World Journal of

Orthopedics

World Journal of *Orthopedics*

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

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2015-2018

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EDITORS FOR THIS ISSUE

EDITORIAL

Neuromuscular scoliosis and pelvic fixation in 2015: Where do we stand?

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Abstract

Neuromuscular scoliosis is a challenging problem to treat in a heterogeneous patient population. When the decision is made for surgery the surgeon must select a technique employed to correct the curve and achieve the goals of surgery, namely a straight spine over a level pelvis. Pre-operatively the surgeon must ask if pelvic fixation is worth the extra complications and infection risk it introduces to an already compromised host. Since the advent of posterior spinal fusion the technology used for instrumentation has changed drastically. However, many of the common problems seen with the unit rod decades ago we are still dealing with today with pedicle screw technology. Screw cut out, pseudoarthrosis, non-union, prominent hardware, wound complications, and infection are all possible complications when extending a spinal fusion construct to the pelvis in a neuromuscular scoliosis patient. Additionally, placing pelvic fixation in a neuromuscular patient results in extra blood loss, greater surgical time, more extensive dissection with creation of a deep dead space, and an incision that extends close to the rectum in patients who are commonly incontinent. Balancing the risk of placing pelvic fixation when the benefit, some may argue, is limited in non-ambulating patients is difficult when the literature is so mottled. Despite frequent advancements in technology issues with neuromuscular scoliosis remain the same and in the next 10 years we must do what we can to make safe neuromuscular spine surgery a reality.

Core tip: We review the historical timeline of posterior spinal fusion in neuromuscular scoliosis. Over 30 years of treatment technology to treat scoliosis has changed drastically, however, we are still not without significant post-operative complications. Questioning how we treat neuromuscular scoliosis will hopefully push our community to advance our thought processes on this

complex pathology and ultimately result in improved patient outcomes.

MANUSCRIPT

Neuromuscular scoliosis is a very challenging problem to treat in a heterogeneous patient population. Of the many aspects that make the treatment of this disorder difficult are the ethical issues surrounding subjecting a frail debilitated patient to a large procedure that we believe will improve their seating comfort, pulmonary function, and quality of life[1,2]. These benefits are weighed against the risks of infection, pseudarthrosis, medical complications, cost, and implant related complications[2-4]. The decision of whether or not to proceed with surgical care is often quite difficult for families, and extensive discussions are often required.

When the decision is made for surgery the surgeon must select a technique employed to correct the curve and achieve the goals of surgery, namely a straight spine over a level pelvis. There has been an evolution in implant design over the past few decades, and the traditional recommendation has been that the spinal instrumentation and fusion extend from the upper thoracic spine to the pelvis in non-ablulating patients. In the late 1970's Allen and Ferguson described the Luque-Galveston technique, in which the distal end of each spinal rod was contoured to insert into the posterior ilium, extending towards the superior acetabulum. Contouring the rod distally was often a challenge and could be time consuming, leading to the development of the unit rod, in which both rods are included in a single, precontoured construct including the distal limbs which insert into the pelvis[5]. Either of these constructs achieved correction through cantilever bending, as the rod was initially attached to the pelvis and then maneuvered towards the spine while sequentially tightening sublaminar wires (Figure 1A). A constant challenge has been achieving arthrodesis at the lumbosacral junction, and pseudarthrosis resulted in "windshield wipering" of the pelvic limbs of the rod[6].

The next change in implant design was the advent of iliac screws (Figure 1B) which could be linked to the spinal rods through a cross connector. This increase in modularity occurred at the same time many surgeons began using pedicle screws in their constructs. An example is the "M-W" technique described by Arlet *et al*[7]. The basic philosophy for curve correction remained the same, although pedicle screw instrumentation with or without posterior osteotomies gave the surgeon a

means to derotate the spine as a component of the corrective maneuver. The results in terms of control over pelvic obliquity seem to have been similar. Similar implant related complications have been observed with iliac bolts, namely failure at the connection point between the screw and the connector, or the rod and the connector, perhaps related to either pseudarthrosis or to the fact that the implants extend across a joint which is not fused (sacroiliac joint)[8].

In 2009, Chang *et al*[9] introduced the S2 alar iliac screw (Figure 1C), which can be directly linked to the spinal rod without a cross connector and without the wider exposure of the posterior ilium required to insert an iliac bolt or unit rod. Once again this modularity works well with constructs based on transpedicular fixation. The correction of pelvic obliquity with the S2 alar iliac screw is similar to that of the previous techniques.

Over the years we have learned from many "risk factors" studies that pelvic fixation itself is likely a risk factor for infection, which is one of the most dreaded (and common) complications of neuromuscular spine surgery[10]. The reasons for this may include extra blood loss, greater surgical time, more extensive dissection with creation of extra dead space, and an incision which extends closer to the rectum in patients who are commonly incontinent. This led McCall *et al*[11] to report on a series of patients using unit rod constructs with pedicle screws in the base ending at L5 in patients without severe pelvic obliquity (Figure 1D). This series showed similar control of curve parameters and pelvic obliquity as those fused across the lumbosacral joint. This series also demonstrated that the patients fixed to L5 had shorter operative times and fewer complications.

Although this approach in which the instrumentation and fusion are extended to the distal lumbar spine in patients without severe pelvic obliquity has not achieved wide acceptance to our knowledge, it certainly merits strong consideration, especially with an early diagnosis and adequate counseling of the family before the curves get to be severe and rigid. Is pelvic fixation really worth the extra complications and infection risk it introduces? While the literature mainly contains reports of radiographic outcomes and complications, there are no reports to our knowledge of patient or caregiver satisfaction with surgery or patient reported outcomes with any of the pelvic fixation techniques, let alone a report comparing the various methods.

