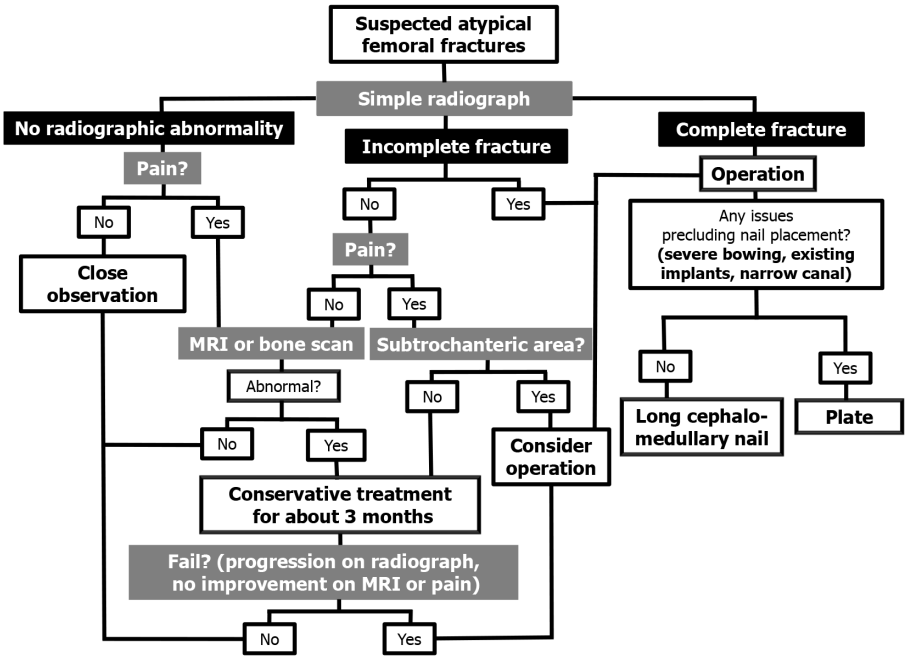

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Figure 5 A proposed treatment algorithm for suspected atypical femoral fracture. MRI: Magnetic resonance imaging.

CONCLUSION

The incidence of AFFs is increasing, and their treatment is challenging in terms of the biological and mechanical aspects. For complete AFFs, the cephalomedullary IMN spanning the entire length of the femur can be primarily used. The various surgical techniques for IMN to overcome the femoral bowing common in AFFs include over-reaming, use of a lateral entry point, external rotation of the nail, and the use of a nail with a small ROC or contralateral nail. In cases of narrow canals, severe femoral bowing, or pre-existing metal implants, plate fixation may be considered as an alternative. For incomplete AFFs, prophylactic fixation depends on potential risk factors such as subtrochanteric location, the presence of a radiolucent line, functional pain, and condition of the contralateral femur, and the same surgical principles as those in complete AFFs can be applied. Finally, once AFF is diagnosed, the clinicians should recognize the increased risk of contralateral AFF, and close surveillance of the contralateral femur is recommended.

FOOTNOTES

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MINIREVIEWS

Amputation in diabetic foot ulcer: A treatment dilemma

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Abstract

Diabetic foot is a clinical manifestation of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, and gangrene, as a consequence of advanced disease. Some diabetic foot cases present general indications for amputation, including dead limb, threat to the patient's life, pain, loss of function, or nuisance. Various tools have been introduced to help decision-making in amputation for diabetic foot. However, it remains a conundrum because diabetic foot involves multiple pathomechanisms and factors that hinder its outcomes. Sociocultural issues often impede treatment from the patient's side. We reviewed different perspectives in diabetic foot management, particularly related to amputation. In addition to deciding whether to amputate, physicians should address amputation level, timing, and ways to avoid patient deconditioning. Surgeons should not be autocratic in these circumstances and should be aware of beneficence and maleficence when considering whether to amputate. The main goal should be improving the patients' quality of life rather than preserving the limb as much as possible.

Key Words: Diabetic foot; Ulcer; Amputation; Decision-making; Perspective

Core Tip: Making a decision regarding amputation for diabetic foot patients is not as simple as following guidelines, such as scoring systems. There are many influential factors that come from different perspectives and are sometimes contradictory. Decision-making should consider other clinical and sociocultural factors, with the improvement of patient quality of life as the main goal.

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INTRODUCTION

The rising prevalence of diabetes represents a major public health and socioeconomic burden on society. Diabetes presents relatively mild symptoms that generally go unnoticed at early stages. Patients commonly seek medical treatment in later stages when complications occur. Diabetic complications are associated with poor glycemic control[1].

Diabetic foot is one clinical manifestation of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, and gangrene, as a consequence of advanced disease (Figure 1). Some diabetic foot cases present general indications for amputation, including dead limb, threat to the patient's life, pain, loss of function, or nuisance[2]. Various scoring systems are applicable for clinicians to determine whether the indication for amputation is present, such as the mangled extremity severity score or diabetic ulcer severity score[3,4]. However, clinicians must address various factors that are not resolvable by these scoring systems in many cases. Therefore, decision-making is complicated. This article reviewed the contributing factors that are often encountered during decision-making in diabetic foot management, especially when it is related to amputation.

CLINICAL CONSIDERATIONS

The etiology of diabetic foot ulcer is multifactorial. Poor glycemic control is the major underlying cause of advanced glycation end product (AGE) accumulation circulating in the body, which affects various organs. AGE formation is one of the main mechanisms responsible for vascular damage in diabetes patients, and it alters the angiogenic reaction[5]. Angiopathy indicates a vascular defect that is associated with angiogenic abnormalities. Angiogenesis itself results from the balanced functions of pro- and antiangiogenic molecules. Defects in this angiogenic balance may result in excessive or antiangiogenesis[6]. The activity of various regulators determine this angiogenesis switch. Vascular endothelial growth factor (VEGF) is a signal protein responsible for blood vessel formation. Hypoxia-inducible factors (HIFs) are transcription factors that respond to decreases in cellular hypoxia. Exposure to high glucose inhibits HIF and VEGF expression in normal cells[6].

Peripheral artery disease (PAD) may be described as atherosclerotic occlusive disease of the lower extremities. Chronic hyperglycemia, dyslipidemia, and insulin resistance in diabetes mellitus patients are responsible for vascular wall derangements *via* promotion of vascular inflammation, endothelial cell dysfunction, abnormalities in blood cells, and factors affecting hemostasis[7]. AGEs contribute to impaired angiogenesis *via* a reduction in collateral vessel development. AGEs also participate in the modification of extracellular matrix molecules, which promote atherosclerotic lesion development[8,9].

Macroangiopathy or microangiopathy has a tendency to inhibit nutrient/oxygen supply. These conditions put the foot at risk for ulceration and hinder the wound-healing process[6]. These vascular problems in combination with increased plantar pressure due to fibrosis-related Achilles tendon contracture and loss of protective sensory function result in recalcitrant complicated foot ulceration[10]. The involvement of infrapopliteal vessels is commonly found in diabetes patients with PAD. When ischemia is established, the restoration of pulsatile blood flow by revascularization is paramount for limb salvage. The treatment options are angioplasty, surgical bypass, or subintimal recanalization with varied results[11,12].

Infection is a common complication in diabetes, and it is particularly attributable to hyperglycemia-related immunosuppression in which polymorphonuclear lymphocyte activity is hindered. Infection results in prolonged inflammation that prevents wound healing and keeps the microorganism portal of entry open, which eventually causes further infections[13]. Diabetic foot infection is difficult to manage. Timely diagnosis and appropriate intervention are essential in management strategies. Diabetic foot osteomyelitis (DFO) is the consequence of a soft tissue infection that spreads into the bone, and it involves the cortex first then the marrow. DFO showed an increase in multidrug-resistant organisms, primarily methicillin-resistant Staphylococcus aureus or extended-spectrum beta-lactamase-producing

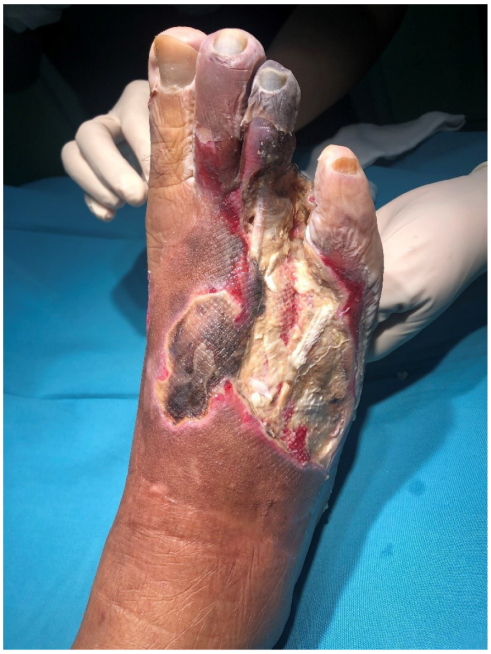

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Figure 1 A complicated diabetic foot ulcer which required a careful decision-making.

bacteria[14,15]. The presence of osteomyelitis impedes infection control and raises the further need for medical treatment and surgeries[16]. Osteomyelitis requires surgery to remove portions of bone that are infected or dead. Although an aggressive surgical approach may be mandatory, retrospective studies showed that conservative treatment effectively promoted wound healing and reduced the risk of major amputations[14,17]. Recurrent ulcers are a significant cause of hospitalization and amputation[18].

Although diabetic foot ulcer is generally painless, it is viewed as the main reason for ulcer formation due to the loss of protective sensory function, and as many as 27% of patients experience painful diabetic peripheral neuropathy (DPN) to various degrees[19]. However, severe neuropathy is not the only cause of pain because there are other causes precipitating pain, including ischemia, infection, and oxidative stress-related mechanisms. Other than clinical findings, DPN may be diagnosed using several adjunct examination tools, such as nerve conduction studies. One of the newest tools is the assessment of transcutaneous oxygen pressure ($TcPO_2$), in which the sitting-supine position difference in $TcPO_2$ is higher in DPN patients than control subjects[20]. Various drugs have been introduced to address this problem, including selective serotonin and norepinephrine reuptake inhibitors, anticonvulsant agents, and opioid receptor agonists, but pain relief remains poor for most patients[21].

Longstanding diabetic foot, particularly when treated insufficiently, may produce some disabling deformities. The wound may be healed in this condition, but functional gait or ambulation is hindered. When physical activity is decreased, static positioning with fibrotic changes within the muscle will lead to contracture formation. Considering the muscle imbalance between the anterior and posterior groups, equinus contracture will likely develop[10]. Combined with muscle atrophy resulting from disuse and neuropathy, deformity and function loss may occur and result in a condition called damned nuisance, in which the limb is functionless, and amputation followed by prosthesis application would be a better solution. The deformity can also occur from osteoarticular destruction or prior autoamputation.

AMPUTATION AND COMMON CONUNDRUMS

Amputation is generally the last choice for the treatment of non-salvageable limbs[22]. The main indications for amputation include various conditions, such as posing a threat to the body, such as the spreading of infection or tumors, the presence of necrotic tissue that constitutes a medium for pathological microorganism growth and a functionless limb, and some situations in which the patient and clinician believe that amputation will yield better results in overall function and quality of life in the absence of dead or dangerous limbs. Clinical decision-making on whether to amputate or to determine the amputation level frequently deviates from the factors that the patient and surgeon initially considered when the patient first presented with diabetes.

Amputation is divided into major or minor, according to its level. Major amputation is defined by any ankle disarticulation, transfemoral amputation, or transtibial amputation, and minor amputation is defined as a toe or transmetatarsal amputation[23]. Determining the amputation level is critical to the

efficacy of management. Amputation should be performed at a level with sufficient blood supply for wound healing. Arterial angiography, Doppler ultrasonography, and perfusion pressure are acceptable methods. The latest advanced examination tools, such as transcutaneous oxygen pressure measurement, are reliable in predicting wound healing in diabetic foot[24]. Soft tissue coverage should also be considered in deciding the amputation level. For great toe gangrenes, ray amputation is preferred over metatarsophalangeal joint disarticulation despite good blood supply and biomechanical advantages of the latter. Less soft tissue bulk and higher pressure at the distal part result in eventual wound breakdown. Exposed cartilage following disarticulation may be a source of infection *via* necrotic tissue formation[22]. In addition to local vascular status, systemic condition will also determine the result. Lower albumin and higher glycated hemoglobin, C-reactive protein, white blood count, and creatinine levels are determinants of failed amputations that need subsequent reamputation[25]. Amputation is contraindicated in these situations and delayed until systemic improvement is achieved, except in emergency situations.

Despite the clear clinical findings prompting amputation, the negative perception of amputation remains, which results in hesitation to undergo amputation[22]. The ability to cope with an amputation is affected by clinical measurements, cosmesis, cultural issues, social support, and the patients' pre-amputation coping style[26]. Although many patients refuse amputation and are discharged against medical advice, they often request that the surgeon perform amputation as distally as possible without understanding the indications. The fact that amputation may be perceived as a taboo makes discussion with patients and their relatives difficult[27].

Leg amputation is related to increased dependence. In addition to the medical benefit obtained from well-indicated amputation, function may be restored using proper prosthetics to regain the patient's independence. However, the recovery of function is not solely based on prosthetics. Older age, poor balance, previously low function level, and higher amputation level are some determinants of disability status[26]. Considering the physical demands, amputee patients spend more energy during walking than able-bodied persons. The energy expenditure of transfemoral amputees is higher than transtibial amputation[28]. Therefore, choosing the amputation level should also be in concordance with further postoperative rehabilitation plans.

DECISION-MAKING

In regard to decision-making for amputation, various factors may be determinants. Choosing the level of amputation is the mainstay of treatment, but the timing of surgery is also important.

While establishing the indication is paramount, its contraindication is also critical. The general contraindication for amputation is the patient's inability to tolerate anesthesia or the surgery itself, such as the accompanying systemic problems. Amputation at a particular level is contraindicated when inadequate blood supply for wound healing is encountered, when the infarcted area is undetermined, or when malnutrition occurs that hinders wound healing. Therefore, amputation is contraindicated when the quality of life is reduced afterward.

PAD and infections are the main causes of lower-leg amputations. Limb salvage in diabetic patients with PAD requires comprehensive management, including medical therapies. Other than glucose-lowering and lipid-lowering drugs, these patients need medications that aim to improve vascular functions, including antiplatelet therapy, protease-activated receptor-1 antagonists, anticoagulants, or vasodilators[29]. Due to ischemic and neuropathic pain, many diabetic foot patients continually consume analgesics, including several anticonvulsants[21]. Antihypertensive and antithrombotics are the major medications related to polypharmacy management for the elderly population, which increase the risk of adverse drug reactions (ADRs)[30]. Chronic kidney disease occurs as a diabetic complication *via* renal fibrosis. Therefore, longstanding drug administration in limb preservation should be monitored carefully. Deprescription should be considered to avoid ADRs. PAD is difficult to treat in diabetes patients due to various comorbidities. Atherosclerotic lesions are multilevel with a high prevalence of long occlusions. New techniques and technologies have been introduced for addressing PAD with various results that were likely related to the individual patient conditions[31,32].

Revascularization is a procedure to restore blood supply to the tissue by addressing the blocked blood vessels. The aim is to salvage the limb by healing the trophic disorder. The indications included critical ischemia with some suggestive vascular examination findings (arterial pressure < 50 mmHg or $TcPO_2$ < 30 mmHg). However, prerequisite conditions must be met, including a satisfactory support bed, a distal artery of a good caliber, and the presence of a plantar arch[11]. Vascular surgeons generally choose between endovascular procedures (transluminal or subintimal), bypasses, or hybrid techniques that include both procedures. The choice of revascularization technique depends on the type of lesion, the presence or absence of stenosis, and thrombosis and their length[11]. Iatrogenic injuries were reported but were mostly self-limited and of minimal clinical significance. Some life-threatening complications may occur, including ruptures, perforations, and pseudoaneurysms. Patient subpopulation selection is important to avoid unpredicted complications[33]. The main objective of revascularization is wound healing and limb salvage. At the one-year follow-up, 60% or more ulcers had healed

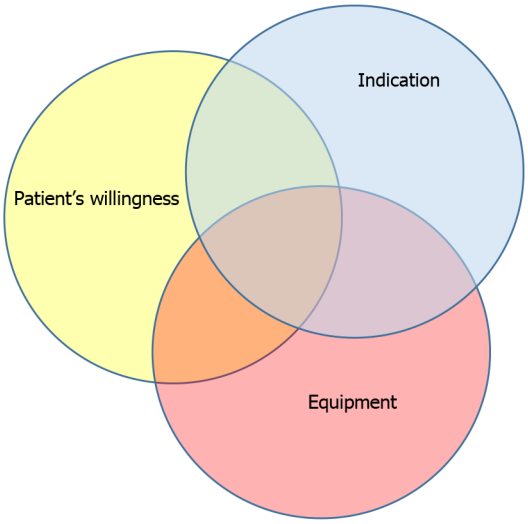

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Figure 2 Contributing factors in decision-making process for amputation.

with endovascular procedures or open bypass surgery. However, the overall results demonstrate improved rates of revascularization compared to conservative treatment[31].

Revascularization is mandatory in ischemic limbs for wound healing and as a prerequisite for further surgical procedures, including debridement and amputation. Otherwise, re-amputation will likely be needed[22]. Many patients presented contraindications for minor or major amputation, systemic or local, including unfeasible revascularization. Autolytic debridement may be an option in this setting, or major amputation at the safe level. Autolytic debridement itself is safe because it uses the natural ability of the body's own enzymes to remove dead tissues. To achieve autolytic debridement, the maintenance of a moist local wound environment is paramount[34].

Regarding limb salvage options, wound bed preparation *via* serial debridement is important, initially to limit the spread of infection. There are various advanced treatment options for recalcitrant diabetic foot wounds, such as hyperbaric oxygen therapy and platelet-rich gel treatment. Hyperbaric oxygen therapy involves the patient entering a pressurized room and breathing almost pure oxygen, which increases the amount of oxygen in the bloodstream and eventually boosting oxygen flow to the wound. Hyperbaric oxygen therapy offers great benefit in diabetic foot ulcer treatment and the reduction of amputation[35,36]. Autologous platelet-rich gel therapy is another option that effectively improves the healing of diabetic foot ulcers by increasing the concentration of platelets and growth factors in the wound and improving the surrounding microenvironment[37]. When the infection is controlled and granulation induces healing, limb reconstruction can proceed. Therefore, vascular flow is predominant. Thorough evaluation and approaches are needed to ensure this reconstructive procedure. Small, vascularized areas with no bone exposed may be grafted for nonbearing areas or local flaps in weight-bearing areas. Complex wounds are considerable for limb reconstructive procedures. Either decision must be made by the team and family[38].

Other than clinical measurements, patients' quality of life is an important factor to evaluate. Diabetic foot has a negative impact on patient quality of life. Pain from ischemia, dependent status, daily ulcer dressing, and unemployment stress were some the major causes of decreased quality of life[39]. Considering the frustrating circumstances and physical deconditioning caused by prolonged immobilization, early major amputation may be a viable option. With early major amputation followed by appropriate prosthesis use, particularly in patients who had lower possibility of successful limb salvage, deconditioning may be avoided, and quality of life is preserved or even improved. Cost analysis must also be considered. Earlier amputation may decrease the costs from the length of hospital stay, repeated surgery, medications, and daily expense. However, patients undergoing major amputation will need proper rehabilitation exercise and prostheses that may be costly as well[40]. Therefore, decisions should be made carefully and promptly.