The objectives of neuromuscular scoliosis surgery remain the same, to maintain adequate seating balance and prevent the complications associated with a progressive curvature. With more advanced techniques, our charge is to find a safer way to achieve this goal. While early diagnosis and treatment should certainly allow our constructs to end at L5, additional strategies including soft tissue release, posterior osteotomies, halopelvic traction, and VEPTR may be also used to achieve suitable correction to allow us to achieve this goal.

Figure 1 Anteroposterior view of the spine showing posterior spinal fusion constructs using the: unit rod (A), iliac bolts (B), S2 alar iliac screws(C), and a construct ending at L5 (D).

Despite numerous advancements in technology issues with neuromuscular scoliosis remain the same including: where does pelvic fixation fit in the treatment algorithm for neuromuscular scoliosis? We as a community should not shy away from questioning the dogma of fusing neuromuscular scoliosis patients to the pelvis as technology continues to change but complications persist without significant improvement in benefits. In the next 10 years we will answer these questions and more to make safe neuromuscular spine surgery a reality.

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EDITORIAL

Adiposity and spinal cord injury

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Abstract

The drastic changes in body composition following spinal cord injury (SCI) have been shown to play a significant role in cardiovascular and metabolic health. The pattern of storage and distribution of different types of adipose tissue may impact metabolic health variables similar to carbohydrate, lipid and bone metabolism. The use of magnetic resonance imaging provides insights on the interplay among different regional adipose tissue compartments and their role in developing chronic diseases. Regional adipose tissue can be either distributed centrally or peripherally into subcutaneous and ectopic sites. The primary ectopic adipose tissue sites are visceral, intramuscular and bone marrow. Dysfunction in the central nervous system following SCI impacts the pattern of distribution of adiposity especially between tetraplegia and paraplegia. The current editorial is focused primarily on introducing different types of adipose tissue and establishing scientific basis to develop appropriate dietary, rehabilitation or pharmaceutical interventions to manage the negative consequences of increasing adiposity after SCI. We have also summarized the clinical implications and future recommendations relevant to study adiposity after SCI.

Key words: Adiposity; Magnetic resonance imaging; Dual-energy X-ray absorptiometry; Ectopic adiposity; Visceral and subcutaneous adiposity; Intramuscular fat; Spinal cord injury

Core tip: The focus of this current editorial is to introduce different adipose tissue types that may impose

significant health risks to individuals with spinal cord injury (SCI). Accurate measuring of this depot of ectopic adipose tissue may require special knowledge; however, it is important considering the dramatic changes in body composition and the extensive loss in skeletal muscle tissue below the level of injury. The clinical implications of studying adipose tissue may encourage further research to decipher the mechanistic links with the metabolic profile after SCI. Our current knowledge is limited and rehabilitation strategies are still pre-mature in targeting ectopic adiposity after SCI.

INTRODUCTION

Adipose tissue is one of the main types of connective tissue in the body and is the storage site of triglycerides. It is not only served as an energy reservoir, but it has been recently considered as the largest endocrine gland in the body[1,2]. The endocrine properties are related to the secretion of regulatory proteins similar to leptin, cytokines and adiponectin that are likely to influence whole body metabolism, energy intake as well as insulin sensitivity[2]. Inflammatory biomarker factors similar to interlukin 6, tumor necrosis factor alpha and C-reactive proteins which are likely to interact with various systems can trigger insulin resistance[2,3]. The inflammatory nature of adipose tissue has been linked to other comorbidities similar to type 2 diabetes mellitus, cancer and cardiovascular disease. Additionally, adipose tissues secrete number of active peptides called adipokines[3].

Interest in studying adipose tissue physiology and anatomical distribution has stemmed from its closest association with disturbance in metabolic profile including carbohydrate, lipid, and bone metabolism[3-7]. Most recently the link between adipose tissue and bone health has been recognized after spinal cord injury (SCI)[7]. This link may contribute to our understanding of different pathways that lead to the development of obesity and osteoporosis. Moreover, the role of exercise in adipose tissue utilization as a primary source of fuel is an active area of continuous research investigation[8-11]. Excessive adipose tissue accumulation imposes significant health risks to populations with physical disability leading to poor quality of life and short life-span. Imbalance between energy intake and energy expenditure may lead to excessive adipose tissue accumulation, a phenomenon which is referred to as obesity[12]. Obesity is further complicated by other factors similar to physical activity, genetic, socio-economical and educational factors. According to a survey conducted by the Center for Disease Control,

more than one-third (34.9%) of adults in the United States are considered obese[13].

SCI is a medical condition resulting from direct or indirect aggravation or insult to the neural pathway located in the vertebral column. The disruption in the efferent and afferent neural transmission between the cortex and the periphery leads to the paralysis of skeletal and smooth muscles as well as somatosensory loss of pain, touch and temperature sensation below the level of injury. A person with SCI is considered to be on the lowest end of the spectrum of physical activity as determined by the lowest oxygen uptake during peak exercise activity[14]. The low level of physical activity, significant muscle loss with changes in regional and total body composition, dysfunction in the autonomic nervous system and diminished anabolic hormones are a typical phenotype profile for a person with SCI[4,15,16].

The significant loss in lean mass within the first year of injury is accompanied with continuous increase in adipose tissue accumulation representing significant health risks after SCI[17]. Time since injury is strongly associated with a greater loss of lean tissue after SCI[17]. A strong effect of time since injury was identified in the legs and total body of monozygotic twins with paraplegia compared to their non-disabled (ND) co-twins, thereby eliminating age and genetic factors, essentially isolates the effect of SCI[18].

The purpose of this editorial is to introduce different types of adipose tissue distribution and their link to health consequences after SCI[19-22]. Considering the role of adipose tissue in the metabolic health variables after SCI, we sought to summarize the available evidence on different forms of adipose tissue. We highlighted the basic findings relevant to ectopic adipose tissue [visceral fat (VAT), intramuscular fat (IMF) and bone marrow fat (BMF)] in persons with SCI and the technical procedures regarding the use of magnetic resonance imaging (MRI) in measuring ectopic adipose tissue[19,22]. The difference in terminology between intermuscular (IeMF) and IMF was addressed as well as the significance of measuring visceral and bone marrow adiposity (Figures 1 and 2).

Finally, the clinical implications and future directions of measuring different types of adipose tissue and cardio-metabolic health were acknowledged. We have also realized the significance of exercise and dietary interventions in addressing the complications of reduction in level of physical activity after SCI. Encouragement to expand leisure time physical activity may help to counteract reduced level of energy expenditure and balanced their daily caloric intake.

For this editorial, we would like to distinguish between the terms "obesity" and "adiposity" relevant to the SCI population. Obesity is simply a metabolic disorder resulted from an imbalance between energy intake and expenditure. Obesity is simply defined using body mass index (BMI), waist and abdominal circumferences. These anthropometric criteria have

Figure 1 Histogram analysis of the whole thigh region representing both muscle (left) and fat (right) peaks as well as the mid-point signal intensity that is used a cut-off point to separate between muscle or inter-intra-muscular fat pixels.

Figure 2 A representative transaxial magnetic resonance imaging of the mid-thigh of a T4 individual with complete spinal cord injury representing different region of interests. Note the white adipose tissue infiltrated between individual muscle groups IMF as well as the white adipose tissue infiltrated within individual muscle IMF. We have collectively referred to both of them as IMF. Also note the HO extended from the bone marrow. [1]Three vasti muscles (m); [2]Vastus intermedius (m); [3]Image background; [4]Hamstrings (m); [5]Gracilis (m); [6]Sartorius (m); [7]Adductors (m); [8]Vastus lateralis (m); [9]Rectus femoris (m); [10]Cortical bone and bone marrow. IMF: Interamuscular fat; HO: Heterotrophic ossification.

not been well validated in the field of body composition and SCI, with a considerable debate about its efficacy in identifying those at risks of developing cardio-metabolic complications. It is well established that BMI underestimates the percentage fat mass (FM) in persons with SCI, with a continuous effort to develop a population specific BMI criteria[17]. The term adiposity refers to infiltration or storage of adipose tissue in subcutaneous or ectopic sites due to inactivity, disruption in hormonal secretion, altered body composition and poor nutritional choices after SCI. Studying whole and regional adiposity may need specialized body composition assessment techniques to accurately quantify adiposity after SCI. Although the prevalence of obesity may easily exceed two-thirds of the SCI population[23]; we believe that that the SCI population suffers from excessive adiposity that exceeds 30% of the whole body mass[6,17]. This may be true in 50% of the SCI population despite having normal BMI, which leads to significant metabolic and health implications[6].

TYPES OF ADIPOSE TISSUE

Advances in imaging technology similar to the use of MRI, ultrasound and dual-energy X-ray absorptiometry (DXA) facilitate the study of the distribution of regional adiposity[19-22]. DXA scans are commonly used in the clinical settings to measure total, regional body composition and bone mineral density or content. However, DXA is limited in distinguishing between subcutaneous adipose tissue (SAT) and ectopic adipose tissue[6]. The anatomy and distribution of adipose tissue is of particular interest to the metabolic health after SCI[5-7,16]. Triglycerides can be either stored in subcutaneous or ectopic sites similar to the peritoneum, visceral adipose tissue (VAT), in the liver (steatosis), in the muscle such as IMF or IeMF and in the bone marrow as BMF. The mechanisms by which triglycerides are stored in subcutaneous or ectopic sites are poorly understood; however, it is linked to genetic and lifestyle factors. Adopting an active lifestyle including routine exercise

is likely to reduce ectopic adipose tissue storage in the general population as well as in persons with SCI[9,10]. This is also accompanied with mitigating the negative consequences of ectopic adipose tissues on the metabolic profile. The role of exercise on SAT is still questionable[9].

Compared with non-disabled (ND) individuals, Spungen *et al*[17] showed that the individuals with SCI were 13% fatter per unit of BMI (kg/m^2). Moreover, the total body fat was 10% greater in the group with tetraplegia and 12% greater in the group with paraplegia compared to ND individuals. Also, percent FM in the arms of tetraplegics was 8% greater than individuals with paraplegia[17]. Persons with SCI are likely to have more than 30% FM of the total body mass; that are stored at the central or peripheral site[23]. The central distribution of adipose tissue may represent up to 25% of total body FM[22]. Gorgey and Gater[6] have highlighted the significance of studying regional and relative adiposity and their associations to metabolic health variables after SCI.

Central adipose tissue

The central adipose tissue refers to quantifying trunk FM which can further be sub-divided into SAT and VAT. In analyzing VAT and SAT volumes, our laboratory has taken advantage of analyzing multiple axial slices acquired during MRI. We have previously shown that using a single axial slice may inaccurately reflect the true volumetric distribution of VAT and SAT[22]. After measuring the CSA of series of axial images, the volume of VAT or SAT can be calculated by summing up all the measured areas. The volume (cm^3) is calculated using the following equation = ($A_1 d_{1-2} + A_2 d_{2-3} + A_3 d_{3-4} .... A_n d_{n-n+1}$) after considering the thickness of the slice. The "A" letter refers to the CSA of a single axial image and "d" refers to the distance (cm) of inter-space

Figure 3 A representative magnetic resonance imaging analysis of subcutaneous and visceral adipose tissues in a person with spinal cord injury. Note the tracing of visceral adipose tissue within the region of interest. The numbers 1, 2, 3 and 4 refer to the visceral fat (VAT) cross-sectional areas of disconnected regions. These 4 regions are later summed to have the total VAT area in the entire region. VAT: Visceral adipose tissue.

between two corresponding axial images.