CONCLUSION

Amputation is an option for patients with diabetic foot ulcers. Although there are absolute or relative indications for amputation, there is also a clinical decision algorithm to determine whether a limb can be salvaged. However, various influencing factors should also be considered (Figure 2). The objective is to reach an immediate optimum state for the patient and increase their quality of life. In contrast to clinical

discussion, cultural values also played a role in patients' willingness to undergo amputation, as suggested. Surgeons should not be autocratic in these circumstances and should be aware of beneficence and maleficence when considering the decision of whether to amputate.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Rotator cuff repair with an interposition polypropylene mesh: A biomechanical ovine study

Winston Shang Rong Lim, Andy Khye Soon Yew, Hannah Lie, Siaw Meng Chou, Denny Tijauw Tjoen Lie

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Abstract

BACKGROUND

Chronic large to massive rotator cuff tears are difficult to treat and re-tears are common even after surgical repair. We propose using a synthetic polypropylene mesh to increase the tensile strength of rotator cuff repairs. We hypothesize that using a polypropylene mesh to bridge the repair of large rotator cuff tears will increase the ultimate failure load of the repair.

AIM

To investigate the mechanical properties of rotator cuff tears repaired with a polypropylene interposition graft in an ovine ex-vivo model.

METHODS

A 20 mm length of infraspinatus tendon was resected from fifteen fresh sheep shoulders to simulate a large tear. We used a polypropylene mesh as an interposition graft between the ends of the tendon for repair. In seven specimens, the mesh was secured to remnant tendon by continuous stitching while mattress stitches were used for eight specimens. Five specimens with an intact tendon were tested. The specimens underwent cyclic loading to determine the ultimate failure load and gap formation.

RESULTS

The mean gap formation after 3000 cycles was 1.67 mm in the continuous group, and 4.16 mm in the mattress group (P = 0.001). The mean ultimate failure load was significantly higher at 549.2 N in the continuous group, 426.4 N in the mattress group and 370 N in the intact group (P = 0.003).

CONCLUSION

The use of a polypropylene mesh is biomechanically suitable as an interposition graft for large irreparable rotator cuff tears.

Key Words: Rotator cuff repair; Massive tear; Interposition graft; Biomechanics; Polypropylene mesh

Core Tip: Our ex-vivo ovine model demonstrates that the use of a polypropylene mesh is mechanically suitable as an interposition graft for large irreparable rotator cuff tears. Its use results in a repair that is at least as robust as an intact rotator cuff tendon. When paired with a continuous suturing technique, its resultant superior mechanical properties may potentially reduce re-tear rates after repairing large or massive rotator cuff tears.

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INTRODUCTION

Rotator cuff tears are one of the most common shoulder conditions that orthopaedic surgeons treat. Chronic large to massive tears are difficult to treat due to development of tendon retraction, muscle atrophy and fatty infiltration. In addition, re-tear after primary repair of large to massive tears are common, reportedly between 40%[1] to 94%[2].

Complete, anatomic rotator cuff repair with restoration of the tendon footprint is the preferred treatment option, but it is often not possible in up to 20% of patients with large to massive rotator cuff tears[3]. Numerous joint-preserving procedures have been attempted to address this group of patients with an irreparable tear – tendon transfers of the latissimus dorsi or pectoralis major, superior capsular reconstruction and patch augmentation are among the salvage procedures described[4].

Several materials have been investigated for the purpose of augmenting the rotator cuff repair. The ideal material should provide a biomechanical advantage, be biocompatible and allow for ingrowth of host tissue. The fascia lata and human dermal allografts have been used in clinical practice to repair massive rotator cuff tears. Fascia lata autograft[5] or allograft[6], and human dermal allografts[7,8] have been used as interposition grafts and are also commonly used for superior capsular reconstruction[9]. Commercially available human dermal allograft has an ultimate load of 313 N at 1.4 mm thickness, while fascia lata allograft had a higher ultimate load of 350 N at 1 mm thickness[10]. In clinical studies, the healing rates when human dermal allograft is used is only between 59% to 74%[7,11].

To improve the healing rates, we propose using a synthetic polypropylene mesh to increase the tensile strength of the repair. The polypropylene mesh has been widely used in ventral abdominal and inguinal hernia repair for decades, and its safety and efficacy are well established[12]. However, the use of polypropylene mesh in rotator cuff repair is not well studied. A clinical study by Ciampi *et al*[13] found that the use of polypropylene patch augmentation for rotator cuff repair resulted in better function and strength, as well as lower re-tear rates compared to collagen patch augmentation or cuff repair alone.

We hypothesize that using a polypropylene mesh to bridge the repair of large rotator cuff tear is a biomechanically sound concept. If proven to be biomechanically viable, it will be the first step towards adopting this widely available, relatively inexpensive material in the clinical setting. Thus, we aim to investigate the time-zero mechanical properties of a rotator cuff repaired with a polypropylene interposition graft in an ovine infraspinatus ex-vivo model. In addition, we aim to compare if continuous stitching of the mesh to the remnant tendon on the greater tuberosity results in higher failure load compared to mattress stitching.

MATERIALS AND METHODS

Specimen preparation

Twenty fresh shoulders from skeletally mature sheep were procured from a local abattoir and used in this study. Ethics approval was not required for this study as it involved commercially available animal specimens. The supraspinatus muscle and tendon, as well as the subscapularis tendon and gleno-

humeral joint capsule were detached to isolate the infraspinatus muscle. In five specimens, the infraspinatus tendon was left intact in order to determine the ultimate failure load of intact tendon (Intact group).

The infraspinatus tendon was sharply detached from its insertion on the greater tuberosity to simulate a full thickness tear in the remaining fifteen specimens. This was followed by resecting a section of tendon 20 mm in length (medial-to-lateral dimension) to further simulate tendon retraction and actual loss of tendon substance due to degeneration at the tendon insertion (Figure 1).

Tendon repair

A polypropylene mesh (PROLENE™, ETHICON, NJ, United States) was cut to match the width of the remnant infraspinatus tendon. The length of the mesh was fixed at 60 mm to provide consistency in the test results. The mesh was then folded lengthwise over the tendon on the infraspinatus end and sutured together with four mattress stitches using Prolene 2-0. On the greater tuberosity side, the mesh was secured to the remnant tendon by continuous stitching with Prolene 2-0 in seven specimens (Continuous group). In eight specimens, the mesh was secured to the remnant tendon at the greater tuberosity by mattress stitches (Mattress group) (Figure 2).

Biomechanical testing

A custom-designed fixture was used to secure the specimens to a universal testing machine (Instron 5566, Instron, MA, United States) with a 10 kN load cell. A hole with diameter 6.5 mm was drilled through the scapula to mount the specimen onto the fixture. A two-piece clamp was used to secure the humerus at the desired abduction angle of 45° (Figure 3). The abduction angle represents the angle the humeral shaft makes with the vertical axis in the direction of cyclic loading.

Biomechanical testing was carried out in three phases – firstly, pre-cycle loading was conducted between 5 and 10 N for 10 cycles to account for the muscle's elastic elements which are pre-stretched by the load. This was followed by cyclic loading between 10 and 180 N at a cross-head velocity of 8.33 mm/s for a total of 3000 cycles. The change in distance of the tendon lateral edge with loading is regarded as the amount of gap formation and this was measured at every 500 cycles. To record the gap formation, a ruler with marking pieces was mounted beside the test specimen's tendon for reference (Figure 3). A digital camera mounted on a tripod with its lens facing the tendon perpendicularly was placed in front of the universal testing machine. After each 500 cycles, a high-resolution digital picture of the tendon was taken. The image is processed in ImageJ (version 1.53a) (National Institutes of Health, Bethesda, MA, United States) where a 50 mm line is drawn parallel to the ruler. The measurements were calibrated by comparing the image pixel value of the 50 mm line to 50 mm on the ruler. This was then used to measure the amount of gap formation in each image.

After 3000 cycles of cyclic loading, the specimen was loaded to failure at a cross-head velocity of 1 mm/s to determine the ultimate failure load. The universal testing machine was stopped manually at the first sign of rotator cuff repair failure, and the mode of failure was identified and recorded. For the intact tendon group, testing was terminated once a tear was observed in the tendon.

Statistical analysis

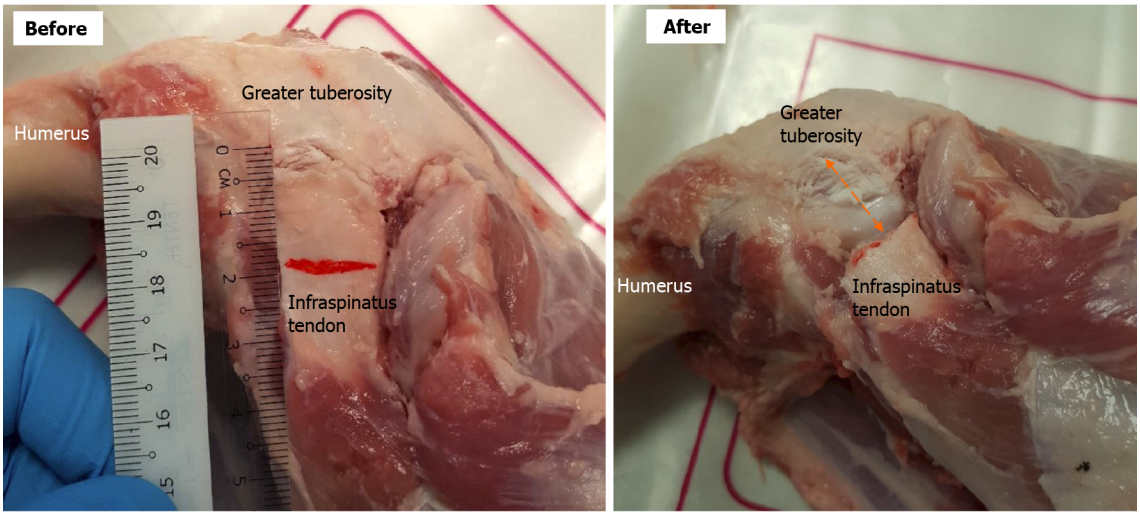
Statistical analysis was performed with SPSS v23.0 (IBM, SPSS Statistics, Armonk NY, United States) statistical software. Student's *t*-test was used to compare gap formation between the two methods of stitching. One-way analysis of variance was used to compare the ultimate failure load between all three groups. Post hoc test was performed using Tukey honest significant difference if one-way analysis of variance was found to be significant. A P value of 0.05 was considered statistically significant.

RESULTS

The mean ultimate failure load in intact tendon was 370 (range 300 N to 425 N, standard deviation 48.1). For the intact group, 3000 cycles of loading could not be completed as tears appeared in the tendons after a mean of 590 cycles and testing was terminated.

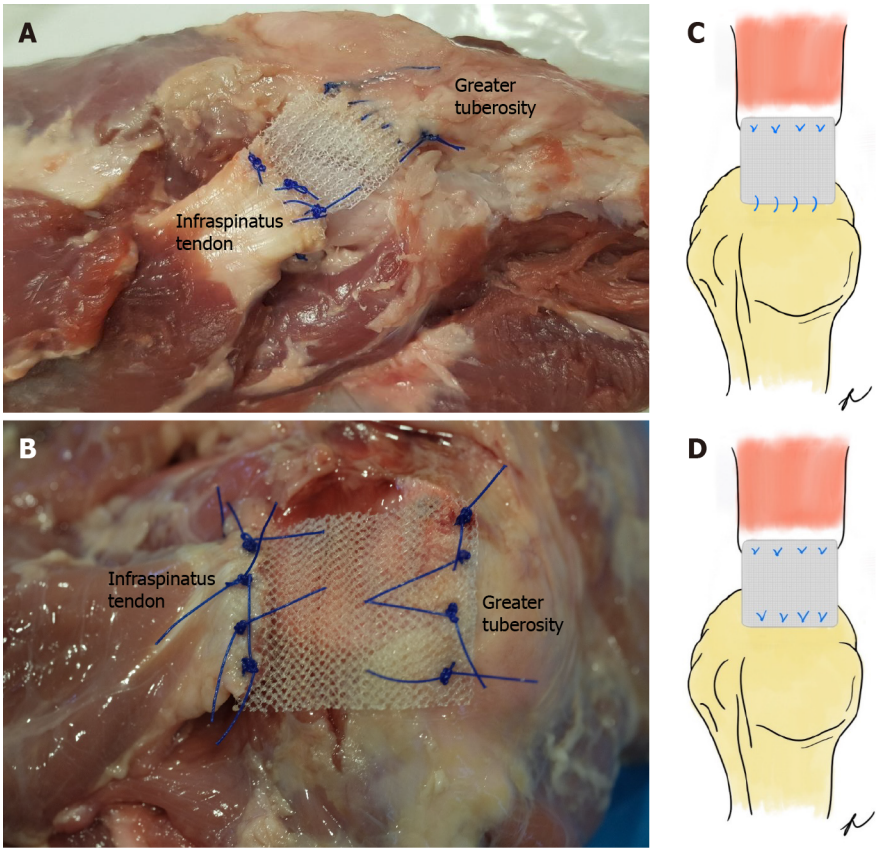
In all fifteen specimens which underwent tendon repair, gap formation increased with progressive cyclic loading through the 3000 cycles. At each interval after 500 cycles, the mean gap formation was significantly lower in the continuous group compared to the mattress group (Figure 4). The mean gap formation after 3000 cycles was 1.7 mm (standard deviation 0.3) in the continuous group, while it was 4.2 mm (standard deviation 1.3) in the mattress group (P = 0.001).

All specimens in the Mattress and Continuous group failed through suture pull-out at the greater tuberosity end of the repair. There was no record of any mesh failure or suture breakage. The ultimate failure load in the continuous group ranged from 416.7 N to 755.9 N and ranged from 403.2 N to 466.1 N in the mattress group. The mean ultimate failure load for the continuous group and mattress group was 549.2 N (standard deviation 127.3) and 426.4 N (standard deviation 106.1) respectively.



DOI: 10.5312/wjo.v14.i5.319

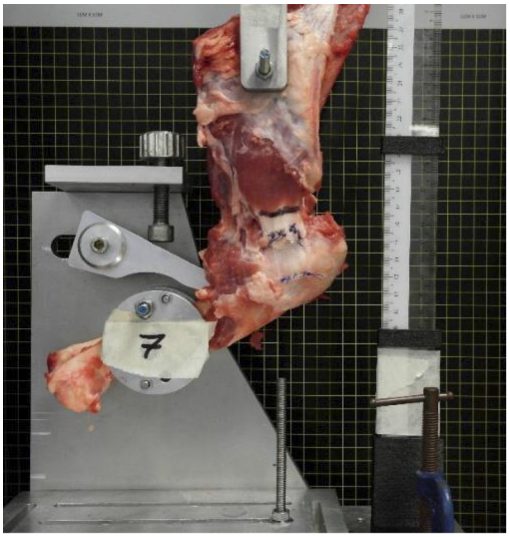
Figure 1 Specimen preparation with arrows indicating 2 cm section of tendon removed.



DOI: 10.5312/wjo.v14.i5.319

Figure 2 Tendon repair with Prolene mesh interposition graft. A: Continuous stitching; B: Mattress stitching; C: Schematic representation of continuous repair; and D: Schematic representation of mattress repair.

The ultimate failure load in the continuous group was significantly higher when compared to the mattress group (P = 0.02) and intact group (P = 0.004). There was no statistically significant difference in ultimate failure load between mattress and intact group (P = 0.45) (Figure 5).



DOI: 10.5312/wjo.v14.i5.319

Figure 3 Mounted specimen for testing.

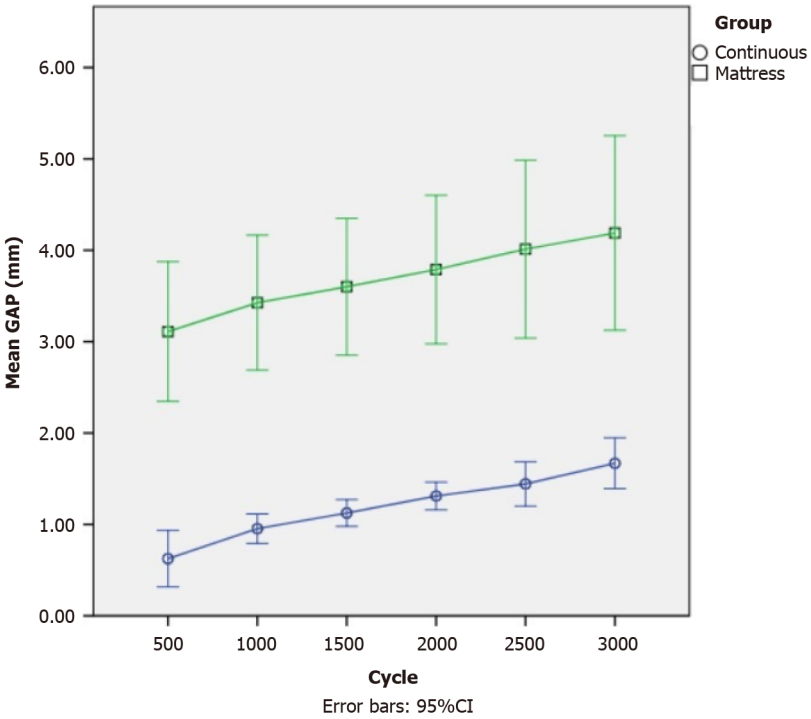


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Figure 4 Mean gap formation at 500 cycle interval (error bars 95% confidence interval).

DISCUSSION

Large or massive rotator cuff tears continue to pose a challenge to shoulder surgeons. The use of scaffolds may play a role in the treatment of such tears. These scaffolds can be used to augment or reinforce an anatomically repairable tear. It can also be used to as an interposition graft, where the scaffold bridges the gap between the irreparable cuff and the humerus[14]. Allografts and xenografts extra-cellular matrix scaffold devices provide mechanical support during the early phases of rotator cuff healing but are eventually degraded to be replaced by a mixture of organized muscle cells, collagenous connective tissue and adipose connective tissue[15]. Mihata's biomechanical analysis of grafts used in superior capsular reconstruction found that human dermal allografts would elongate by 15% with loading, while fascia lata grafts did not change significantly after testing and was also able to completely restore superior glenohumeral joint stability[16]. Due to the stiffness of fascia lata grafts, post-operative shoulder stiffness would be a concern. In addition, there are concerns that biologic grafts may

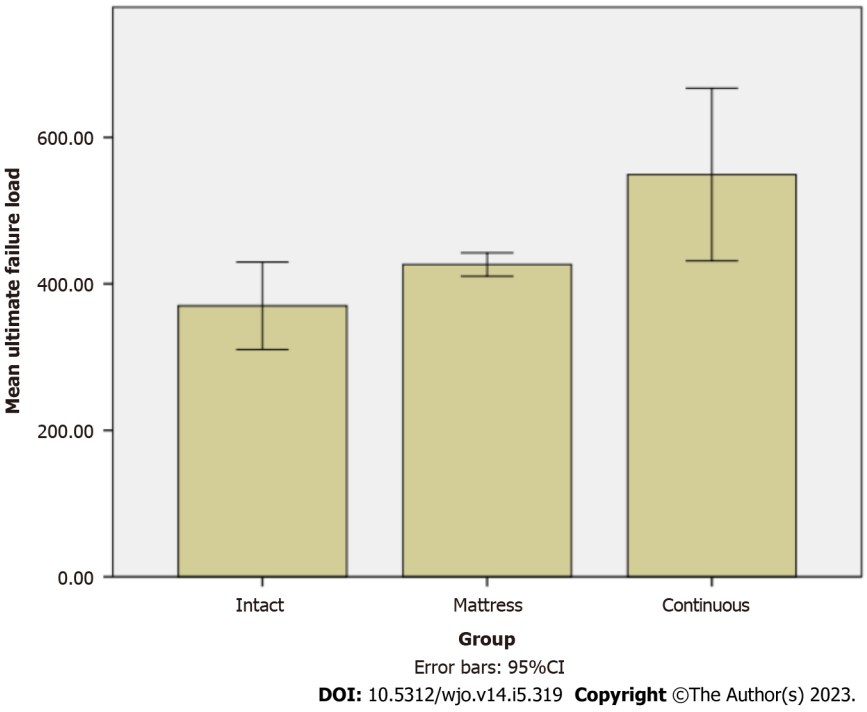

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Figure 5 Mean ultimate failure load of specimens (error bars 95% Confidence interval).

potentially incite a host inflammatory response that may cause breakdown of the repair[15,17].