SAT: SAT is layered superficial to the outer muscular wall of the abdominal region and skeletal muscle, and immediately below the dermal layer of the skin[5,22]. Abdominal SAT is superficial to the abdominal and back muscles and lies beneath the hypodermis. SAT is measured by tracing the outer edge of the abdominal region (hypodermis) and along the outermost point of the muscular abdominal wall. The area in between these two traces will be considered the cross-sectional area (CSA) in cm^2 of this slice (Figure 3).

The level of injury strongly determines the severity of SCI as well as the associated changes in body composition. Individuals with tetraplegia population have a greater leg FM/trunk FM (45%) and leg FM/body FM (26%) and lower trunk FM/body FM (29%) ratios than individual with paraplegia[6]. This may suggest that persons with tetraplegia have the tendency to accumulate greater leg FM compared to those with paraplegia. Surprisingly, persons with tetraplegia have a lower ratio of trunk FM to whole body FM compared to persons with SCI[6]. These findings were confirmed when MRI was used to separate trunk VAT from SAT. The SAT CSA was non-significantly greater in persons with paraplegia compared to tetraplegia[24]. The hyperactivity of sympatho-adrenergic peripheral innervation to SAT may be responsible for the lower trunk adipose tissue in persons with tetraplegia and may explain the tight association that was documented between SAT CSA and lipid profile[24,25].

VAT: VAT is defined as intra-abdominal fat bound by parietal peritoneum or transversalis fascia, excluding the vertebral column and paraspinal muscles[5,22]. VAT may extend from the xyphoid process of the sternum to both greater trochanters of the femoral bones. VAT is measured by tracing out the innermost muscles of the abdominal cavity and the other abdominal organs present in a single slice. The area is quantified in cm^2 which shows the amount of VAT present within the abdominal organs.

It is important to be meticulous and not trace over any fat tissue as it will yield inaccurate results. Increase in VAT accumulation has been identified as an independent risk factor of developing cardiovascular disease, insulin resistance and mortality[26]. This is mainly because of the close proximity of the VAT to the portal circulation. Further analysis using MRI showed that about 6% of whole body FM is VAT and 10% is SAT[22]. Persons with SCI have 58% and 48% greater VAT CSA and VAT/SAT CSA compared to ND controls[27]. It is apparent that VAT and increase VAT/SAT ratio are likely to have detrimental effects on the metabolic profile after SCI[5].

The pattern of VAT distribution may vary greatly among individuals with SCI. It is likely to be impacted by the level of injury and the de-innervation of the anterior abdominal muscles[24]. Further analysis based on the level of the injury did not reveal major differences in VAT between persons with paraplegia and tetraplegia[24]. However, the sample size was limited and future studies need to consider large sample size to study the differences in central adiposity based on the level of injury.

There are several points that need to be considered when using MRI to measure central adiposity in persons with SCI including the type of the injury, date of the injury, spinal fusion, and ability of the persons to hold his or her breath. All of these factors may influence the quality of the scan and may interfere with the ability of the examiner to accurately analyze the images[5,22,24]. For example, a gunshot wound may lead to bullet fragments in the spinal canal that will be of high risk to be exposed to a magnetic field. This bullet fragments may accidently move and lead to further damage to the intact cord or the surrounding blood supplies. A person with high level of injury, similar to C5, may lack the ability to hold his breath for 20-22 s to capture the whole trunk region. This may require the examiner to break the whole scan into multiple scans to allow short breath holding time that does not exceed 10 s. Other limitations may include the exact positioning of the

participant inside the magnet mainly because of pelvic or trunk obliquity or uncontrolled spasticity that may be triggered before or during the scans and require special handling from positioning and stabilizing lower extremities, this is specifically important to accurately match the pre and post-MRI images in a longitudinal study.

The scans are captured from the xyphoid process to both greater trochanters. It becomes apparent that using a flexible trunk coil compared to the whole body magnet improves the quality and resolution of the captured images as well as higher signal to noise ratio. It is highly recommended that multiple axial images are sequenced to ensure the appropriate anatomical organization before the analysis. This is a crucial step before measuring the volume of the SAT or VAT. Different software programs may be available allowing appropriate segmentation of VAT and SAT in a single axial slice to measure the CSA without including other visceral regions similar to the intestines or the blood vessels in the region of interest.

Studying SAT and VAT distribution have revealed two body composition phenotypes[5,6]. The first phenotype is likely to store adipose tissue in subcutaneous compared to visceral sites and this phenotype may protect against developing metabolic disorders. The second phenotype has a greater tendency to store adipose tissue in visceral sites with the tendency to develop insulin resistance, dyslipidemia and other metabolic disorders. The exact mechanisms behind these two phenotypes have yet to be deciphered. Anecdotal evidence from our laboratory suggests that gender may play a definite role in the distribution of VAT and SAT after SCI. Women with SCI have greater SAT and smaller VAT CSAs than men with SCI (Gorgey *et al* unpublished results). This may shed the light on the significance of studying hormonal differences and adiposity after SCI.

Peripheral adipose tissue

The peripheral distribution may vary between arms and legs. Legs are likely to have on average 34%-38% of the whole body FM[6,17]. The increase storage of adipose tissue is primarily accompanied with process of lower-extremity disuse, skeletal muscle atrophy and autonomic nervous system dysfunction[16]. This will eventually contribute to infiltration and accumulation of adipose tissue in non-subcutaneous sites (muscle and bone). This ectopic accumulation of adipose tissue leads to serious metabolic consequences after SCI. The use of MRI manages to segment and compartmentalize adipose tissue based on its high signal intensity from the atrophic skeletal muscles, allowing accurate quantification of muscle size in response to disuse and exercise[9,10,16]. In our laboratory (Figures 1 and 2), we have managed to distinguish between IMF, IeMF, subfacial and SAT accumulation in persons with SCI[9,10].

The storage of triglycerides in ectopic locations is linked with chronic inflammation, impaired glucose tolerance, increased total cholesterol, and decreased strength and mobility[1,2]. There is growing interest in studying different peripheral adipose tissue compartments to determine its link to metabolic profile after SCI[6,26]. Moreover, there is anecdotal evidence supporting the notion that nutritional status and dietary habits may influence these compartments; because persons with SCI are likely to consume high fat diet, which is close to 40% of the total caloric intake[9,28].