Synthetic materials, such as those made of polyurethane, polypropylene or expanded polytetrafluoroethylene (PTFE) are able to maintain their mechanical properties over a long period of time, thus stabilizing the repair till tissue healing occurs. Our study suggests that using a polypropylene mesh to augment rotator cuff tendon repair is at least as strong as an intact tendon. When continuous suturing is performed, the ultimate failure load is significantly increased compared to intact tendon.

One of the technical aims of a good rotator cuff repair is to achieve sufficient strength to withstand the pull of the rotator cuff during early passive motion. Burkhart calculated that the maximal contraction force across the rotator crescent to be 302 N[18]. Mall suggested that tendon repairs resist 300 N to 350 N of tensile force to allow for early post-operative motion to help prevent stiffness and maximize healing potential[19]. All our repaired specimens were able to withstand at least 350 N of cyclic loading. Our study also demonstrated that continuous suturing at the greater tuberosity was superior to mattress sutures, with lesser gap formation and higher ultimate failure load.

Several authors have suggested a gap formation of 5 mm at the repair site to be clinically significant [20,21]. In our study, only two specimens in the mattress group exceeded 5 mm of gap formation. In a rodent model, Killian found that the greater the gap between the post-repair tendon-to-bone attachment, the greater the scar formation and presence of disorganized tendon insertion to bone[22]. This suggests that gap formation plays an important role in repair outcomes. It is promising that our mean gap formation was only 1.7 mm in the continuous group, however, *in vivo* studies using relevant large ovine animal models are still required to determine if this will translate into better tendon-to-bone healing.

Clinical studies of interposition synthetic grafts have been encouraging. Nada *et al*[23] reported on the use of a polyester Dacron ligament in 21 patients with chronic massive rotator cuff tears. The mean Constant and Murley score increased from 46.7 pre-operatively to 84.5 post-operatively. Petrie *et al*[24] used the polyester Ligament Augmentation and Reconstruction System in 31 shoulders and reported a mean improvement of Oxford shoulder score from 46.7 to 30.6. Audenaert *et al*[25] also used a polyester (ethylene terephthalate) mesh in 41 patients and the mean Constant and Murley score increased from 25.7 pre-operatively to 72.1 post-operatively. Hirooka *et al*[26] used a Gore-Tex expanded PTFE patch in 28 shoulders and reported the average total Japanese Orthopaedic Association score increased from 57.7 to 88.7. Our study suggests that the inexpensive, widely available polypropylene mesh may have a potential role in strengthening the repair of chronic large rotator cuff tears. The polypropylene mesh may even be used in combination with a fascia lata graft to improve graft healing rate as demonstrated by Kholinne when done for superior capsular reconstruction[27].

There are limitations to an ex-vivo animal study. While our study has demonstrated that the polypropylene mesh has good mechanical properties, there have been concerns over its potential to incite a vigorous foreign body and chronic inflammatory response. This may lead to contracture, scar and adhesion formation and chronic pain, particularly troubling in up to 3.6% patients who undergo mesh repair for abdominal hernia[28-30]. However, it is encouraging to note that Ciampi's study reported no

adverse events such local inflammation, fibrosis, and subacromial adhesions affecting joint function in 52 patients with polypropylene mesh augmented rotator cuff repair[13]. Our study did not attempt to undertake histological analysis of the specimens to examine for host-tissue maturation and host-implant biocompatibility as the study was not performed on live animals.

Another limitation of our study is our use of healthy rotator cuff specimens from sheep. While the sheep infraspinatus tendon has similar geometry and mechanical properties to human supraspinatus tendon[31], the healthy rotator cuff specimens may not be representative of the typical degenerate tendon seen in patients with massive rotator cuff tears. In addition, the use of suture anchors to secure the mesh to the tuberosity side could have provided greater biomechanical strength to the repair and prevent suture pull out from the tuberosity, which was the mode of failure in all our specimens. Our study serves as a proof of concept that a polypropylene mesh as an interposition graft may be an option in rotator cuff repairs. Further studies such as comparing the biomechanical properties of the polypropylene mesh to other types of commercially available grafts, and an *in-vivo* ovine study should be undertaken before adopting its use in human patients.

CONCLUSION

The use of a polypropylene mesh is mechanically suitable as an interposition graft for large irreparable rotator cuff tears. Its use results in a repair that is at least as robust as intact rotator cuff tendon. When paired with a continuous suturing technique, its resultant superior mechanical properties may potentially reduce re-tear rates after repairing large or massive rotator cuff tears.

ARTICLE HIGHLIGHTS

Research background

Augments and scaffolds are increasing in importance in patients with large to massive cuff tears. There is limited data on the mechanical properties of such materials.

Research motivation

The polypropylene mesh is a time tested, bio-compatible material with strong mechanical properties that may be used in rotator cuff repairs to improve the strength of the repair.

Research objectives

To investigate the mechanical properties of rotator cuff tears repaired with a polypropylene interposition graft in an ovine ex-vivo model.

Research methods

We used a polypropylene mesh as an interposition graft between the ends of the tendon to repair a tear in the infraspinatus of fresh sheep shoulders. The mesh was secured to remnant tendon by continuous stitching in seven specimens while mattress stitches were used for eight specimens. Five specimens with an intact tendon were tested. The specimens underwent testing to determine the ultimate failure load and gap formation.

Research results

The mean gap formation after 3000 cycles was significantly lower in the continuous group than the mattress group. The mean ultimate failure load was also significantly higher in the continuous group when compared to mattress stitching or intact tendon.

Research conclusions

The use of a polypropylene mesh is biomechanically suitable as an interposition graft for large rotator cuff tears.

Research perspectives

Further studies such as comparing the biomechanical properties of the polypropylene mesh to other types of commercially available grafts, and an *in-vivo* ovine study should be undertaken before adopting its use in human patients.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Mid-term results of sub-trochanteric valgus osteotomy for symptomatic late stages Legg-Calvé-Perthes disease

Khaled M Emara, Ramy Ahmed Diab, Ahmed K Emara, Mohamed Eissa, Mostafa Gemeah, Shady Abdelghaffar Mahmoud

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Abstract

BACKGROUND

The treatment of late stages of Legg-Calvé-Perthes disease (LCPD) is controversial. Although the concept of femoral head containment is a well-established technique of treatment, its use remains debatable in the late stages of the disease, as it does not improve symptoms in terms of limb length discrepancy and gait.

AIM

To assess the results of subtrochanteric valgus osteotomy in symptomatic patients with late-stage Perthes disease.

METHODS

From 2000 to 2007, 36 symptomatic patients with late stage of Perthes disease were surgically treated with subtrochanteric valgus osteotomy and followed-up for 8 to 11 years using the IOWA score and range of motion (ROM) variables. The Mose classification was also assessed at the last follow-up to reflect possible remodeling. The patients were 8 years old or older at the time of surgery, in the post-fragmentation stage, and complaining of pain, limited ROM, Trendelenburg gait, and/or abductor weakness.

RESULTS

The preoperative IOWA score (average: 53.3) markedly improved at the 1-year post follow-up period (average: 85.41) and then slightly improved at the last follow-up (average: 89.4) (P value < 0.05). ROM improved, with internal rotation

increased on average by 22° (from 10° preoperatively to 32° postoperatively) and abduction increased on average by 15.9° (from 25° preoperatively to 41° postoperatively). The mean Mose deviation of femoral heads was 4.1 mm at the end of the follow-up period. The tests used were the paired *t*-test and Pearson correlation test, where the level of significance was a *P* value less than 0.05.

CONCLUSION
Subtrochanteric valgus osteotomy can be a good option for symptomatic relief in patients with late-stage of LCPD.

Key Words: Legg-Calvé-Perthes disease; Femoral head avascular necrosis; Valgus osteotomy; Deformity correction; Post fragmentation stage; Late stage Perthes

Core Tip: This is a retrospective study on 36 patients with ages ranging from 8 to12 years with late stage Perthes disease (re-ossification and healing stages) underwent femoral valgus osteotomy with rotational component which result in pain relief, improved gait, and increased range of motion. In addition, relative neck lengthening is also achieved that can correct limb length discrepancy resulting from head deformity associated with the disease which for many patients may be the only problem encountered Preoperative hip arthrography is done to see the sphericity of the hip and whether there are lateral osteophytes or not.

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INTRODUCTION

Legg-Calvé-Perthes disease is the childhood onset of osteonecrosis of the femoral head and its etiology remains poorly understood. The incidence of the disease among children varies from 0.2 per 100000 to 19.1 per 100000, with white populations being the most affected and East Asians being the least affected [1]. The prognosis of Perthes disease is controversial, with some studies showing a benign long-term outcome[2,3], while others suggest that it may lead to poor long-term sequalae (Stulberg classification type IV and V)[4-6]. Consequently, the optimal treatment approach for this condition remains debatable.

Although varus femoral osteotomy[7-10] and pelvic osteotomy[11-16] are well-established techniques for enhancing femoral head containment in the treatment of Perthes disease, their use in the late stages of the disease is controversial. They do not appear to improve symptoms such as limb length discrepancy (LLD) and may even worsen them[17-20]. Therefore, head containment should not be the primary target of treatment, particularly in the late stages of Perthes disease[7-9]. The prognosis depends more on the disease stage rather than the type of surgery performed[21], and there is no significant difference in outcomes using Stulberg radiographic criteria between conservative treatment and containment surgery in late Perthes disease[17,22].

Valgus femoral osteotomy is usually described for treatment of hinged abduction that is associated with late stages of Perthes disease[23-26]. The benefits are gained by moving the abutting epiphyseal fragment away from the acetabulum and lateralizing the greater trochanter increasing the abductor lever arm and the offset, and hence the abductor function. This results in pain relief, improved gait, and increased range of motion (ROM). In addition, relative neck lengthening is also achieved that can correct LLD resulting from head deformity associated with the disease[25]. Valgus osteotomy is also used to treat severely deformed Perthes disease, Herring classification system type B-C and C, in the fragmentation stage that showed greater congruency with adduction with improved clinical and radiological outcomes[27].

To our knowledge, no prior studies have investigated the role of femoral valgus osteotomy in the symptomatic late stages (re-ossification and healing) of Perthes disease in the absence of hinged abduction. Our hypothesis is that this approach can improve symptoms and function without targeting remodeling, as it is not possible after the fragmentation stage. We conducted a study to evaluate the clinical and radiological outcomes of this approach, with an average follow-up period of nine years.

MATERIALS AND METHODS

This retrospective cohort case series study was conducted on human participants from 2000 to 2007, performed by a single surgeon at an institutional hospital, and followed-up over 8-11 years (mean 9.36). It was conducted in accordance with the 1964 declaration of Helsinki and its later amendments/clarifications and with approval from the ethics and search committee, approved and analyzed prior to invitation of the study. Inclusion criteria were: (1) Ages 8 years or older; (2) femoral heads in the re-ossification or healing stages according to the Waldenström classification[28]; and (3) exhibition of symptoms in the form of Trendelenburg gait, abductor weakness, limping, LLD, pain, and/or limited ROM. Exclusion criteria were: (1) Patients below 8 years of age; (2) a Waldenström classification of initial or fragmentation stages; (3) asymptomatic patients; (4) patients with hinge abduction deformity; and (5) history of previous hip or pelvic surgeries.

The study included 36 patients, 23 males and 13 females, with Perthes disease in re-ossification or healing stage, 11 and 25 respectively, presented by symptoms. The symptoms varied and included pain, abductor weakness (Trendelenburg gait), external rotation gait, LLD, and/or limited abduction (Table 1). Asymptomatic Perthes disease (20 cases) was excluded from the study. None of the patients included had hinged abduction deformity confirmed by examination under general anesthesia according to Kruse *et al*[14] and Rhienker *et al*[29] definitions. The age range was between 8-12 years (mean 9.41). All the patients in the study group were treated with subtrochanteric valgus osteotomy and fixation was by pre-contoured plate in 23 cases (63.9 %) or dynamic hip screw (DHS) in 13 cases (36.1 %) (Table 2)[30-32]. All patients reached skeletal maturity at the time of last follow up.

The patients underwent a thorough clinical assessment focusing on functionality and pain history, as well as clinical examination that addressed gait, ROM, and deformity. Hence, the IOWA hip score[33] and ROM were evaluated once preoperatively and twice postoperatively (1st at 1 year postoperative and 2nd at the end of the follow-up period). The IOWA hip score is a 100-point scale that evaluates the hip by assessing different functional activities (35 points), freedom from pain (35 points), gait abnormality (10 points), deformity (10 points), and ROM (10 points), with the highest point scale indicating the best function[33]. Data collection was performed by the 2nd, 3rd, and 4th authors.

Surgical technique

The extent of limb deformity was carefully evaluated both clinically and radiologically (using plain X-rays, computed tomography scans, and intraoperative arthrography) to plan for the required planes and degrees of correction and to identify the most deformed part of the femoral head, with the goal of unloading it (Figure 1). The degree of valgus and rotation performed was measured by using the unaffected limb as a reference. If the patient was affected bilaterally, we relied on hip arthrography and neck shaft angle (NSA) and performed the valgus and rotation to the degree that brought lateral osteophytes away from the required range of motion and made the NSA more than 130 degrees. Therefore, the degree of correction was tailored to each patient individually.

Patients were placed supine on a radiolucent table. A direct lateral approach was utilized to access the femur. First, hip arthrography is done to confirm the sphericity of the head and to see whether there are lateral osteophytes or not, also the hip arthrography determines the direction of our osteotomy according to the site of osteophytes as mentioned above (Figure 2). The level of osteotomy was determined under an image intensifier, which was always subtrochanteric. In some cases, a pre-contoured plate (narrow plate) was used, and the plate was contoured to the desired degree of valgus and loosely fixed with a screw to the neck. In cases involving DHS, the desired degree of valgus was achieved by adjusting the inclination of the guide wire of the lag screw accordingly. The osteotomy was performed using multiple drill holes to weaken the cortex then completed by an osteotome. The osteotomy aimed to perform valgus, internal rotation, lateral translation, and extension of the distal femur if any limitations in the preoperative flexion range were discovered. Additionally, the osteotomy was oblique to provide inherent stability, and a de-rotation element was added to unload the affected portion, thereby relieving pain and correcting the external rotational deformity that is frequently associated with Perthes disease. After plate fixation, frequent irrigation was performed, followed by tissue closure in layers (Figures 3 and 4).

Postoperative protocol included non-weight bearing for 6 wk, followed by physical therapy for gait training, balance, and abductor muscle strengthening. Subsequently, partial weight bearing was allowed with crutches, which was then progressed to full weight bearing without crutches.

Statistical analyses

Statistical analysis was conducted to determine the significance of functional outcomes, patients' age at the time of surgery, and the follow-up period for the improvement of symptoms. IBM SPSS statistics (version 24.0, IBM Corp., United States, 2016) was used for data analysis. The data were presented as mean ± SD for quantitative parametric measures and as numbers and percentages for categorized data. The following tests were performed: (1) Paired t-test was used to compare two dependent groups for parametric data; and (2) Pearson correlation test was used to analyze the possible association between each two variables among each group for parametric data. The level of significance was set at $P < 0.05$.

Table 1 The clinical picture of the surgically treated patients with their proportions, *n* (%)

Clinical picture	Count
Pain	31 (86.1)
Trendlenburg gait and abductor weakness	30 (83.3)
External rotation gait	29 (80.5)
Limb length discrepancy	34 (94.4)
Limited abduction	3 (8.3)
Fixed flexion deformity	9 (25)

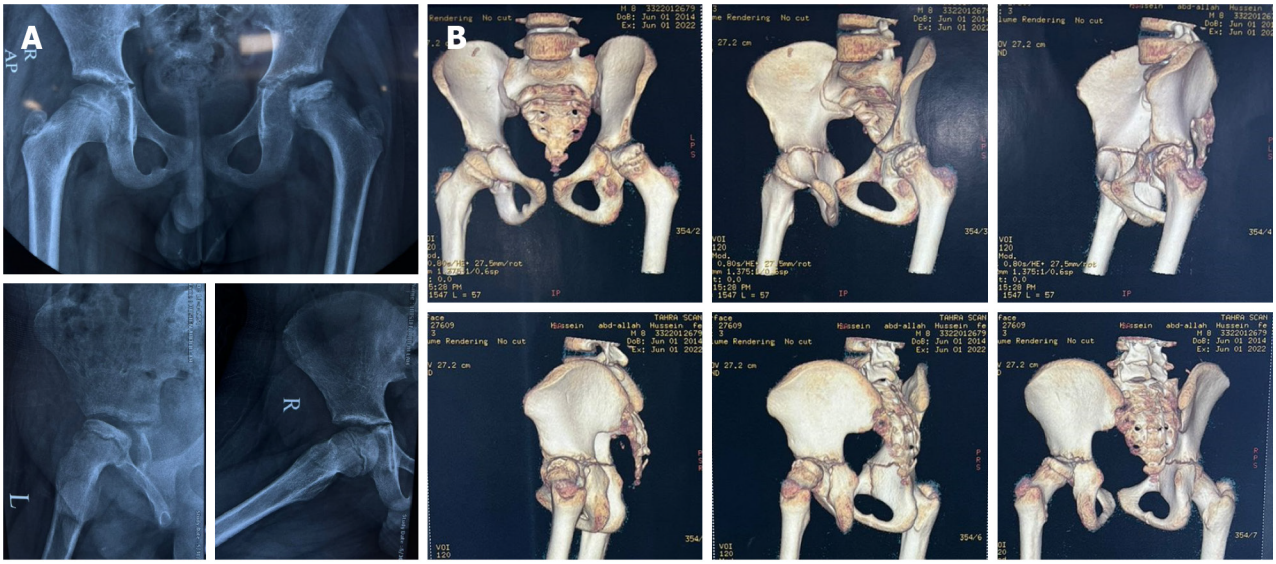

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Figure 1 The extent of limb deformity. A: Preoperative Plain X ray of 11 years male patient with left Perthes disease (Waldenström: Healing stage); B: Preoperative 3D-computed tomography scan.

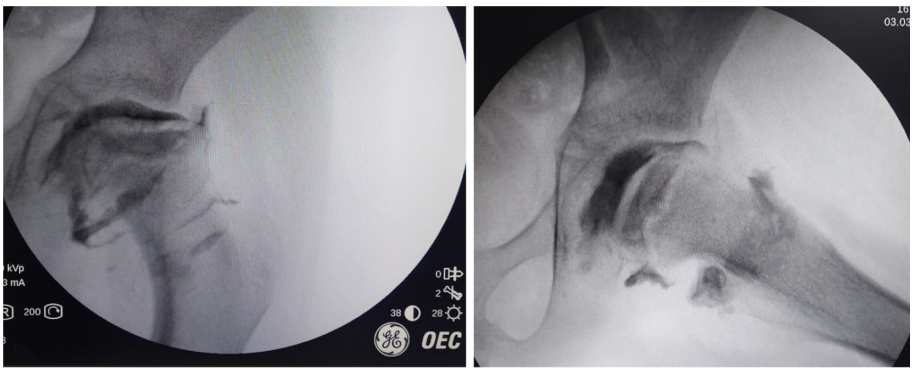

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Figure 2 Intraoperative arthrography of the previous patient showing that the head is aspherical with lateral osteophytes.