IMF *vs* IeMF: Previous studies have focused on the metabolic impact of intramyocellular lipid (IMCL) content (*i.e.*, lipid droplets stored in the cytoplasm of muscle cells) and extramyocellular lipid (EMCL) content, which can reliably be assessed by proton magnetic resonance spectroscopy (1 H-MRS). The deposition of IMCL could be altered in prediabetic or obese subjects, and could probably be associated with insulin resistance[29,30]. A study that compared persons with paraplegia to ND controls showed that IMCL was not different in the paralyzed muscles. However, the study noted greater EMCL in the paraplegic muscles, which was negatively associated with insulin sensitivity. The same study noted a 57% lower succinate dehydrogenase activity in person with SCI compared to controls[29].

The definition of IMF refers to infiltration of adipose tissue within individual muscle. It is measured by determining the attenuation property of computerized tomography (CT) or the signal intensity of MRI[31,32]. The storage of IMF is dramatically elevated after SCI and it is closely linked to other fat compartments, especially to VAT (Figures 2 and 3). It seems that IMF and VAT share an analogous pattern in distribution and association with insulin sensitivity[5,26,27,31,32]. Using MRI, Gorgey and Dudley[16] showed that IMF was 126% greater in persons with incomplete SCI compared to the matched ND controls. IMF CSA continued to increase in the 3-mo follow-up MRI scan[16]. Elder *et al*[31] reported that IMF and skeletal muscle atrophy in the thigh accounted for 70% of glucose intolerance after SCI. The same study noted that IMF and subfacial fat appeared to be increased in chronic individuals with SCI when compared to ND controls[31]. It is interesting to note that unlike SAT, IMF decreases in response to spasticity and exercise activity similar to resistance training[9,33].

Although IMF is likely to be visualized, it is nearly impossible to be traced in order to be quantified. IeMF refers to fatty infiltration of adipose tissue between individual muscle groups[30]. This fatty infiltration is highly accumulated in the posterior compartment of the thigh and visually can be traced or separated based on its high signal intensity (Figure 2). A controversial area of debate is whether MRI can be used to quantify IMF. The histographic analysis has helped differentiating between IeMF and IMF infiltration (Figure 1).

Reliance on histographic analysis can help distinguish between muscle from fat voxels (*i.e.*, the volume of a pixel). This histographic analysis allows previous

quantification of IMF in individuals' thigh muscles. We have previously felt more comfortable referring to adipose tissue as IMF and not IeMF because it composed both the fat infiltrated within the muscle as well as the fat infiltrated between individual muscles. This may further shed the light on the significance of separating IMF from IeMF accumulation and the associated links with metabolic consequences after SCI.

The histogram (pixel number versus signal intensity) produced from analysis of the whole thigh (muscle, fat and bone) showed two distinct muscle and fat peaks based on the variations in the signal intensity to the magnetic field[9,10,16,33]. The ranges and values for these peaks differ from individual to individual. The left peak was distinct, thin, and representing skeletal muscle area. This is due to the lower signal intensity that skeletal muscle is represented through MRI. The higher signal intensity peak is on the right side and representing the fat peak (Figure 1).

There is a greater infiltration of IMF most notably in the areas of the quadriceps, hamstrings, and adductor muscles. After determining the cut-off point between muscle and fat based on the signal intensity, the percentage of IMF within each individual muscle can be accurately measured. A crucial point that needs to be considered is measuring muscle size after accounting for IMF percentage. Failure to separate IMF from the measured muscle CSA overestimates the actual skeletal muscle size. For example, measuring the muscle CSA of the three vasti equated to 29.34 cm^2. After applying the muscle-fat cut off technique, the percentage IMF was 26.25% with an area of 7.702 cm^2. This means that failure to account for IMF overestimated muscle size by more than 26%. The accumulation of IMF within muscle has been previously considered in measuring muscle size in individuals with SCI[9,10,16,33].

From the rehabilitation point of view, IMF may impede the progression of the current in the exercising muscles during neuromuscular electrical stimulation[34]. This may result in an unnecessary increase of the amplitude of the current of neuromuscular electrical stimulation and lead to rapid muscle fatigue of the paralyzed muscles.

Bone marrow adipose tissue: The relationship between the alarming prevalence of obesity and osteoporosis is considered an area of a growing research interest. It is unclear whether there is a common origin from where excessive adiposity and continuous loss in bone mass originates after SCI. The mesenchymal progenitor stem cells (MSC) can be differentiated based on the mechanical stimulus applied into either bone and muscle cells or adipose tissue[35-37]. This differentiation may be very important in providing the appropriate mechanical stimulus necessary for the development of muscle and bone tissue compared to adipose tissues after SCI. Our initial observation showed that persons with motor complete SCI had 2-3 times bone marrow adipose tissue compared to matched able-bodied controls; primarily because of unloading on lower extremities[7]. This is accompanied with 1.5-2 times lower cortical bone CSA in persons with SCI compared to able-bodied controls[7]. Moreover, the bone marrow adipose tissue was inversely related to the bone mineral density and bone mineral content as measured by DXA. This preliminary evidence suggests that there is inverse relationship between increasing bone marrow adiposity and both cortical bone as well as bone mineral density[7]. This may suggest that MSC need to be considered as a therapeutic anatomical target for future interventions to cease the progress in adiposity and osteoporosis after SCI.

Anecdotal evidence based on recent imaging analysis showed that MSC differentiation into bone marrow adiposity can leak outside and contribute to the development of intermuscular adipose tissue or IMF infiltration in the atrophic skeletal muscle. In Figure 3, we have traced an abnormal growth of heterotrophic ossification (HO) within the thigh region. It is clear that this HO has been developed as a leakage from the bone marrow region. This abnormal bone growth within the skeletal muscle has a signal intensity that it is closely related to the signal intensity of the yellow bone marrow and lower than that of adipose tissue. This may speculatively suggest that HO development started as an abnormal fatty infiltration from that yellow marrow followed by calcium deposition in this region.