RESULTS

ROM

On average, the internal rotation increased by 22° (range: 10°-40°), from an average of 10° preoperatively to an average of 32° postoperatively with SD 5.72. Abduction increased by an average of 15.9° (range: 10°-35°) from an average of 25° preoperatively to an average of 41° postoperatively with SD 5.18. LLD improved in 30 cases (average improvement 0.9 cm) and remained unchanged in 6 cases. LLD was measured using the tape method and approximated to 0.5 cm, 1 cm, 1.5 cm, and so on. The difference

Table 2 Details of patients treated by femoral valgus osteotomy

Case	Sex	Age at surgery	Waldenström classification	Joseph classification[30]	Catterall classification[31]	Stulberg classification	Mose[32] at last F.U. (mm)	Follow up period	Implant
1	M	9	Re-ossification	IIIb	III	III	3	9	Contoured plate
2	M	8	Re-ossification	IIIa	III	III	2	8	Contoured plate
3	F	9	Healing	IV	IV	IV	5	10	DHS
4	M	11	Re-ossification	IIIb	III	IV	8	11	DHS
5	F	10	Re-ossification	IIIb	IV	III	5	9	Contoured plate
6	F	8	Healing	IV	III	III	6	9	Contoured plate
7	M	9	Re-ossification	IIIb	II	II	1	8	Contoured plate
8	M	9	Re-ossification	IIIa	II	II	2	9	Contoured plate
9	M	12	Healing	IV	IV	III	4	10	DHS
10	F	10	Healing	IV	IV	III	5	9	Contoured plate
11	M	9	Re-ossification	IIIa	III	IV	9	8	Contoured plate
12	F	8	Healing	IV	II	II	1	8	DHS
13	M	9	Healing	IV	III	III	3	9	Contoured plate
14	M	10	Re-ossification	IIIb	III	III	4	10	Contoured plate
15	F	11	Re-ossification	IIIb	IV	III	4	9	Contoured plate
16	M	10	Re-ossification	IIIb	III	IV	8	9	DHS
17	F	11	Healing	IV	II	II	1	8	Contoured plate
18	M	9	Healing	IV	IV	IV	7	11	Contoured plate
19	F	8	Re-ossification	IIIa	III	III	2	9	DHS
20	M	9	Healing	IV	III	III	4	10	Contoured plate
21	M	8	Healing	IV	II	II	1	11	DHS
22	M	9	Re-ossification	IIIb	III	II	2	9	Contoured plate
23	F	9	Re-ossification	IIIa	II	III	6	8	DHS
24	M	8	Re-ossification	IIIa	III	III	5	9	Contoured plate
25	F	10	Healing	IV	IV	IV	8	10	DHS
26	F	11	Healing	IV	III	II	1	9	Contoured plate
27	M	9	Healing	IV	IV	IV	5	9	Contoured plate
28	M	9	Re-ossification	IIIa	III	III	2	9	Contoured plate
29	F	8	Re-ossification	IIIa	II	II	2	9	DHS

30	M	8	Healing	IV	III	III	4	10	Contoured plate
31	M	9	Re-ossification	IIIb	III	III	5	8	DHS
32	M	10	Re-ossification	IIIb	III	IV	4	8	DHS
33	M	11	Re-ossification	IIIb	II	II	2	9	Contoured plate
34	M	10	Healing	IV	IV	IV	6	9	Contoured plate
35	M	9	Healing	IV	IV	IV	10	9	DHS
36	F	12	Healing	IV	III	II	1	10	Contoured plate

DHS: Dynamic hip screw; F: Female; M: Male.

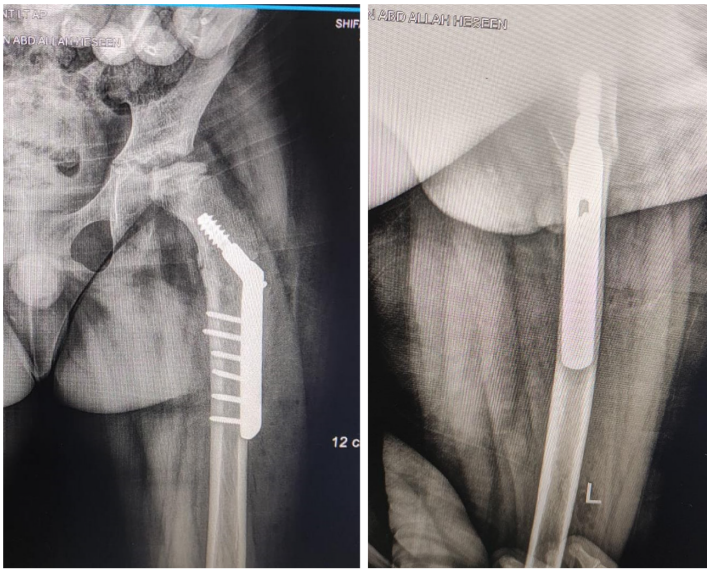

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Figure 3 Immediate post operative pregnane X receptor of the previous patient fixed with dynamic hip screw. 10° valgus, 10° extension and 15° internal rotation were done.

between the preoperative and postoperative measures was statistically significant ($P < 0.05$) (Table 3).

IOWA score

Twenty-three boys and 13 girls underwent unilateral subtrochanteric valgus osteotomies. The average age was 9.4 years (range 8-12) with an average follow-up period of 9.1 years (range 8-11). Clinical outcomes were assessed using the IOWA hip score[33] preoperatively, at 1-year postoperative, and at the last postoperative follow-up. The preoperative IOWA score had an average of 53.3 and SD 10.1, and it showed a marked improvement at the 1-year postoperative follow-up, with an average of 85.4 and SD 5.4. There was a slight improvement at the final follow-up, with an average of 89.4 and SD 5.2. The improvement was significant in pain, with an average of 22.4 preoperative to an average of 36.2 postoperative, walking tolerance, with an average of 4.7 preoperative to an average of 8.7 postoperative, gait, with an average of 3.5 preoperative to an average of 12.9 postoperative, shortening, with an average of 1.2 preoperative to 2.6 postoperative, and Trendelenburg absence, with an average of 2 preoperative to 0 postoperative. The difference between preoperative and final outcomes was statistically significant ($P < 0.05$).

Mose's circles

At the end of the follow-up period, Mose classification[32] was evaluated to assess any remodeling, with physis closure ensured. The mean Mose deviation was 4.11 mm, ranging from 1-10 mm.

Table 3 Statistical analysis of valgus osteotomy case series

Descriptive statistics	*n*	Min	Max	mean ± SD
Age	36	8	12	9.4 ± 1.5
Follow up	36	8	11	9.36 ± 2.2
IOWA score preoperative	36	30	70	53.3 ± 10.1
Postoperative after 1 yr	36	77	100	85.4 ± 5.4
Final	36	79	100	89.4 ± 5.2
Internal rotation degree	36	10	40	22.1 ± 5.26
Abduction degree	36	10	35	15.7 ± 6.2

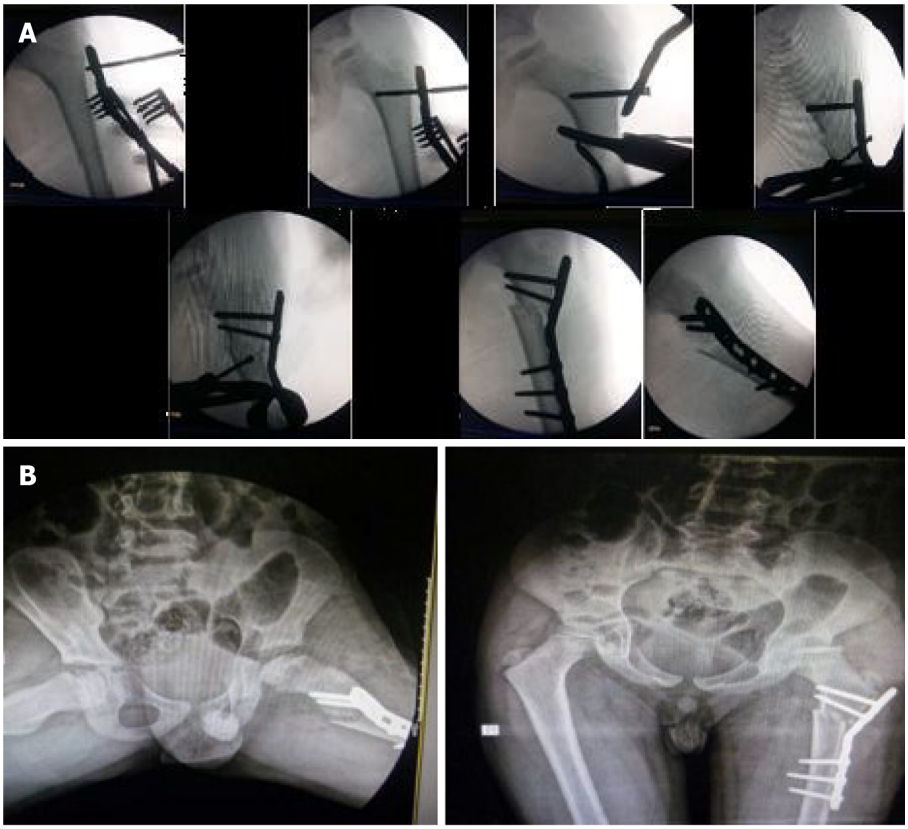

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Figure 4 Treatment of a femoral valgus osteotomy in a 10-year-old man with left Pertes disease. A: Intra-operative surgical steps of another 10 years old male patient with left Perthes disease (Waldenström: Re-ossification stage) treated with femoral valgus osteotomy using pre-contoured plate. Note the extension component of the osteotomy was evident in the lateral shot to compensate associated fixed flexion deformity of the hip; B: Immediate post operative pelvic X-ray of the same patient.

Complications

Superficial infection occurred in four cases, which were treated with daily dressings and a parenteral antibiotic course with no sequels. Six cases required hardware removal due to pain.

DISCUSSION

The optimal treatment approach for late stages of Perthes disease is still debatable. Although achieving proper femoral head containment (such as varus femoral osteotomy and pelvic osteotomy) to promote head remodeling and delay the need for total hip replacement (THR) has been widely accepted in the surgical treatment of the disease, there are many clinical and pathological aspects that raise concerns about the use of this surgical method in late symptomatic stages[34]. Firstly, the relationship between Perthes disease and osteoarthritis (OA) is atypical. According to Stulberg classification[4], only

aspherical incongruent cases carry a risk of severe OA, which usually doesn't develop before the 5th decade. Additionally, there is no correlation between symptom severity and osteoarthritic radiographic changes in Perthes disease. Furthermore, Perthes OA affects the medial joint compartment rather than the superior compartment, which is typically affected in age-related degenerative joint diseases. This different pattern of OA carries a better prognosis than the typical superior compartment one[5,22]. Larson *et al*[17] studied the outcomes of conservative management on 58 hips with a mean follow-up of 20.4 years, where only three patients required hip arthroplasty, and one patient required a pelvic osteotomy. This study supports the atypical relationship between Perthes disease and OA. Regarding varus femoral osteotomy, its use in treating Perthes disease has many limitations. Its effectiveness in providing the desired remodeling potential is restricted to cases in the early avascular and fragmentation stages. Therefore, its use in the re-ossification or healing stages is of questionable value[7, 9]. It is also limited to cases with a skeletal age of 8 years or more at onset, particularly Herring classification system group B and B/C border[5,21]. Sponseller *et al*[10] even concluded that the use of varus femoral osteotomy in patients older than 10 years yielded poor results, indicating that its use may be restricted to Herring classification system group B and B/C border in patients aged 8-10 years in the early avascular or fragmentation stages. Moreover, although varus femoral osteotomy may relieve pain associated with the disease by providing containment, it exacerbates the symptoms of limping due to the shortening of the affected limb[8]. It also worsens the Trendelenburg gait by increasing the abductor weakness[18,20]. Watanabe *et al*[19] studied gait analysis after varus femoral osteotomy and found that the stance phase was shorter, cadence was faster, and the strength ratio of hip abductor muscles was lower in operated patients *vs* non-operated and healthy subjects.

Arthrodiastasis has been studied in cases of late-stage Perthes disease with advanced Catterall stages and has shown satisfactory clinical and radiological outcomes. However, its effect is most significant when the disease is in the early avascular or fragmentation stages, as it can prevent head collapse and speed up recovery[27,35].

Two surgical approaches have been utilized to treat patients with healed Perthes in adulthood; safe surgical dislocation and combined acetabular and femoral osteotomies[36-38]. Safe surgical dislocation has been used to treat complex femoral deformities resulting from Perthes disease, with positive outcomes and statistically significant results. Trochanteric advancement and osteochondroplasty have been performed to address short neck, chondral and labral lesions, and femoro-acetabular impingement that may complicate Perthes disease in adulthood[36-38]. Clohisy *et al*[37] described a combined periacetabular osteotomy and intertrochanteric valgus osteotomy to treat femoral head deformities complicated by acetabular dysplasia. The procedure was performed on 42 cases (mean age 22.7 years) and followed up over 4.5 years, with statistically significant improvement in the Harris hip score. However, none of these procedures were used to treat Perthes disease before healing during childhood.

In addition, head remodeling is not limited to the containment concept. Yoo *et al*[24] studied the effect of valgus extension osteotomy on remodeling potential in hinge abduction cases and observed favorable remodeling in young cases that were at the fragmentation or early re-ossification stages. This is supported by Kim *et al*[27], who studied valgus osteotomy on patients at the fragmentation stage who had better containment by adduction. All femoral head roundness measures and the Shenton line were improved, with the best results demonstrated in severely deformed heads with Herring classification type C. This indicates that patient characteristics and disease stage at the time of intervention are the main determinants of head remodeling, rather than the type of surgery performed[24]. In delayed stages of Perthes disease, such as re-ossification and healing stages, containment can no longer be achieved, and the potential for remodeling is lost[39]. Many of these cases develop hinged abduction, and several studies have described the use of valgus femoral osteotomy in an attempt to move the abutted head away, with good outcomes[23-26]. Bankes *et al*[25] described the use of extension valgus osteotomy in 48 cases in the re-ossification stage, resulting in improved symptoms with a ten-year follow-up, but no prospective scoring system was used to quantify the improvement. Yoo *et al*[24] added sagittal and coronal rotational components to accurately accommodate different hinging patterns, resulting in improved mean IOWA score from 71 to 92 in a long-term study on 31 patients. The same results were achieved by Myers *et al*[26] in a short-term study, with an improved mean Harris hip score by 41.

However, no studies have discussed valgus femoral osteotomy among symptomatic late-stage Perthes disease in the absence of hinged abduction. We conducted a retrospective study on such a population group with ages ranging from 8 to 12 years. Our chosen operative intervention was femoral valgus osteotomy with a rotational component, and we observed the patients over a period of 8-11 years, assessing them clinically using the IOWA score[33] (Figure 5). Preoperative hip arthrography was done to assess the sphericity of the hip and the presence of lateral osteophytes. This simple surgical procedure, femoral valgus osteotomy, can relieve existing symptoms such as pain, limping, limb length discrepancy, limited ROM, and abductor weakness, which for many patients may be the only problem encountered.

On the other hand, we considered the re-ossification and healing stages to be critical periods, as we could not guarantee containment *via* varus femoral or pelvic osteotomy, and the potential complication of OA later on was uncertain to have a significant impact on the functional activity of the diseased patients compared to other patients who might eventually develop it. The controversies regarding the prognosis of Perthes disease compelled us to focus on relieving existing symptoms and improving the

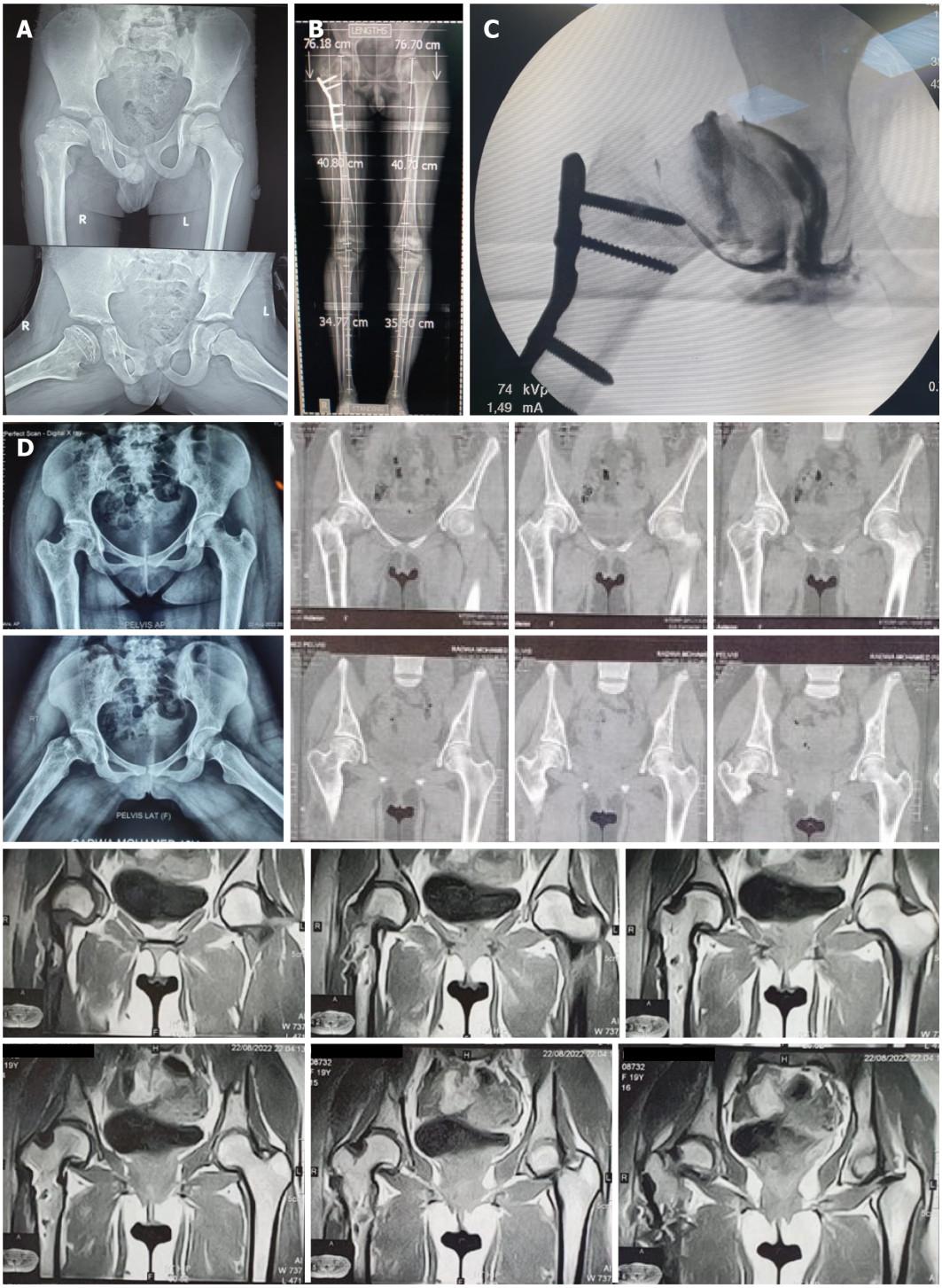

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Figure 5 Clinical evaluation for 8-11 years in patients with femoral valgus osteotomy with a rotational component. A: Preoperative pelvic X-ray (PXR) of 9 years old male patient with right Perthes disease (Waldenström: Healing stage); B: Follow up scanogram after 10 years showing no limb length discrepancy nor hip arthritis; C: Intraoperative hip arthrography just before plate removal that show smooth head with no osteophytes; D: Post removal PXR, computed tomography and magnetic resonance imaging respectively that show normal hip.

quality of life of these patients. In this study, the clinical outcomes significantly improved from an average IOWA score of 53.3 preoperatively to 89.4 at the end of the follow-up period, with a highly significant *P* value ($P < 0.01$). ROM increased, which is reflected in the patient's quality of life. Internal rotation and abduction improved by an average of 22° and 15.9° degrees, respectively. The mean Mose deviation was 4.11 mm, reflecting the lack of remodeling in these stages, and this is consistent with results of Yoo *et al*[24], which showed no improved radiographic indices in such an entity. There was a positive relationship between the age at the time of surgery and functional improvement, with a *P* value of 0.001, making it a potential good option in the treatment of older symptomatic patients with Perthes disease. There was no correlation between the duration of the follow-up period and functional

improvement, with a *P* value of 0.979. This necessitates further evaluation by long follow-up studies.

There is no proof that other types of surgery could change the natural history of late-stage Perthes disease or add value in improving patient symptoms, articular impingement, weak abduction, and limb length discrepancy. Therefore, our protocol to deal with symptomatic late-stage Perthes disease is either to leave the patient with no surgery, just conservative treatment for symptoms, or to do valgus de-rotation osteotomy to bring the osteophyte away from the joint articular surface. Hip arthrography is needed for proper dynamic assessment of the articular surface.