White vs brown adipose tissue
It has been discovered that humans contain both white and brown adipose tissue which possess two distinct developmental origins and functions[38-42]. The brown adipose tissue has yet to be studied in humans with SCI; however, its potential contribution to increase the metabolic rate is important considering the prevalence of obesity after SCI.

White adipose tissue: White adipose tissue takes on a critical role in maintaining energy homeostasis throughout the entire body. Homeostasis is maintained by storing triglycerides when energy is in surplus, releasing fatty acids as fuel during energy storage, and secreting adipokines which regulate glucose and lipid metabolism[2,38]. Recent studies indicate that white adipose tissue serves as an active endocrine organ which secretes numerous hormones, cytokines, and chemokines that are essential for regulating energy homeostasis in the body[2]. Two specific hormones released by white adipose tissue are leptin and adiponectin. Leptin is positively associated with white adipose tissue and serves to suppress food intake and increase energy expenditure[2]. The hormone adiponectin is inversely correlated with white adipose tissue and has been considered a promising biomarker for the indication of insulin sensitivity[2,39]. In addition to these secreting hormones, white adipose tissue can

also secrete proinflammatory factors including tumor necrosis factor alpha, interleukin-6, and monocyte chemotactic protein-1[2]. The various adipose tissue compartments, such as subcutaneous and visceral depots follow a distinct pattern of hormone and adipokine secretion[39]. The adipocytes in subcutaneous depots have a higher capacity for adipogenesis and differentiate more rapidly compared to visceral depots. White adipose tissue in the visceral abdominal region has been shown to increase insulin resistance, thereby, it is less harmful to store white adipose tissue in subcutaneous compartment compared to the visceral region[38].

Brown adipose tissue: Brown adipose tissue contains lipid droplets and is rich in mitochondria[40-42]. The thermogenetic adipocytes increase energy expenditure through the uncoupling of oxidative metabolism from ATP production[41]. Thermogenesis of the brown adipose tissue is stimulated by the the sympathetic nerve terminals in the extensive vascular and nerve supply. Uncoupled thermogenesis is highly active metabolically and predominately utilizes lipid as fuel, but may also take up glucose as well[41,42]. Activation of brown adipose tissue has anti-obesity as well as glucose- and lipid-lowering effects.

Stimulation of the sympathetic nervous system below the level of SCI is impaired in this population. Therefore, the activation of brown adipose tissue in SCI may be limited. In response to exercise, the sympathetic nervous system in able-bodied individuals releases epinephrine to initiate the process of lipolysis as a source of fuel in cellular respiration[42]. In the SCI population, this process is altered and it is thought that muscle hypertrophy may trigger lipolysis instead of epinephrine release[9,10].

Uncoupling protein in brite adipose tissue: The phenomenon known as the "browning" effect occurs when white adipose tissue begins to accumulate the uncoupling protein (UCP 1) that characterizes brown adipose tissue. This transformed white adipose tissue is referred to as brite/beige adipose tissue[41,42]. Although it possesses the UCP 1 which essentially mediates adaptive thermogenesis, it is unclear as to how effective the mitochondria with UCP 1 in beige adipose tissue are in performing thermogenesis[41,42]. This is especially significant in the medical field as a further understanding of this phenomenon could lead to new therapeutic strategies for obesity, diabetes, and other metabolic disorders. Due to the lack of sympathetic nervous system in SCI and decrease in energy expenditure, finding a therapeutic approach of transforming adipose tissue into thermogenetic cells may allow SCI individuals to decrease adipose tissue accumulation.

Pharmaceutical techniques which may activate the UCP 1 in beige adipose tissue may cause significant declines in white adipose tissue, further benefiting the metabolic profile and body composition after SCI.

SIGNIFICANCE AND FUTURE IMPLICATIONS

The rapid loss in muscle mass following SCI leads to serious metabolic consequences similar to extensive decline in basal metabolic rate (BMR), insulin resistance and impaired glucose tolerance. The evidence suggests that there is up to 22%-40% decline BMR in persons with SCI based on their level of injury and about 50%-75% suffer from impaired glucose tolerance or type Ⅱ diabetes mellitus[43,44]. Dyslipidemia, as manifested by decreased level of circulating high density lipoprotein-cholesterol and increased levels of triglycerides and low density lipoprotein-cholesterol, contributes to an accelerating atheorgenic process to the cardiovascular system after SCI[4,45]. The economic impact and burden of these comorbidities may be of paramount significance to study the regional and ectopic adipose tissue changes after SCI.

The disruption in the energy balance process predisposes these individuals to become fat building machines with a fat storage capacity that exceeds more than 30% of their total body mass[23]. There are also substantial shifts in substrate utilization from reliance on fat as a source of energy to the exercised muscles to be dependent on the short-term energy supply of the glycogen storage. This is primarily impacted by the transformation of slow oxidative to fast fatigable muscle fibers[46]. Talmadge *et al*[46] estimated that by 24 wk, the vastus lateralis, gastrocnemius, and soleus muscles, approximately 90% of muscle fibers, are fast twitch fibers compared to 6 wk at baseline. The process typically manifests between 4 and 7 mo post-injury and can continue up to 70 mo post-injury before plateauing into a steady state of predominantly type IIx, fast-glycolytic twitch muscle fibers[46]. This transformation renders the skeletal muscle to be highly fatigable and susceptible to skeletal muscle damage after exercise.

Disruption in the process of lipolysis as a result of injury to the sympathetic chain may be another important factor that needs to be considered[25]. An acute bout of functional electrical stimulation cycling has failed to increase delivery of the circulating fatty acids to the exercised muscles[11]. We have shown that 12 wk of evoked resistance training using neuromuscular electrical stimulation and ankle weights resulted in decrease of IMF and VAT without changing SAT[9].