The limitations of this study include its retrospective nature and lack of control groups that receive other treatments such as conservative and other surgical procedures. Longer follow-up periods are also needed to assess the end fate of the hips and the risk of OA development, although the mid-term outcomes display promising efficacy and safety. It is also important to determine whether the deformity of the proximal femur would remodel or have any impact on future THR surgery. Further studies to tailor the use of sub-trochanteric valgus osteotomy according to the patient's age of onset and the disease stage are also required.

CONCLUSION

We hypothesize that valgus femoral osteotomy is a valid option for patients with late-stage Perthes disease. This procedure can effectively alleviate symptoms such as pain, limping, and limb length discrepancy, which may be the only problems encountered by many patients for an extended period of time. Therefore, valgus femoral osteotomy could be used beyond its role as a salvage option in hinge abduction cases.

ARTICLE HIGHLIGHTS

Research background

Legg-Calvé-Perthes disease is a condition that affects the hip joint, most commonly in children between the ages of 4 and 10. In this disease, the blood supply to femoral head. The treatment of late-stage Perthes disease remains controversial, and there is debate about the most effective techniques for managing symptoms and improving long-term outcomes.

Research motivation

The motivation for this study was to contribute to the ongoing debate about the most effective treatment approaches for late-stage Perthes disease, and to evaluate the potential benefits of subtrochanteric valgus osteotomy in improving symptoms and long-term outcomes.

Research objectives

The objective of this study was to evaluate the outcomes of subtrochanteric valgus osteotomy in patients with late-stage Perthes disease.

Research methods

The study included 36 symptomatic patients with late-stage Perthes disease who underwent subtrochanteric valgus osteotomy between 2000 and 2007. The patients were aged 8 or older at the time of surgery, in the post-fragmentation stage of the disease, and experiencing pain, limited range of motion, Trendelenburg gait, and/or abductor weakness.

Research results

The results of the study showed that subtrochanteric valgus osteotomy significantly improved hip function and range of motion in patients with late-stage Perthes disease.

Research conclusions

The study concluded that subtrochanteric valgus osteotomy can be an effective treatment option for relieving symptoms and improving hip function and range of motion in patients with late-stage Perthes disease. The results of the study suggest that this surgical technique can be a valuable addition to the range of treatment options available for this condition.

Research perspectives

The study provides important insights into the potential benefits of subtrochanteric valgus osteotomy for patients with late-stage Perthes disease. However, further research is needed to confirm the findings of this study and to evaluate the long-term outcomes of this treatment approach.

FOOTNOTES

Author contributions: Emara KM designed the study, analyzed the data, done the operations, and reviewed the manuscript critically; Diab RA analyzed the data, reviewed the manuscript critically, approved the final version to be published; Emara AK and Eisa M analyzed the data and reviewed the manuscript critically; Gemeah M collected the data reviewed the manuscript critically; Mahmoud SA collected the data, designed the study, and wrote the manuscript.

Institutional review board statement: This study has been reviewed and approved by the Institutional Review Committee at Ain Shams University School of Medicine.

Informed consent statement: As our study is a retrospective study, signed informed consent form is not needed. However, the institutional Hospital has given permission to access data and conduct this study.

Conflict-of-interest statement: Authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Retrospective Study

Spinal fusion is an aerosol generating procedure

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Abstract

BACKGROUND

Transmission of severe acute respiratory syndrome coronavirus 2 can occur during aerosol generating procedures. Several steps in spinal fusion may aerosolize blood but little data exists to quantify the risk this may confer upon surgeons. Aerosolized particles containing infectious coronavirus are typically 0.5-8.0 μm.

AIM

To measure the generation of aerosols during spinal fusion using a handheld optical particle sizer (OPS).

METHODS

We quantified airborne particle counts during five posterior spinal instrumentation and fusions (9/22/2020-10/15/2020) using an OPS near the surgical field. Data were analyzed by 3 particle size groups: 0.3-0.5 μm/m^3, 1.0-5.0 μm/m^3, and 10.0 μm/m^3. We used hierarchical logistic regression to model the odds of a spike in aerosolized particle counts based on the step in progress. A spike was defined as a > 3 standard deviation increase from average baseline levels.

RESULTS

Upon univariate analysis, bovie (P < 0.0001), high speed pneumatic burring (P = 0.009), and ultrasonic bone scalpel (P = 0.002) were associated with increased 0.3-0.5 μm/m^3 particle counts relative to baseline. Bovie (P < 0.0001) and burring (P < 0.0001) were also associated with increased 1-5 μm/m^3 and 10 μm/m^3 particle counts. Pedicle drilling was not associated with increased particle counts in any of the size ranges measured. Our logistic regression model demonstrated that bovie

(OR = 10.2, $P < 0.001$), burring (OR = 10.9, $P < 0.001$), and bone scalpel (OR = 5.9, $P < 0.001$) had higher odds of a spike in 0.3-0.5 μm/m^3 particle counts. Bovie (OR = 2.6, $P < 0.001$), burring (OR = 5.8, $P < 0.001$), and bone scalpel (OR = 4.3, $P = 0.005$) had higher odds of a spike in 1-5 μm/m^3 particle counts. Bovie (OR = 0.3, $P < 0.001$) and drilling (OR = 0.2, $P = 0.011$) had significantly lower odds of a spike in 10 μm/m^3 particle counts relative to baseline.

CONCLUSION

Several steps in spinal fusion are associated with increased airborne particle counts in the aerosol size range. Further research is warranted to determine if such particles have the potential to contain infectious viruses. Previous research has shown that electrocautery smoke may be an inhalation hazard for surgeons but here we show that usage of the bone scalpel and high-speed burr also have the potential to aerosolize blood.

Key Words: Optical particle sizers; Aerosol; COVID-19; Orthopaedic procedures; Spinal fusion; SARS-CoV-2

Core Tip: In this study we use a handheld optical particle sizer to measure the generation of aerosols during surgical steps in spinal fusion because of the risk this may confer upon surgeons in regards to the airborne transmission of severe acute respiratory syndrome coronavirus 2. Several steps in spinal fusion, specifically the bone scalpel and high-speed burr, were found to be associated with increased airborne particle counts in the aerosol size range.

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INTRODUCTION

The World Health Organization has warned that airborne transmission of severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019, COVID-19) can occur during medical procedures that generate aerosols, especially those involving the airway[1]. Instrumentation of the upper and lower airways is often considered high risk and some research has indicated that these procedures are aerosol-generating procedures (AGPs)[2]. Certain tools used in orthopaedic surgery have previously been shown to generate blood containing aerosols less than 5 μm in diameter[3]. Despite this potential hazard, there are no previous reports describing the risk of aerosolization of body fluids during spinal fusion.

The naked COVID-19 virus is 0.06-0.14 μm in diameter but aerosolized particles containing infectious virus are typically 0.5-8.0 μm. Particles greater than 5 μm are generally considered droplets whereas those less than 5 μm represent aerosols that remain suspended for periods of time and travel significant distances, though there is some controversy over these definitions[4]. In a 2010 study researchers found that electrocautery, bone saws, reamers and drills appear to produce aerosols[5]. Other authors have raised the theoretical concern that aerosolized blood during spine surgery could put members of the surgical team at risk for exposure to infectious viral particles, but there is little *in vivo* data to help quantify this risk[6].

The current guidelines for personal protective equipment during orthopedic surgery vary by institution but generally providers are advised to wear N95 masks during intubation and other procedures considered to be aerosol generating[7-9]. However, controversy remains over which procedures or components of procedures should be considered AGPs, leaving policy makers with a lack of evidence to guide decisions related to infection control. Here we present a pilot study using handheld optical particle sizers (OPSs) to evaluate the potential for various surgical steps during spinal fusion to aerosolize blood and other body fluids. We hypothesize that surgical steps of interest, mainly bovie electrocautery, burring, drilling, and harmonic bone scalpel, will significantly increase airborne aerosol particle counts during spinal fusion.

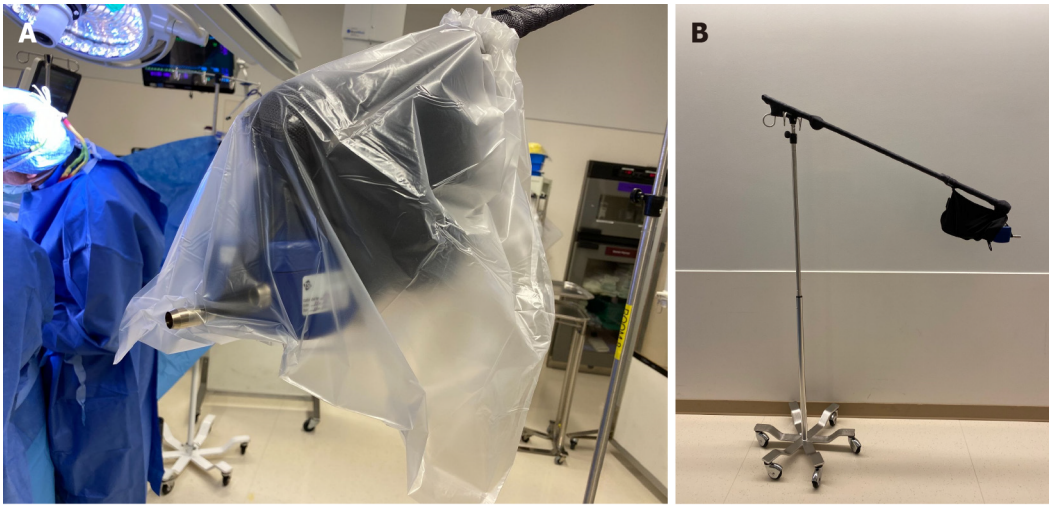

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Figure 1 Aerotrak handheld airborne particle counter. A: In a sterile bag; B: Suspended in a hanger.

MATERIALS AND METHODS

Study design

We quantified airborne particle counts throughout the course of five posterior spinal instrumentation and fusions (9/22/2020-10/15/2020). The University Institutional Review Board (IRB No. 58206) granted an IRB waiver with a determination that no human subjects were involved in this study. This pilot study was designed as a quality improvement assessment for our institution.

Device/sampling

An Aerotrak Handheld Airborne Particle Counter (Model 9306-V2) from TSI Incorporated (Shoreview, Minnesota) was used as the OPS. Before each procedure, a Zero Check was performed in the operating room on the OPS by attaching the high efficiency particulate air (HEPA) zero filter assembly to the inlet nozzle and running a two-minute purge. This step was repeated until one or less particles of any size were counted. The zero filter was then removed and the Stainless-Steel Isokinetic inlet was attached for sampling. The OPS was secured to a hanger to ensure consistent sampling height and distance to the patient and stabilized with a sandbag (Figure 1A).

A sterile bag was placed over the OPS and hanger. The vented aspects of the OPS used for sampling remained uncovered (Figure 1B).

Because this study is primarily evaluating the risk to the surgical team, the OPS was positioned next to the surgical staff hanging over the central operating area at a comparable height and distance to the wound as the surgeon's face.

Throughout the procedure, the OPS took continuous 30-s samples and reported the sum of particles sizes 0.3 μm/m^3, 0.5 μm/m^3, 1.0 μm/m^3, 3.0 μm/m^3, 5.0 μm/m^3, and 10.0 μm/m^3 in each 1.4 L sample. Based on the usage of high-speed power tools and shear forces, the following surgical steps were identified for study: Bovie, burring, drilling, and bone scalpel. As the OPS sampled, researchers recorded the start and end times of each surgical step of interest, the approximate distance from the wound/central operating area to the particle sensor, and the maximum number of people in the operating room at any point during the sampling period (excluding the patient). The operating rooms used for sampling in this study have an airflow of 25 air exchanges per hour with laminar flow ceilings that create an air curtain about four feet on each side of the patient. There were two low wall returns in each room that used a recirculated system with HEPA filtration.

Statistical analysis

The data was downloaded using the TSI TrakPro Lite Secure 3.1 software in an XML format and analyzed in RStudio version 1.1.456 using a two-sided level of significance of 0.05. Each 30 s sample was labeled with the surgical step of interest that was occurring. If there was more than one step occurring during a 30 s sample, this was labeled as multiple steps. Each 30 s sample labeled with a surgical step of interest was compared to baseline samples when there were no steps of interest occurring. In addition, the 30 s samples before and after a sample with a step of interest occurring were removed from the analysis to reduce the potential of biasing the data with leftover aerosols.

Multivariable hierarchical logistic regression models were used to model the odds of a spike in particle counts, accounting for within-surgery variability and autocorrelated errors. Surgical steps, the sensor distance, and the maximum number of people in the operating room were included in these

Table 1 Logistic regression analysis of surgical steps of interest for 0.3-0.5 μm/m³ particle counts

Variable	OR	Lower 95%	Upper 95%	Z score	*P* value
Bovie	10.20	7.80	13.30	16.80	< 0.001
Burring	10.90	6.60	18.00	9.40	< 0.001
Drilling	0.50	0.20	1.10	-1.70	0.099
Bone scalpel	5.90	3.20	10.90	5.70	< 0.001
Max in room	1.40	0.90	2.00	1.60	0.116
Sensor distance	0.03	0.01	0.10	-4.70	< 0.001

OR: Odds ratios.

Table 2 Logistic regression analysis of surgical steps of interest for 1-5 μm/m³ particle counts

Variable	OR	Lower 95%	Upper 95%	Z score	*P* value
Bovie	2.60	2.00	3.5	6.5	< 0.001
Burring	5.80	3.40	10.2	6.2	< 0.001
Bone scalpel	4.30	2.00	9.3	3.7	0.005
Max in room	1.40	0.90	2.4	1.3	0.179
Sensor distance	0.05	0.01	0.4	-2.9	0.004

OR: Odds ratios.

models. A spike in particle counts was defined as a greater than 3 standard deviations increase in particles from baseline levels. Data were analyzed by grouping the particle sizes into 0.3-0.5 μm/m³, 1.0-5.0 μm/m³, and 10.0 μm/m³. This division in particle sizes was not alterable and based on the internal settings of the OPS. To adjust for potential confounding, we used a regression model to control for the variables of sensor distance to the surgical field and the maximum number of people in the room during sampling.

RESULTS

The logistic regression analysis revealed that bovie (OR = 10.2; 95%CI: 7.8, 13.3; $P < 0.001$), burring (OR = 10.9; 95%CI: 6.6, 18.0; $P < 0.001$), and bone scalpel (OR = 5.9; 95%CI: 3.2, 10.9; $P < 0.001$) had significantly higher odds of a spike in 0.3-0.5 μm/m³ particle counts ("spike" being defined as a greater than 3 standard deviation increase from average baseline levels) (Table 1). Drilling was not significantly associated with a spike in 0.3-0.5 μm/m³ particle counts (OR = 0.5; 95%CI: 0.2, 1.1; $P = 0.099$).

Bovie (OR = 2.6; 95%CI: 2.0, 3.5; $P < 0.001$), burring (OR = 5.8; 95%CI: 3.4, 10.2; $P < 0.001$), and bone scalpel (OR = 4.3; 95%CI: 2.0, 9.3; $P = 0.005$) had significantly higher odds of a spike in 1-5 μm/m³ particle counts (Table 2). Drilling was excluded in this analysis because no spikes in the 1-5 μm/m³ particle size range were recorded during drilling.

Bovie (OR = 0.3; 95%CI: 0.2, 0.4; $P < 0.001$) and drilling (OR = 0.2; 95%CI: 0.1, 0.7; $P = 0.011$) had significantly lower odds of a spike in 10 μm/m³ particle counts (Table 3). Burring (OR = 1.0; 95%CI: 0.4, 2.2; $P = 0.962$) and the bone scalpel (OR = 1.3; 95%CI: 0.3, 5.7; $P = 0.724$) were not significantly associated with a spike in 10 μm/m³ particle counts. All logistic regression results are visually presented as forest plots (Figure 2).

In addition, using generalized least squares (GLS) regression models, we compared average particle counts found within a certain step to the baseline defined before and after the steps. The results from this analysis are highly consistent with those of the logistic regression. The bovie ($P < 0.001$), burring ($P = 0.009$), and bone scalpel ($P = 0.002$) were associated with an increase in the average 0.3-0.5 μm/m³ particle counts relative to baseline, while drilling was not ($P = 0.323$). Bovie ($P < 0.001$) and burring ($P < 0.001$) were associated with an increase in the average 1-5 μm/m³ particle counts, while drilling ($P = 0.748$) and bone scalpel ($P = 0.110$) were not. Bovie ($P = 0.032$) was associated with a decrease in the average 10 μm/m³ particle counts, while burring ($P < 0.001$) was associated with an increase in the average 10 μm/m³ particle counts. Drilling ($P = 0.403$) and the bone scalpel ($P = 0.638$) were not

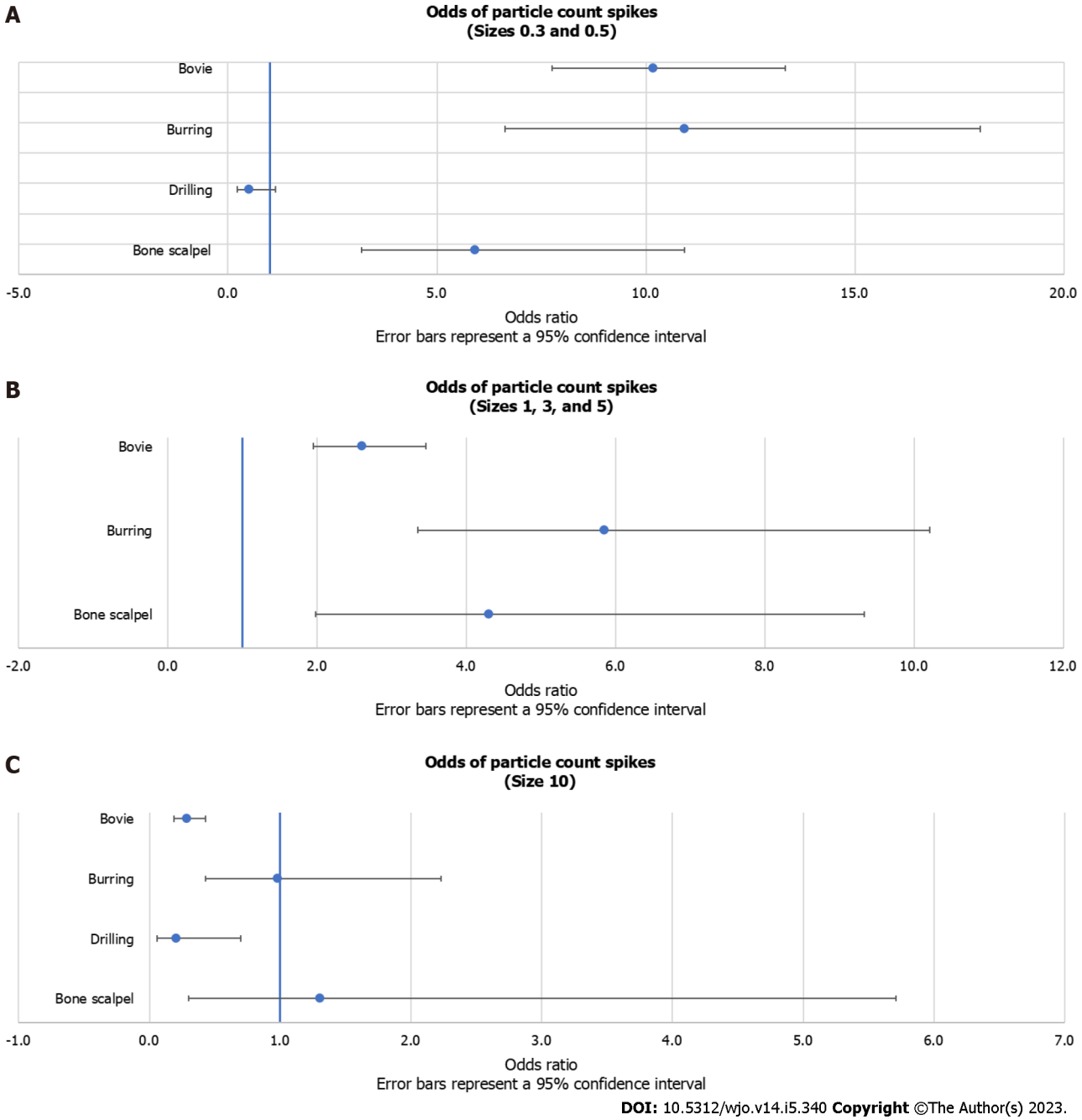

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Figure 2 Forest plot. A: Odds ratios (ORs) for each surgical steps of interest for 0.3-0.5 μm/m^3 particle counts; B: ORs for each surgical steps of interest for 1-5 μm/m^3 particle counts; C: ORs for each surgical steps of interest for 10 μm/m^3 particle counts.

associated with changes in the average 10 μm/m^3 particle counts.

DISCUSSION

Handheld OPSs are common tools used to quantify particles present in an air sample. OPSs have previously been employed in the healthcare setting to quantify aerosol generation during medical and surgical procedures[10-14]. In this study we use an OPS to demonstrate that several steps in spinal fusion are associated with increased airborne particle counts in the aerosol size range. Specifically, bovie, burring, and the bone scalpel showed consistently higher odds of spikes, while drilling did not. Although bovie and drilling had lower odds of a spike in 10 μm/m^3 particle counts, this was likely due to the large number of 10 μm/m^3 particle counts at baseline, which may have influenced our ability to recognize a spike in this range.

Table 3 Logistic regression analysis of surgical steps of interest for 10 μm/m³ particle counts

Variable	OR	Lower 95%	Upper 95%	Z score	*P* value
Bovie	0.3	0.2	0.4	-6.0	< 0.001
Burring	1.0	0.4	2.2	0.0	0.962
Drilling	0.2	0.1	0.7	-2.5	0.011
Bone scalpel	1.3	0.3	5.7	0.4	0.724
Max in room	1.7	0.9	3.5	1.6	0.111
Sensor distance	0.02	0.001	0.2	-3.0	0.003

OR: Odds ratios.

CONCLUSION

It is well established that the bovie produces large clouds of aerosolized particles[9]. This study has confirmed this finding and given validity to our methodology of identifying aerosol producing surgical steps. Previous research has shown that electrocautery smoke may be an inhalation hazard for surgeons but here we show that usage of the high speed burr and bone scalpel have the potential to aerosolize blood and other body substances[11,15]. Of note, burring confers less heat than bovie and bone scalpel, potentially making the aerosol particles it produces a larger risk if they are carrying infectious agents. These steps generate an abundance of particles in a size range that has been established to carry infectious particles. Multiple lines of evidence have confirmed that viral particles are detectable in the blood, but further research is warranted to determine if such particles have the potential to contain infectious viruses. Furthermore, if aerosolized blood has the potential to transmit the COVID-19 virus further research would be needed to determine if and whether the blood aerosolized through the surgical techniques described here is an infectious hazard or if particles are heated up to the point that they are no longer infectious[12,16-18].

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic has raised awareness of aerosol generation during medical procedures as an occupational hazard. Several authors have speculated that certain steps during spinal fusion have the potential to generate aerosols, however there is a dearth of data to quantify this risk. Publishing the type of data, we present here is critical to help hospitals create evidence-based workplace safety policies. As such, we believe that the findings presented here will be of interest to the readership of your journal and will hopefully inform future research and clinical care.

Research motivation

Several steps in spinal fusion are associated with increased airborne particle counts in the aerosol size range. Further research is warranted to determine if such particles have the potential to contain infectious viruses.

Research objectives

Upon univariate analysis, bovie ($P < 0.0001$), high speed pneumatic burring ($P = 0.009$), and ultrasonic bone scalpel ($P = 0.002$) were associated with increased 0.3-0.5 μm/m³ particle counts relative to baseline. Bovie ($P < 0.0001$) and burring ($P < 0.0001$) were also associated with increased 1-5 μm/m³ and 10 μm/m³ particle counts. Our logistic regression model demonstrated that bovie (OR = 10.2, $P < 0.001$), burring (OR = 10.9, $P < 0.001$), and bone scalpel (OR = 5.9, $P < 0.001$) had higher odds of a spike in 0.3-0.5 μm/m³ particle counts. Bovie (OR = 2.6, $P < 0.001$), burring (OR = 5.8, $P < 0.001$), and bone scalpel (OR = 4.3, $P = 0.005$) had higher odds of a spike in 1-5 μm/m³ particle counts.

Research methods

We quantified airborne particle counts during five posterior spinal instrumentation and fusions (9/22/2020-10/15/2020) using an optical particle sizer (OPS) near the surgical field. Data were analyzed by 3 particle size groups: 0.3-0.5 μm/m³, 1.0-5.0 μm/m³, and 10.0 μm/m³. We used hierarchical logistic regression to model the odds of a spike in aerosolized particle counts based on the step in progress.

Research results

In this study we use a handheld OPS to measure the generation of aerosols during surgical steps in spinal fusion because of the risk this may confer upon surgeons in regards to the airborne transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Research conclusions

Several steps in spinal fusion may aerosolize blood but little data exists to quantify the risk this may confer upon surgeons.

Research perspectives

Transmission of SARS-CoV-2 can occur during aerosol generating procedures. Several steps in spinal fusion may aerosolize blood but little data exists to quantify the risk this may confer upon surgeons.

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FOOTNOTES

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Does orthotics use improve comfort, speed, and injury rate during running? A randomised control trial

Alice E Fortune, Jonathan M G Sims, George Ampat

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Abstract

BACKGROUND

Running is a hugely popular sport. Unfortunately, running-related injury (RRI) rates are high, particularly amongst amateur and recreational runners. Finding ways to reduce RRI rates and maximise comfort and performance for runners is important. Evidence regarding whether orthotics can successfully improve these parameters is limited and contradicting. Further research is required to provide runners with clearer guidance on the usefulness of orthotics.

AIM

To investigate the effect of Aetrex Orthotics on comfort, speed and RRI rates during recreational running.

METHODS

One hundred and six recreational runners were recruited on a voluntary basis *via* running clubs and social media pages and randomised into either the intervention or control group. Participants in the intervention group ran with Aetrex L700 Speed Orthotics inserted in their usual running shoes, whilst participants in the control group ran in their usual running shoes with no orthotics. The study ran for an 8-wk period. Participants provided data relating to running comfort, distance, and time during weeks 3-6. Participants provided data relating to any RRIs they sustained during all 8 wks. Running distance and time were used to calculate running speed in miles *per* hour (mph). For each outcome variable, 95% confidence intervals and *P* values were calculated to assess the statistical significance between the groups. For comfort and speed data, univariate multi-level analysis was performed, and for outcome variables with significant between

group differences, multi-level multivariate analysis was performed to evaluate any confounding effects of gender and age.

RESULTS

Ninety-four participants were included in the final analysis (drop-out rate = 11%). Comfort and speed from 940 runs and 978 injury data reports were analysed. Participants who ran with orthotics reported, on average, speeds 0.30 mph faster (P = 0.20) and comfort scores 1.27 points higher ($P \leq 0.001$) than participants who ran with no orthotics. They were also 2.22 times less likely to sustain an injury (P = 0.08) than participants who ran with no orthotics. However, findings were only significant for comfort and not for speed or injury rates. Age and gender were found to be significant predictors of comfort. However, the improvements in comfort reported by participants who ran with orthotics were still significant after adjusting for age and gender.

CONCLUSION

This study found orthotics to improve comfort and speed and prevent RRIs whilst running. However, these findings were only statistically significant for comfort.

Key Words: Running; Foot orthoses; Running related injuries; Pain; Patient comfort; Athletic performance.

Core Tip: Running-related injuries are common, necessitating research into ways to prevent injury. Foot orthotics have been suggested as a method to reduce running-related injury rates and improve comfort and performance, which are important components of running. Previous evidence regarding this is limited and mixed. This randomised control trial finds that running with Aetrex L700 Speed Orthotics inserted into normal running shoes reduces the rate of running-related injuries and improves both comfort and speed. These findings were only statistically significant for comfort. Providing increased comfort may encourage individuals to take up running, improving their health and decreasing the demand on healthcare systems.

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INTRODUCTION

Running is a highly popular sport, likely due to its accessibility and wide range of health benefits. It has been found to prevent many common health conditions and reduce overall mortality[1-5]. However, amongst people who run, there are high rates of injuries reported[6,7]. Several studies have found running-related injury (RRI) rates to be particularly high amongst amateur and recreational runners compared to professional runners[8-11]. Common RRIs include medial tibial stress syndrome, Achilles tendinopathy and plantar fasciitis[12-14]. RRIs frequently lead to pain and discomfort and may cause individuals to stop running or seek medical treatment[14]. The high prevalence of RRIs necessitates research into prevention, especially when considering the need to encourage individuals to run in order to gain the many health benefits.

Comfort is an important factor whilst running. It has been shown that increased comfort of running can, in turn, lead to improved running performance[15]. Additionally, the experience of pain and injury overlaps with the experience of discomfort and therefore comfort. Hence, improving comfort may reduce pain and subsequently reduce reported injury rates and time taken off work or any activity due to injury. There is, therefore, a substantial incentive to improve comfort for runners.

Orthotics are a type of shoe insert often used within the running community. They can be prefabricated or custom-made to fit an individual's foot shape and size. Orthotics act to correct lower limb alignment by reducing foot pronation[16], whilst also providing enhanced cushioning, support and comfort for the foot[17]. As well as injury and comfort, another factor important to many runners is performance: Typically measured as running speed. Previous research into the benefits of orthotics on running performance, comfort and injury rates is limited and, at times, contradicting. Some studies have found orthotics to improve running performance and comfort, whereas others have shown orthotics to negatively impact these parameters[18-22]. Evidence regarding the impact of orthotics on RRI rates is also mixed[23-25]. Hence, further research is required to determine the relationship between orthotics and running comfort, running speed and RRI rates. Exploring modalities to improve comfort,

performance and injury rates whilst running is important and valuable, as this would hopefully encourage more people to take up running, leading to substantial health benefits. Exploring ways to prevent RRIs in amateur and recreational runners is particularly relevant as these groups are thought to have the highest injury rates[8-11].

The aim of this study is to explore the effects of prefabricated Aetrex[26] Orthotics on running comfort, running speed and RRI rates compared to running with no orthotics. The results of this study will add to the current evidence concerning orthotics usage in running, building on previous work by Ampat *et al*[27]. This will provide runners with enhanced guidance on the possible benefits of orthotics and, hopefully, if the results are positive, encourage non-runners to take up running, thereby improving their health[1].

This article presents the findings from the full study cohort, building on the findings in the preliminary study report[28]. The study design was previously registered in clinical trials (https://www.ijclinicaltrials.com/index.php/ijct/article/view/586) in May 2021 (NCT04901442) and published [29].

MATERIALS AND METHODS

This study was conducted as a randomised control trial. The primary objective was to investigate whether running with prefabricated orthotics inserted into participants' usual running shoes *vs* running without would improve comfort and speed and reduce injury rates.

Recruitment

Results of our previous study found an improvement of two points on the comfort scale when using orthotics compared to usual running trainers with no orthotics[27]. For the sample size estimate for this study, a conservative improvement of 1.5 points, with a standard deviation of 2.45, was used. Based on this, a target sample size of one hundred and six participants was determined through a sample size calculation, using a target significance level of 5%, target power of 80% and allowing for a 20% dropout rate. All 106 participants were recruited between July 2021 and April 2022 on a voluntary basis *via* advertisements displayed on social media pages and at local running clubs. Individuals who contacted the research team were screened for eligibility and provided with a participant information sheet (PIS). Recipients were allowed sufficient time to read and understand the PIS in full. If, following this, they were willing to participate, a phone call with the lead investigator was arranged to answer any remaining questions. Following this, individuals willing to participate provided informed, written consent, either by post or online *via* legalesign.com.

Inclusion criteria for the study were: Aged 18 and over and used to completing runs of at least 5km distance during the last year. Exclusion criteria were: Current use of prescription orthotics, having any ongoing pain or deformity in the foot, having any serious health condition which had led to a doctor advising them not to exercise or having undergone any surgery in the past six months or any surgery to the feet during their lifetime. Participants were informed that they could withdraw from the study at any time if they wished to, without needing to provide a reason.

Randomisation

Following recruitment, participants were randomised into one of two groups using a 1:1 allocation: Group A (intervention group), in which participants ran with Aetrex[26] L700 Speed Orthotics inserted into their usual running shoes, or Group B (control group), in which participants ran in their usual running shoes with no orthotics. Randomisation and group allocation occurred using pre-filled and sealed envelopes, each containing a note to assign a participant to either Group A (intervention group) or Group B (control group). All envelopes were shuffled thoroughly before opening and randomly selected and opened by an individual independent of the study. Blinding of participants and researchers to group allocation was not possible due to the nature of the study intervention.

Participants allocated to Group A (intervention group) received a pair of Aetrex[26] L700 Speed Orthotics in their correct shoe size *via* post. They also received an instruction sheet clearly explaining how to use the orthotics. The Aetrex[26] L700 Speed Orthotics provided to Group A (intervention group) in this study are pictured in Figure 1.

Data collection

Upon recruitment to the study, basic demographic information was collected from each participant. Collection of data for all three primary outcomes (comfort, speed, and injury rate) then took place over an 8-wk period. To minimise confounding variables and risk to participants, participants were asked to run as they usually would during the 8-wk study period, with no changes made other than the addition of the orthotics for the intervention group. Participants provided all data remotely and could choose whether they wished to provide data *via* an online or a paper survey provided to the researchers *via* post. All participants opted to provide data *via* the online method.

Figure 1 Aetrex L700 Speed Orthotics. Image of Aetrex L700 Speed Orthotics, provided to participants in the intervention group. Reprinted with permission of Aetrex, Inc. © 2022.

The majority of data collection took place during weeks 3, 4, 5 and 6 of the 8-wk data collection period. Weeks 1 and 2 were allocated as an 'acclimatisation period' to allow individuals in the intervention group to become familiar with using the orthotics. Weeks 7 and 8 were allocated as a 'run-through period' with the purpose of collecting data regarding any injuries that occurred following the main data collection weeks. During weeks 3, 4, 5, and 6, participants provided data relating to running comfort, running duration, and running distance immediately after every run they completed. Participants were asked to complete and provide data from at least 10 runs during this 4-wk period. Comfort was scored using a self-report visual analogue scale (VAS) of 0 to 10, where 0 represented "No Comfort" and 10 represented "Maximum comfort". VAS was selected as this is a widely used and validated method of scoring patient-perceived comfort[30,31]. Running duration was reported in hours and minutes, and running distance was reported in miles/kilometres. Running duration and distance were used to calculate running speed in miles *per* hour (mph). Speed was used to represent running performance in this study, in line with the way that running performance is measured in running events around the world.

Participants were asked to provide data relating to any RRIs they had sustained at least once *per* week during the whole 8-wk period. This data was reported *via* a self-report survey, and all participants were provided with an injury identification sheet about common RRIs to assist them in providing this data, as depicted in Figure 2. Data was submitted regarding whether the injury led to disruption of running (disruption of distance, speed, duration, or frequency of running), and if so, how long for. Participants also self-reported the nature of the injury (*e.g.*, iliotibial band syndrome, Achilles tendinopathy) based on the injury identification sheet and whether the injury was new or pre-existing. For an injury to be included in analysis, it had to meet the definition "running-related musculoskeletal pain in the lower limbs that causes a restriction or stoppage of running (distance, speed, duration, or training) for at least 7 d or 3 consecutive scheduled training sessions". This is the consensus definition presented by Yamato *et al*[32] following their work on defining RRIs. Pre-existing injuries were included only if they flared up during the study period.

Data collection was monitored by a data monitoring committee consisting of an orthopaedic surgeon, a patient and a statistician, all independent of the research team.

All individuals who took part in the study were provided with a free pair of Aetrex[26] L700 Speed Orthotics to thank them for their time and participation in the study. Those in Group B (control group) were provided these after the data collection period.

Statistical analysis

All participants were analysed (intention to treat) within their original assigned groups. The primary outcomes comfort and speed data were analysed using multi-level univariate analysis. This was done to group together the data provided by each individual (*i.e.*, runners having data on multiple runs), allowing any internal correlations to be accounted for. 95% confidence intervals and *P* values were calculated for each outcome variable to determine if between-group differences were statistically significant. This was done using the Chi-squared test for comfort and speed data and Fisher's exact test for injury data. Statistical significance was considered if $P < 0.05$. For outcome variables with significant findings, multi-level multivariate analysis using a logistic regression model was performed to evaluate any confounding effects of gender or age on the findings.

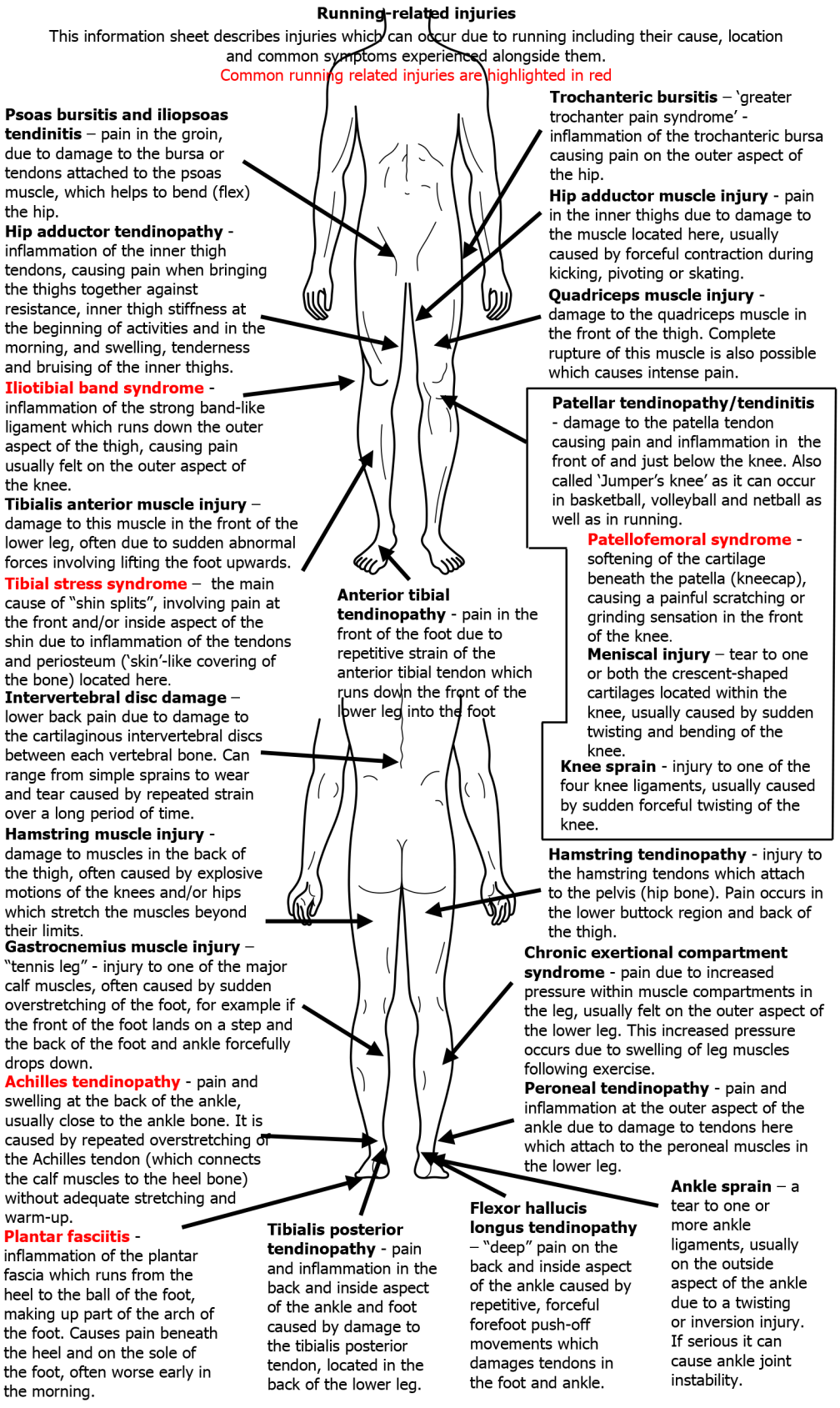

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Figure 2 Injury identification sheet. Injury identification sheet regarding common running-related injuries provided to participants to assist them in reporting injuries.