We should acknowledge that persons with SCI consume close to 40% of their dietary intake as fat; which is likely to be a major source of the continuous and longitudinal changes in body FM[9,28]. This is accompanied with low consumption (less than 20%) of dietary protein intake[9,47]. Dietary intake can be manipulated to enable more effective utilization of macronutrients[47]. The American diet is especially prone to consume

excessive carbohydrates and fats which alter blood glucose levels and increase adipose tissue if not expended. Individuals generally consume a high-fat diet that may further disrupt their metabolism. Therefore, dietary intake is equally important as an exercise after SCI. Dietary habits can be more easily manipulated and controlled than exercise intervention due to various existing exercise barriers in the SCI population[48].

Administering of pharmaceutical interventions similar to testosterone replacement may be another vehicle that can be utilized to overcome that reduced anabolic level after SCI. Using DXA to measure body composition, Bauman *et al*[49] did not observe changes in whole body and regional body FM after administration of 1 year (5-10 mg) of Testosterone replacement in hypogonadal men with chronic SCI. The study noted signifcant increase in lean mass and resting energy expenditure[49]. It is yet to be studied the long-term effects testosterone administration on ectopic adipose tissue sites and the interaction with exercise after SCI.

Individuals with SCI are limited in their physical activity to the muscle mass above the level of injury. According to guidelines generated by an expert panel, adults with SCI should engage in at least 20 min of aerobic exercise training twice weekly prescribed at moderate-vigorous intensity or 3 sets of 8-10 repetitions of resistance training to the major muscle groups[50].

Once weekly of exercise training in SCI has also shown to maintain overall body composition, combating the otherwise inevitable increase in adipose tissue characterized by this disease. Our research found that once weekly of upper extremity circuit resistance training or neuromuscular electrical stimulation did not impact body FM after SCI[51,52]. Limited transportation interferes with accessing clinical settings; home-based training may be possible to allow for training programs especially with advancing in tele-health communication similar to the video conferencing.

CONCLUSION

Different adipose tissue compartments have been highlighted in the current review. Their full contribution to the metabolic health after SCI is not fully understood. The use of sophisticated imaging techniques allow to distinguish these compartments and to quantify their changes in response to SCI and training. Different rehabilitation interventions similar to exercise, electrical stimulation, bionic suits, dietary and pharmaceutical interventions may be available; however, their effects on subcutaneous and ectopic adipose tissues are yet to be studied and their effects may be attenuated by the disruption of autonomic nervous system and limited access to these rehabilitation interventions. Strategies targeted towards skeletal muscle hypertrophy and gain in lean mass are likely to improve the basal energy expenditure, reduce adipose tissue stacking and improve metabolic profile after SCI. Therefore,

individuals with SCI may require a very personalized treatment plan in a multidisciplinary approach to prevent the excessive gain of adipose tissue and loss of lean muscle mass. This interdisciplinary approach is most beneficial and may be of great benefit in attenuating the changes in whole and regional body composition after SCI.

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Aetiology and mechanisms of injury in medial tibial stress syndrome: Current and future developments

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Abstract

Medial tibial stress syndrome (MTSS) is a debilitating overuse injury of the tibia sustained by individuals who perform recurrent impact exercise such as athletes and military recruits. Characterised by diffuse tibial anteromedial or posteromedial surface subcutaneous periostitis, in most cases it is also an injury involving underlying cortical bone microtrauma, although it is not clear if the soft tissue or cortical bone reaction occurs first. Nuclear bone scans and magnetic resonance imaging (MRI) can both be used for the diagnosis of MTSS, but the patient's history and clinical symptoms need to be considered in conjunction with the imaging findings for a correct interpretation of the results, as both imaging modalities have demonstrated positive findings in the absence of injury. However, MRI is rapidly becoming the preferred imaging modality for the diagnosis of bone stress injuries. It can also be used for the early diagnosis of MTSS, as the developing periosteal oedema can be identified. Retrospective studies have demonstrated that MTSS patients have lower bone mineral density (BMD) at the injury site than exercising controls, and preliminary data indicates the BMD is lower in MTSS subjects than tibial stress fracture (TSF) subjects. The values of a number of tibial geometric parameters such as cross-sectional area and section modulus are also lower in MTSS subjects than exercising controls, but not as low as the values in TSF subjects. Thus, the balance between BMD and cortical bone geometry may predict an individual's likelihood of developing MTSS. However, prospective longitudinal studies are needed to determine how these factors alter during the development of the injury and to find the detailed structural cause, which is still unknown. Finite element analysis has recently been used to examine the mechanisms involved in tibial stress injuries and offer a promising future tool to understand the mechanisms involved in MTSS. Contemporary accurate diagnosis of either MTSS or a TSF includes a thorough clinical examination to identify signs of bone stress injury and to exclude other pathologies. This should be followed by an MRI study of the whole tibia. The cause of the injury should be established and addressed in order to

facilitate healing and prevent future re-occurrence.

Core tip: Medial tibial stress syndrome (MTSS) is an overuse injury characterised by diffuse tibial antero-medial or posteromedial surface subcutaneous periostitis, usually in conjunction with underlying cortical bone microtrauma. Nuclear bone scans or magnetic resonance imaging findings need to be considered in conjunction with clinical symptoms and patient history for an accurate diagnosis. Compared to exercising controls, MTSS patients have low bone mineral density and low values of a number of tibial cortical bone geometric parameters such a cross-sectional area. Recent research includes the development of computational models for studying tibial stress injuries. These models offer a tool to study the exact causes of MTSS, which are still unknown.