All statistical analysis was reviewed by a National Institute for Health and Care Research-funded statistician from the Department of Biostatistics, University of Liverpool.

RESULTS

One hundred and six individuals were recruited to the study; 53 were randomised to the intervention group and 53 to the control group. During the study, 12 participants withdrew (6 from the intervention group, and 6 from the control group), two due to illness, two due to injury and eight stopped responding. This left a total of 94 participants to be included in the analysis (drop-out rate of 11%). Full details of participant flow, including reasons for withdrawal, are detailed in Figure 3.

The final study cohort (n = 94) ranged in age from 19 to 66 years old, with an overall mean age of 39 and a higher proportion of males than females. The intervention group contained slightly more women than men (n = 24 *vs* 23), whereas the control group contained more men than women (n = 29 *vs* 18). On average, participants in the intervention group were older than those in the control group, with mean ages of 40.8 and 37.9, respectively. Complete demographic data for the study population can be found in Table 1.

All the 94 participants included in the analysis provided data from at least 10 runs across weeks 3, 4, 5 and 6, and injury data at least once *per* week during weeks 1-8. The first 10 runs provided by each participant were included in the analysis. From these, comfort, and speed data for runs over two hours long were considered outlier variables and excluded from the analysis. Such runs, of which there were 65 in total (6.91%), were removed because the purpose of this study is to investigate amateur and recreational runners, for whom a run longer than two hours is not considered typical. The injury data of the two participants who withdrew from the study due to injury was removed from the analysis. This left a total of 875 sets of comfort and speed data and 978 sets of injury data in the final analysed dataset.

Regression coefficients, 95% confidence intervals and P values for comfort and speed data are provided in Table 2. On average, participants who ran with Aetrex[26] Orthotics reported comfort scores that were 1.27 points higher than those who ran with no orthotics. This finding was statistically significant, with a P value of < 0.001. Running speeds reported by participants in the intervention (orthotic) group were, on average, 0.30 mph faster than those reported by participants in the control (no orthotic) group. However, this finding was not statistically significant (P = 0.20).

Numbers of injuries reported by both groups and the odds ratios, 95% confidence intervals and P values calculated for injury data are provided in Table 3. Participants in the intervention group were 2.22 times less likely to report an injury that disrupted running for ≥ 7 d compared with participants in the control group). However, these findings were not statistically significant (P = 0.08).

Table 4 reports data for injuries lasting ≥ 7 d in more detail, showing the frequency of injury at different sites and overall injury rates. Upper leg and knee injuries were rarely reported in the intervention group, whilst they were the most common injured sites in the control group. Overall, injuries occurred less frequently in the orthotic group; however, of the injuries that did occur, a large proportion of these was in the ankle. One participant from each group experienced two injuries that lasted ≥ 7 d. Hence, 5 participants reported 6 injuries lasting ≥ 7 d in the orthotic group, and 10 participants reported 11 injuries in the control group.

The orthotic group reported three ankle injuries, all of which were ankle sprains. Conversely, the control group reported no ankle sprains. To explore the potential reason for this discrepancy, all participants who experienced an ankle sprain were contacted to enquire about the type of terrain on which they were running when the ankle sprain occurred (on or off road). All three participants reported that they were running off-road at the time of the injury.

Multilevel multivariate analysis of comfort scores is provided in Table 5. Age and gender were found to be significant predictors of comfort scores. Male participants provided scores that were, on average, 0.55 points higher than females (P = 0.039), and comfort scores increased by 0.04 points for every one-year increase in participant age (P = 0.003). However, the increase in comfort scores in the intervention group remained significant after adjusting for the effects of gender and age ($P \leq 0.001$).

Generally, the spread of data for all variables was broad, reflected by wide confidence intervals, and this was wide enough to produce non-significant findings for injury and speed.

It was ensured that no participants experienced any additional harm or injury by participating in the study. This was mitigated by instructing all participants to run as they normally would, without changing the running frequency, speed, or duration. The only alteration was the addition of orthotics in intervention group, who were shown to have a reduced RRI rate as compared to the control group. Two participants withdrew from the study due to injury. However, the participants did not require any medical intervention other than cessation of running.

DISCUSSION

This randomised control trial explores the effect of orthotics on running comfort, speed and RRI rates. It finds that participants who ran with Aetrex[26] L700 Speed Orthotics reported, on average, higher comfort scores, higher running speeds and lower injury rates over the 8-wk study period than participants who ran with no orthotics. These findings, however, were statistically significant for comfort only and not for injury or speed.

Table 1 Basic demographic information for participants included in analysis, *n* (%)

	Intervention (orthotic) group	Control (no orthotic) group	Both groups
Sex			
Male	23 (48.94)	29 (61.70)	52 (55.32)
Female	24 (51.06)	18 (38.30)	42 (44.68)
Age (yr)			
< 20	1 (2.1)	1 (2.13)	1 (1.06)
20-29	9 (19.1)	9 (19.15)	16 (17.02)
30-39	10 (21.3)	15 (31.91)	26 (27.66)
40-49	16 (34.0)	13 (27.66)	30 (39.91)
50-59	8 (17.0)	7 (14.89)	16 (17.02)
60-69	3 (6.4)	2 (4.26)	5 (5.32)
Mean age	40.79	38.49	38.97
Total	47	47	94

Table 2 Findings and multi-level analysis of comfort and speed data for both groups

Outcome measure	Regression coefficient (95%CI)	*P* value
Comfort	1.27 (0.69 - 1.84)	< 0.001
Speed	0.30 (-0.16 - 0.75)	0.20

Table 3 Findings and statistical analysis of injury data for both groups

Outcome measure	Participants experiencing outcome in intervention (orthotic) group	Participants experiencing outcome in control (no orthotic) group	Odds ratio (95%CI)	*P* value
Injury	5	10	2.27 (0.71 - 7.25)	0.26

Table 4 Frequency of injuries lasting > 7 d for both groups classified by injury site

Injury site	Injury frequency		
	Intervention (orthotic) group	Control (no orthotic) group	Both groups
Upper leg	0	6	6
Knee	1	3	4
Lower leg	1	1	2
Ankle	3	1	4
Foot	1	0	1
All sites	6	11	17

Previous studies have similarly found that orthotics provided non-significant improvements in injury rates and/or speed but significant improvements in comfort[27,33]. Ampat *et al*[27], reported on 37 participants who ran with and without the orthotics on alternate weeks, reporting distance, time, comfort and RRIs. In line with the current findings, Ampat *et al*[27] found significant improvements in comfort only and non-significant improvements in both injury rate and performance. Mündermann *et al*[33] assessed the effects of various shoe inserts on comfort and injury frequency in military personnel. As compared to the control condition (no insert), all shoe inserts allowed for significantly higher comfort ratings. The incidence of injury and pain at various locations was also reduced, albeit not significantly. However, this study assessed these effects during general physical activity, and not exclusively whilst running. Whilst these studies found somewhat similar findings to the current,

Table 5 Findings from multivariate analysis of comfort data

Outcome measure = comfort		
Variable	**Regression Coefficient (95%CI)**	***P* value**
Group (Intervention *vs* control)	1.22 (0.67 - 1.78)	< 0.001
Gender	0.55 (0.03 - 1.07)	0.039
Age	0.04 (0.01 - 0.06)	0.003

discrepancies in findings exist within the literature. For instance another study found only non-significant improvements in comfort[20]. However, unlike the current study, this assessed the effects of custom-made orthotics on well-trained male athletes in a controlled setting, in which participants ran on a treadmill for six minutes at high and low speeds in three footwear conditions; standardized footwear (control), custom made orthotics made from ethyl-vinyl acetate, and custom-made orthotics made from expanded thermoplastic polyurethane. Although not significant, arch height comfort and medio-lateral control comfort were improved in both orthotic conditions[20]. Additionally, a 2017 systematic review found significant reductions in overall injury rates with orthotics but non-significant reductions in injury rates when data for individual types of injury were analysed[23]. Contrastingly, a 2007 meta-analysis found orthotics to significantly reduce rates of lower limb overuse injuries specifically[30]. In summary, findings in the literature vary greatly. A likely factor contributing to this is the variation in RRI definitions used between studies. This has led to wide variation in reported RRI rates, ranging from 15.6% to 79.3% in previous studies[7,10,34]. For comparison, the overall number of participants who experienced a RRI in this study was 16%. Another likely contributor to the heterogenicity between study findings is the influence of various confounding variables. These variables include terrain, speed, experience, history of previous injury and distance. This study could have been improved by exerting greater control over confounding variables, such as those listed above. However, a strength of this study was the use of the consensus definition for a RRI, which was agreed upon in work done by Yamato and colleagues[32].

In this study, the rate of injuries lasting ≥ 7 d was lower in the intervention group at all sites except for the foot and ankle, where injuries were more common amongst individuals running with orthotics. Such findings from the orthotic group are harmonious with the findings of a 2012 systematic review which investigated the incidence and prevalence of running-related musculoskeletal injuries and found that foot and ankle injuries may be some of the most prevalent[35]. The higher rate of ankle injuries with the orthotic, namely ankle sprains, may also be explained by the fact that all participants in the orthotic group who experienced such injuries did so when running off-road. Ankle sprains are the most common injury to occur during off-road running[36]. This suggests that the terrain might have contributed to the injury, rather than the use of orthotics.

Unlike barefoot runners, who experience more accurate proprioceptive input from the feet during running and usually land on the ball of the foot[37], individuals who wear trainers whilst running have poorer proprioception and often land with their heels hitting the ground first. This causes overpronation of the foot and internal rotation of the lower limb joints, with simultaneous external rotation of the patella, which can lead to injury. The current working principle is that orthotics act to reduce this, as well as to distribute pressure more evenly across the foot[38-40]. The redistribution of pressure is illustrated in Figure 4. Additionally, orthotics are thought to provide impact cushioning, absorbing some of the forces that pass through the foot and lower leg during running, thereby reducing injury[17]. It would be beneficial for the running population that such orthotics are readily accessible and affordable. Prefabricated orthotics, which are at least 2.5 times less costly than custom-made orthotics, would be preferred[27]. This preference is supported by the results of previous research, which suggest that there is no significant difference when using pre-fabricated orthotics instead of customised orthotics to prevent RRIs[30].

The strengths of this study include power analysis prior to commencement, achievement of target sample size, and a drop-out rate of just 11%, well below the drop-out rate allowed for, in the study size calculation. This allowed data collection of sufficient quantity and power to produce statistically significant findings. The wide range of ages of participants in this study increases its applicability to the broader running population. Additionally, the collection of data detailing the length of disruption to running following an injury, and injury sites, allowed more detailed exploration into the effect of orthotics usage on RRIs.

The study was not without limitations. No blinding of researchers or participants to group allocation took place. Some participants in the intervention group may have expected that the orthotics would improve their running experience, which could have created bias. This risk of bias is further emphasized when taking into consideration the newly developed 'comfort filter' paradigm, which suggests that injury risk is automatically reduced if a shoe or insert is deemed more comfortable by the runner as assessed by their own 'comfort filter'[41]. Additionally, comfort could have been explored in more

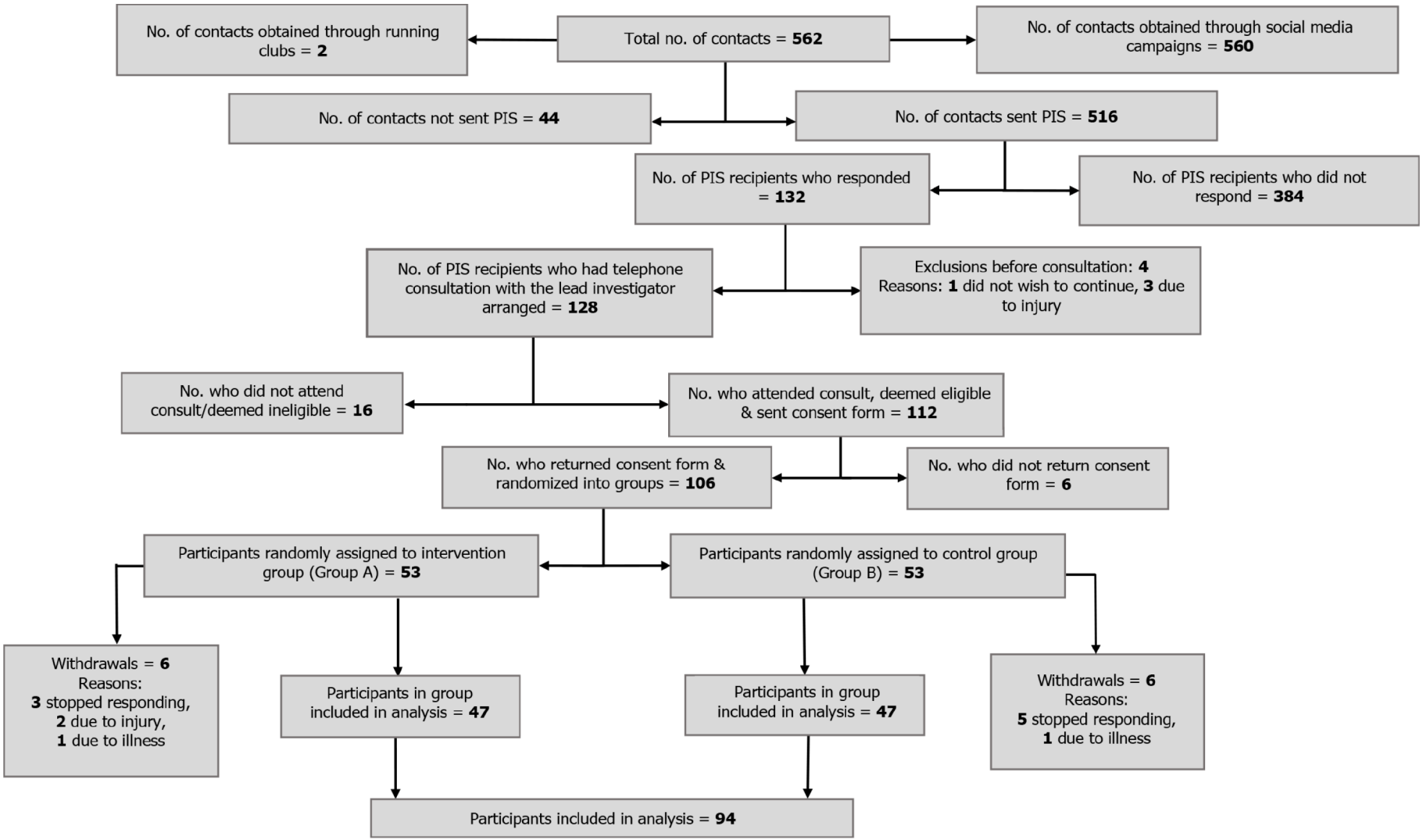

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Figure 3 Participant flow. Participant flow, including randomised group assignment and any withdrawals. No.: Number; PIS: Participant information sheet.

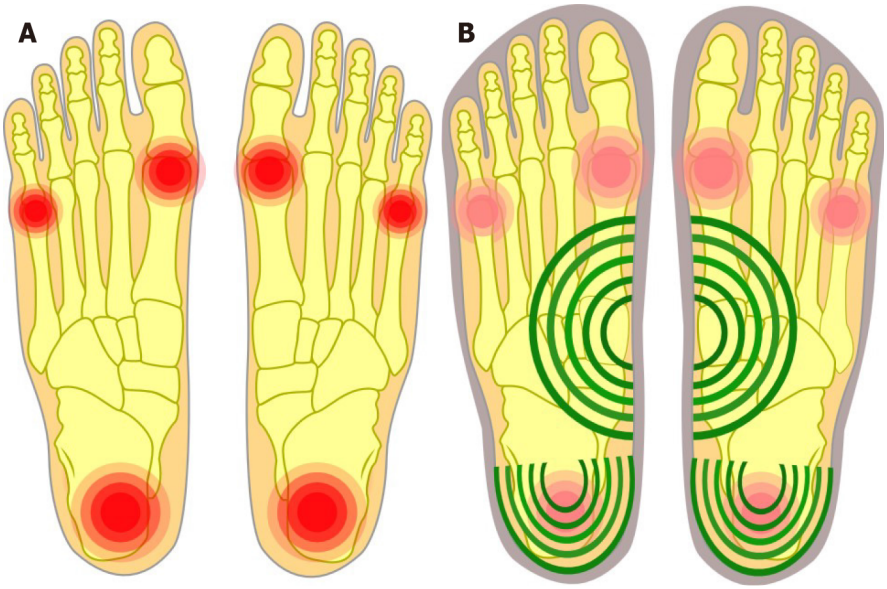

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Figure 4 Comparison of pressure in the feet with and without orthotics. A: Increased pressure at three points without orthotics compared to; B: Reduced pressure using orthotics with arch support and a cupped heel.

depth by assessing comfort in various parts of the foot, as done in other studies[33], rather than simply an overall comfort measure. Furthermore, the study results may have benefited from all participants being queried further regarding their running experience. Recreational runners have been defined as individuals with over 3 mo of running experience, whilst anyone with less than 3 mo of running experience is referred to as novice runners[8]. Experienced runners have been defined as runners who have been running for over a year[9]. It has been found that the incidence of RRIs is significantly higher in novice than experienced runners, with one study finding that novice runners experience 8.78 RRIs *per* 1000 hours of running, as compared to 4.24 *per* 1000 hours for experienced runners[9]. Hence, whilst the current study aimed to focus on recreational runners, the use of these definitions to sub-group participants would have been advantageous, as it would have allowed for further analysis into the relationship between running experience and its effects on injury rate. It would have also been beneficial for the researchers to evaluate participants history of previous RRIs, as this has been associated with an increased likelihood of a further injury and a poorer prognosis following a new injury[42]. Again, the inclusion of this data would have allowed sub-group analysis, enabling any existing correlations to be identified. The collection of data regarding each participant's usual running terrain is also a consideration for future studies as, once more, it would have allowed sub-group analysis to ascertain the relationship between the terrain on which participants ran and their injury types and injury rate. The lack of data collection concerning the participants running footwear could also be viewed as a limitation. Gathering this data would have allowed for sub-group analysis to determine if differences in footwear effected running performance or injury rate, as bias may exist. However, the researchers did not wish to control the participants running shoes, as the aim of the study was to ascertain the level of benefit orthotics can provide to general runners, irrespective of their usual running footwear. To improve the clarity of findings, it could also be favorable if future studies request a maximum of one weekly injury report and one comfort report for the entire week.

In this study, there was a much higher proportion of males (n = 29) than females (n = 18) in the control group. The UK running population is estimated to contain more males than females[43], but not at such an extreme ratio as in this participant group. In contrast, the intervention group contained slightly more females (n = 24) than males (n = 23). This difference in numbers of males and females in each group is relevant as it will have confounded the study findings, as demonstrated in the multivariate analysis of comfort. Closer monitoring of the participant recruitment process in future studies and using a sampling technique, such as stratified sampling, would prevent discrepancies like this from occurring in the future.

The wide confidence intervals found during the analysis of all outcomes demonstrate a wide spread of data from the mean values for each outcome and each group. These confidence intervals were wide enough to cause the improvements in speed and injury rate to be non-significant. This broad spread of data may be partially explained by the nature of the outcomes explored by this study. Natural tendencies for injury, running speeds and expectations for comfort vary between individuals, which may have led to a wider spread of data.

The burden of cardiovascular diseases, cancers and diabetes mellitus within the general population is substantial, and lack of exercise is a significant contributor to this[2-5,44-46]. Recreational running is an accessible, affordable way to exercise and reduces the risk of these health conditions[47,48]. This study finds that Aetrex L700 Speed Orthotics allows at least some improvements in performance and injury reduction and significant improvements in comfort.

This study advances current knowledge regarding the use of prefabricated orthotics in reducing RRI rates and improving running comfort and speed. However, the lack of significant findings for injury and speed necessitates further research. This is particularly important as reducing discomfort and injury may encourage more individuals to take up running and improve their health thereby decreasing the strain on healthcare services.

CONCLUSION

This randomised control trial finds that running with Aetrex[26] L700 Speed Orthotics improves comfort and speed whilst running and reduces RRI rates compared to running with no orthotics. However, data were only significant for comfort and not for injury rate or speed.

ARTICLE HIGHLIGHTS

Research background

Current evidence regarding the effect of orthotics on comfort, speed and injuries during running is limited and mixed.

Research motivation

Running is a highly popular sport; however, the rate of running-related injuries is high. Exploring the ability of orthotics to reduce injury and improve speed and comfort during running would be valuable to runners and, if the results are positive, encourage individuals to take up running, thereby improving their health.

Research objectives

To explore whether running with Aetrex[26] Orthotics inserted into normal running shoes reduces the rate of running-related injuries and improves comfort and speed.

Research methods

In this randomised control trial, participants were recruited on a voluntary basis and allocated to either the intervention (orthotic) group or the control (no orthotic) group. Participants in the intervention group were asked to run with a pair of Aetrex[26] L700 Speed Orthotics inserted into their normal running shoes, whilst participants in the control group were asked to run in their normal running shoes with no orthotics. Data for any related running-related injuries was collected over an 8-wk period. Comfort scores and run duration and distance data were collected immediately after any run performed during weeks 3-6. Univariate multi-level analysis was performed for comfort and speed data. Odds ratios were calculated for injury data, and 95% confidence intervals and *P* values were calculated for all three outcomes. Multilevel multivariate analysis was performed for outcomes with significant findings between groups to evaluate any confounding effects of gender and age.

Research results

Data from 94 participants were included in the final analysis. On average, participants in the intervention (orthotic) group reported higher comfort scores, faster running speeds and fewer injuries. This data was significant for comfort but not for injury rates or running speed. Gender and age were found to significantly affect comfort, but significant improvements in comfort when wearing the orthotic were still present after adjusting for gender and age.

Research conclusions

This study provides evidence that running with prefabricated orthotics inserted into normal running shoes increases comfort and speed and reduces the rate of running-related injuries. However, data were only significant for comfort and not for speed or injury rates.

Research perspectives

Further research on this subject is required due to the ongoing need to find a cost-effective way to reduce injury rates in recreational runners and encourage individuals to take up running to improve their health. Future studies should consider collecting data regarding the tendency for running injury

and usual running speeds to allow adjustment of results for these confounding variables.

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FOOTNOTES

Author contributions: Fortune AE, Sims JMG, and Ampat G designed the research study; Sims JMG was involved in recruitment and data collection; Ampat G performed telephone consultations with all participants on enrolment to the study; Fortune AE and Sims JMG analysed the data. Fortune AE, Sims JMG and Ampat G wrote the manuscript; All authors have read and approved the final manuscript.

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Informed consent statement: All study participants gave their informed, written consent (*via* an online e-form) prior to study inclusion.

Conflict-of-interest statement: George Ampat and Jonathan M G Sims are Directors/employees of Talita Cumi Ltd. Talita Cumi Ltd has a commercial relationship with Aetrex, Inc. 414 Alfred Avenue Teaneck, NJ 07666, USA. Alice E Fortune has no conflict of interest.

Data sharing statement: The anonymised dataset is available from the corresponding author at g.ampat@liverpool.ac.uk. Participants gave informed consent for sharing of anonymised data.

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CASE REPORT

Intra-abdominal myositis ossificans - a clinically challenging disease: A case report

Gabriele Carbone, Valentina Andreasi, Paola De Nardi

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Peer-review model: Single blind

Peer-review report's scientific quality classification

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Grade B (Very good): B, B
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Abstract

BACKGROUND

Myositis ossificans (MO) is an uncommon disorder characterized by heterotopic ossification within soft tissues. Only a few cases of intra-abdominal MO (IMO) have been described in the literature. Histology could be difficult to understand and a wrong diagnosis could lead to an improper cure.

CASE SUMMARY

We herein report the case of IMO in a healthy 69-year-old man. The patient presented with an abdominal mass in the left lower quadrant. A computed tomography scan showed an inhomogeneous mass with multiple calcifications. The patient underwent radical excision of the mass. Histopathological findings were compatible with MO. Five months later the patient showed a recurrence causing hemorrhagic shock due to intractable intralesional bleeding. The patients eventually died within three months since recurrence.

CONCLUSION

The case described could be classified as post-traumatic MO that developed close to the previously fractured iliac bone. The subsequent surgical procedure was ineffective and the disease rapidly recurred. The misleading intraoperative diagnosis led to improper surgical treatment with a dramatic evolution.

Key Words: Myositis ossificans; Post-traumatic; Diagnosis; Surgical treatment; Prognosis; Case report

Core Tip: Myositis ossificans (MO) is a rare condition of heterotopic bone formation within muscle or soft tissues. Intra-abdominal MO is even rarer usually arousing following abdominal surgery or trauma. Its presentation is non-specific and physical examination is usually unremarkable until the mass reaches large dimensions. Laboratory examinations are within normal limits. Computed tomography scan is essential for the diagnosis, since it can show the typical "zonal patterns" of the calcifications. Histopathology can differentiate MO from infections and malignancies. However, histology could be misinterpreted for fibromatosis or sarcoma, thus leading to improper cure. The treatment may be complex and should be based on patients' symptoms. Most patients can be treated conservatively and surgical procedures should be reserved for selected patients since repetitive surgery promotes further and more aggressive calcifications.

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INTRODUCTION

Myositis ossificans (MO) is a rare and benign connective tissue disorder characterized by non-neoplastic heterotopic ossification in the context of soft tissues. MO tends to be secondary to trauma. It is mostly found in adolescents or young adults and the lesions are predominantly located in the large skeletal muscles of the arms and thighs. This form, also known as post-traumatic MO (PTMO), is usually self-limiting thus not requiring specific surgical treatment. However, the clinical, radiological, and histological presentation of MO is often non-specific and can mimic a soft tissue malignancy, resulting in misdiagnosis and inappropriate management. We herein report a very rare case of intra-abdominal MO (IMO) and review the main features of this rarely encountered, but clinically demanding condition.

CASE PRESENTATION

Chief complaints

A 69-year-old man presented at the surgical clinic with a painless abdominal lump, located in the left iliac fossa. The patient did not refer any systemic symptom.

History of present illness

The mass had slowly increased in size over the last couple of months.

History of past illness

His past medical history included an appendectomy during his childhood. Four years earlier a car accident occurred resulting in abdominal trauma and left iliac bone fracture.

Personal and family history

The patient denied any family or personal history of malignancies.

Physical examination

Clinical examination revealed a non-tender, firm, oval-shaped abdominal mass with smooth surface in the left lower quadrant.

Laboratory examinations

Laboratory findings were within normal range.

Imaging examinations

An abdominal ultrasound showed a 7-cm ovoidal lesion with a mixed echo structure, diffuse calcifications and increased vascular density at the color-Doppler control (Figure 1). A computed tomography (CT) scan was obtained with evidence of an 8 cm × 6.5 cm × 7 cm, highly inhomogeneous mass composed by multiple calcifications at the periphery (Figure 2).

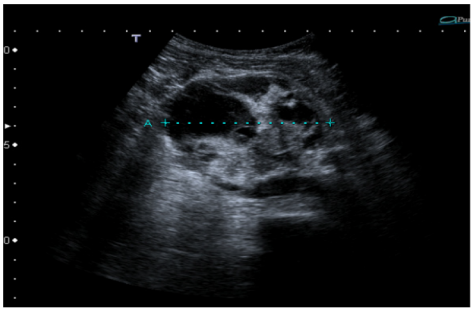

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Figure 1 Abdominal ultrasound showed a 7-cm ovoidal lesion with a mixed echo pattern. It was possible to distinguish fluid and solid components (including diffuse calcifications).

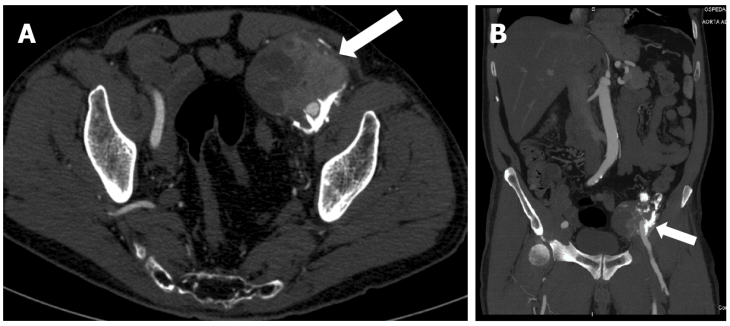

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Figure 2 Computed tomography image revealed an 8 cm × 6.5 cm × 7 cm, highly inhomogeneous mass composed by multiple calcifications at the periphery. A: Axial view; B: Sagittal view.

FINAL DIAGNOSIS

The imaging features were strongly suspicious for a malignancy originating from mesenchymal cells. Based on these findings, a surgical exploration was performed.

TREATMENT

A bulky tumor with dense adhesions to the left iliac bone was found and the intraoperative histological examination was consistent with osteosarcoma. A radical excision of the mass was then carried out.

Gross examination of the surgical specimen revealed a partially capsulated, 8.5 cm × 8 cm × 6 cm mass with hemorrhagic and calcified areas. The lesion presented trabecular architecture characterized by a central area consisting of fiber cells and by a peripheral area consisting of osteoblasts, producing osteoid and bone matrix. Histopathological findings were compatible with IMO (Figure 3).

OUTCOME AND FOLLOW-UP

The post-operative course was complicated by a chylous fistula that was managed conservatively. Additionally, a complete thrombosis of the left femoral vein was diagnosed. The patient was then discharged with anticoagulant therapy.

Five months later, the patient returned to the Emergency Department complaining rapidly worsening abdominal pain, nausea, and vomiting. The radiological examinations showed disease recurrence with an inhomogeneous pelvic mass measuring approximately 20 cm in diameter and causing compression of the sigmoid colon (Figures 4A and 5). Because of the bowel obstruction, an explorative laparotomy was planned. At surgery, a hard, hyper vascular lesion strongly adherent to the anterior abdominal wall and to the deep posterior planes was found. Thus, due to the high risk of bleeding, only a biopsy of the mass was performed and the histopathological diagnosis confirmed an IMO. During the postoperative course the patient developed a hemorrhagic shock caused by multiple intralesional bleedings (Figure 4B). An angiography, with embolization of vessels originating from the left iliac artery, was performed with cessation of the bleeding. The lesion, however, continued to grow rapidly, infiltrating

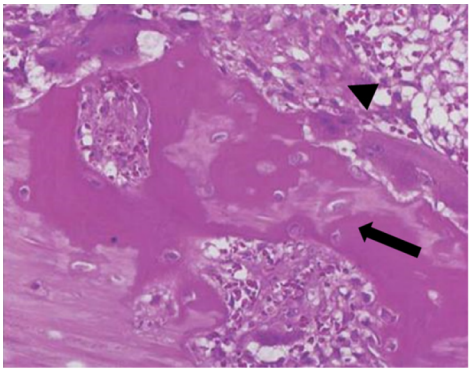

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Figure 3 Microscopic findings of myositis ossificans. Haematoxylin and eosin staining showing a mature lamellar bone neo-formation (arrow) and fibroblasts with elongated nuclei (arrowhead) arranged in short irregular fascicles with the typical "zonation pattern" placed in loose myxoid or collagenous stroma. Occasional mitoses can be observed, in the absence of cellular atypia.

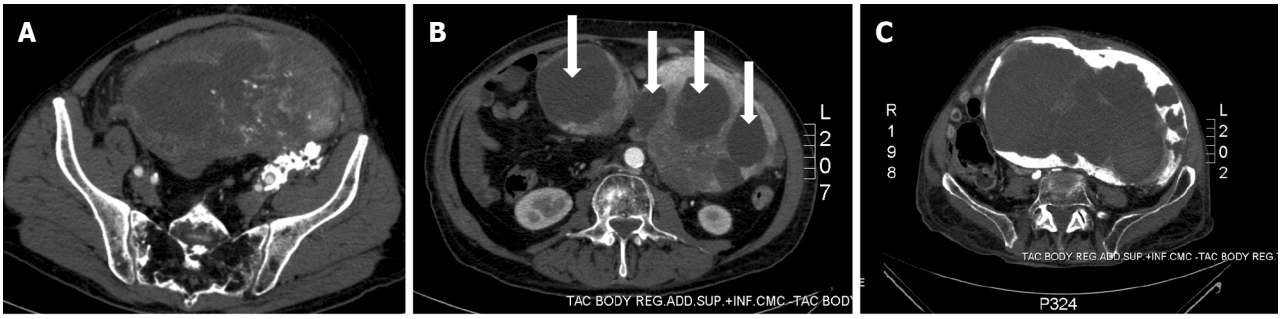

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Figure 4 The computed tomography scan. A: An inhomogeneous pelvic mass measuring almost 20 cm in diameter; B: A mass with multiple haemorrhagic areas (arrows); C: A huge mass filling almost all the abdominal cavity and infiltrating the aortic plane and both ureters.

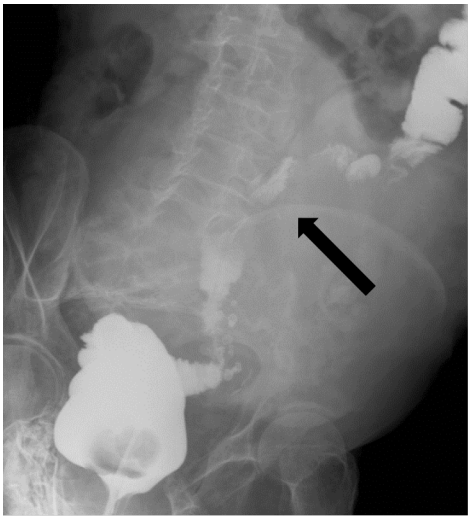

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Figure 5 Barium enema showing compression of the sigmoid colon (arrow).

the aortic plane and both ureters (Figure 4C). Eventually, the patient dramatically died eight months after the first diagnosis.

DISCUSSION

MO is an infrequent and non-malignant disease distinguished by abnormal heterotopic bone formation within soft tissues[1]. Two different clinical entities of MO have been reported in the literature: Progressive or genetic MO and acquired MO[2,3].

Progressive MO (PMO), also known as Munchmeyer disease, is a rare genetic autosomic dominant disorder characterized by congenital malformation of big toes and progressive heterotopic ossification of connective tissue. It usually begins in the spine and proceeds in a proximal to distal, cranial to caudal or axial to appendicular direction[4]. PMO normally develops in the first decade of life and the evidence of malformed great toes may lead to the correct diagnosis[5].

Acquired MO can be classified into neurogenic (associated with paraplegia) and non-neurogenic; the latter group can be divided into post-traumatic and idiopathic/pseudo malignant[2,3]. The case described in our report was reasonably a PTMO and, in the present article, we will discuss this clinical entity, which represents the most frequent form of MO, accounting for almost 70% of cases[6].

PTMO usually presents within the second and third decade of life, but lesions can arise at any age, as showed in our patient. PTMO typically originates in the context of the large skeletal muscles of the limbs. Quadriceps and brachialis muscles are the two most affected regions because of the high risk of traumas and injuries. However, PTMO can occur in almost every site of the body and even cases of PTMO in the hand have been described in the literature[7].

Abdominal PTMO mostly arises from a midline surgical incision or a trauma site[8], while IMO is an extremely rare condition associated with neoplasms of gastrointestinal tract or previous intra-abdominal surgery[9]. In the few IMO cases reported in literature[10,11], lesions developed inside the mesentery or the omentum after a surgical procedure and tended to grow rapidly, often resulting in bowel obstruction. Interestingly, in our patient the IMO lesion was located next to the previously fractured iliac bone and the mechanical trauma was likely the primum movens for the development of the lesion. The following surgical stress was probably responsible for disease recurrence and especially for the rapid growth evolution.

The clinical presentation of PTMO is highly variable, depending also on the site of origin. In case of PTMO of the limbs, it may range from an incidental finding to a rapidly enlarging painful mass with reduced range of movement. Otherwise, as mentioned before, patients with IMO can present with bowel obstruction. In some cases, clinical symptoms can mimic those of an aggressive malignant sarcoma, representing a diagnostic challenge[12,13].

The diagnosis of PTMO depends strictly on radiological and histological features since symptoms can be vague and clinical history is often silent (the only relevant element may be a trauma in the affected area). CT is the preferred imaging technique for PTMO as it best demonstrates the typical "zonal pattern". This feature is represented by a low-attenuating center with a well-circumscribed, high-attenuating, peripheral rim of calcification. CT may also show the classical "string sign", a thin radiolucent cleft which separates MO from adjacent bone. In our case, imaging revealed an inhomogeneous and hyper vascularized lesion with calcifications located only in one third of the circumference. These features were highly suspicious for a malignant lesion[14,15].

The "zone phenomenon" is also observed on histological tissue samples with a well-organized mature lamellar bone at the periphery, an intermediate osteoid region, and a central immature non-ossified fibroblastic focus[16]. The evidence of that histological feature makes MO diagnosis certain, since malignant neoplasms as osteosarcomas usually have a disorderly growth with a "reverse zoning effect". However, in some cases, a biopsy from the central zone that represents the least organized portion can be histologically suggestive of malignancies, leading to incorrect diagnoses[17]. This is what happened in our case, with an intraoperative histological exam positive for osteosarcoma that led to a surgical excision. Immunohistochemistry is not strictly essential for a correct diagnosis, but it helps to differentiate MO from malignant lesions, especially in atypical cases. MO samples generally include a large number of osteoblasts, which are positive for the marker SATB2. On other hand, osteosarcomas may be characterized by MDM2 and CDK4 overexpression[18,19]. The surgical specimen of our patient demonstrated organized mature lamellar bone at the periphery of the lesion, with a great amount of SATB2 positive cells, thus confirming MO diagnosis.

The management of PTMO is controversial and depends on the severity of patient's symptoms. PTMO is generally self-limiting and lesions often decreases in volume within two years. For this reason, most patients can be treated conservatively with nonsteroidal anti-inflammatory drugs, acetic acid therapy, iontophoresis treatment, magnesium therapy, and etidronate disodium[20,21]. In case of severe and persistent symptoms, surgery is the definitive treatment even if it is associated with local recurrence [22,23]. Particularly, IMO tends to recur and, since this condition is clearly exacerbated by surgery, surgical procedures should be reserved for selected patient[11]. The highest risk of recurrence is reached when surgical excision is performed within 6 mo of previous trauma. Therefore, it is preferable to perform a surgical procedure at least six months after the trauma when the lesion is completely mature and ossified[24]. As discussed before, we decided to proceed with a surgical excision based on pre-operative and intra-operative data and the disease recurrence was dramatically extraordinary in term of growing time. To the best of our knowledge, such aggressive behavior was only described in the literature for genetic forms of MO[25] that usually present in the first decade of life and have a life

expectancy of forty years[26].

CONCLUSION

MO is an uncommon and benign condition that can develop in any part of the body. The diagnosis may be difficult even with multiple imaging modalities, especially when MO develops in atypical locations. Biopsy is the gold standard, but in some case it can be misleading. Surgical treatment should be reserved for symptomatic patients because of the risk of recurrence. The present case emphasizes the challenges and pitfalls a clinician has to face to ensure a correct diagnosis and an appropriate management of this disease.

FOOTNOTES

Author contributions: Carbone G and De Nardi P contributed to manuscript writing and editing, and data collection; Andreasi V contributed to data collection and conceptualization; all authors have read and approved the final manuscript.

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