BACKGROUND

Medial tibial stress syndrome (MTSS) is a debilitating overuse injury of the tibia sustained by individuals who perform recurrent impact exercise such as athletes and military recruits. It is characterised by diffuse tibial anteromedial or posteromedial surface subcutaneous periostitis, most often on the medial border near the junction of the mid and distal thirds of the tibia[1]. Although the injury was identified in runners as early as 1913, when it was termed "spike soreness", it was believed to be a type of tibial stress fracture (TSF) rather than a separate entity[2].

Devas[3] (1958) was one of the first physicians to study "shin soreness" in athletes, although like earlier researchers, he believed it to be a type of TSF. Using both clinical observations and plane radiographs, Devas described shin soreness as "a type of stress fracture involving a disruption of the periosteum over a varying distance". He noted there was tibial tenderness, soft tissue "thickening" of the subcutaneous surface of the tibia and periosteal oedema, with radiological changes either late onset, or not visible at all. In 1966, after soliciting the views of a large number of physicians and other individuals involved in sports medicine, "shin splints" was defined by the American Medical Association

as "pain and discomfort in leg from repetitive running on hard surface or forcible excessive use of foot flexors; diagnosis should be limited to musculotendinous inflammations, excluding fatigue fracture or ischemic disorder"[4]. The following year, Slocum[5] presented a detailed review of the injury, highlighting the fact that shin splints was a specific syndrome with its own clinical symptoms and aetiology.

In the late 1960s and during the 1970s, advancements in nuclear medicine techniques led to the development of Triple Phase Bone Scintigraphy (TPBS), or nuclear bone scans, as a diagnostic tool. The technique enables inflammation and increased bone metabolism to be visualised after injection of a radioisotope and could be used in conjunction with a clinical diagnosis for positive identification of MTSS, or shin splint syndrome as it was then still called. However, despite these advances, the term "shin splints" was still being used as a generic expression for general pain in the tibia and for various lower limb injuries such as compartment syndrome. For this reason, the term "MTSS" was coined in the early 1980s[6] and was subsequently adopted by nuclear medicine experts[7,8] as well as some researchers and clinicians.

In the 1980s, a number of nuclear medicine studies led to more specific diagnostic criteria for MTSS. This included identifying the appearance of MTSS on nuclear bone scans, which consisted of an elongated uptake of radionuclide, visually seen as a "double stripe" pattern, differing from the localised fusiform pattern characteristic of a TSF[7-10]. This was later followed by studies where tibial stress injuries were identified and classified using magnetic resonance imaging (MRI), which has the advantage of depicting periosteal and bone marrow oedema[11,12]. However, despite these studies and more recent research into the aetiology of the injury, MTSS, but more commonly the term "shin splints", is sometimes still used as a generic expression for tibial pain; however, this is gradually changing as the mechanisms of the injury are further understood.

CORTICAL BONE FATIGUE IN MTSS

MTSS was initially believed to be an anteromedial and/or posteromedial subcutaneous soft tissue injury only with an associated periostitis; a reasonable assumption given that no fracture or microfractures could be visualised on plane radiographs or computed tomography (CT) images. This is unlike a TSF, where a small partial cortical bone fracture can sometimes be identified at the site of pain and oedema, occasionally on a radiograph but more readily on CT, depending on the views imaged. However, it is now known that MTSS involves cortical bone microfractures associated with the periostitis, if not in all cases, then certainly in the majority of cases.

Johnell *et al*[13] first demonstrated microtrauma was a cause of MTSS from bone biopsies obtained from chronic MTSS patients undergoing fasciotomy after failing to respond to conservative treatment, and

bone biopsies from control subjects at autopsy or who were undergoing surgery for other injuries. They found MTSS patients had increased osteoblastic activity and vascular ingrowth along with the inflammatory changes to the soft tissue, while none of the non-injured controls demonstrated these changes. As the majority, but not all, MTSS patients had bone changes on biopsy (22 of 35 patients), the authors concluded MTSS was caused by microfractures in most, but not in all cases[13]. Although a limitation of this study was the bone biopsies were all extracted from the same region, the medial surface of the tibia, which may not have been the exact injury site in some patients so some of the bone changes may have been missed, it clearly demonstrated that microtrauma was a cause of MTSS.

Bone fatigue was examined in a number of studies published in the 1970s and 1980s; although this research was not for the specific purpose of understanding MTSS aetiology, it provided critical insights on how microcracks develop in cortical bone. Carter, Caler, Hayes and others performed a series of investigations on cortical bone samples which were tested under cyclic loading in order to understand the biological mechanisms of fatigue failure in cortical bone.

Using bovine femora cortical bone specimens under fully reversed loading (cyclic loading where the mean stress is zero), they found that tensile cyclic loads result in tensile stresses which cause failure at osteon cement lines, *i.e.*, the osteons debond from the surrounding interstitial bone, whereas compressive cyclic loads cause oblique microcracks to develop along the planes of high shear (tangential) stress, which are oblique to the loading direction, and these microcracks are influenced to some extent by the vascular canals and lacunae[14,15]. Thus, cortical bone under cyclic loading fails in both tension and compression; however, the mode of failure differs in each case. It was also found that the tensile failure will occur first, before any compressive failure occurs[16], which differs from most engineering materials, where cyclic loading results only in tensile failure.

Cortical bone specimen tests also demonstrated load frequency had a strong influence on the number of cycles to failure: a higher frequency resulted in less damage, but did not affect the total time to failure[17]. Importantly, the number of cycles to failure in cortical bone was affected by the strain range (amplitude) but not by the mean strain or the maximum strain; bone specimens subjected to a smaller strain range had a longer fatigue life[15,17].

As summarised by Martin and Burr[18], microcracks in cortical bone under cyclic tensile loading initially develop and propagate through the thickness of the lamellae: in areas of cortical bone under tension, the primary crack develops transversely, and are accompanied by secondary cracks which develop longitudinally, *i.e.*, in the direction of the lamellae, which helps dissipate energy and thus slow the advancement of the primary (transverse) crack. The secondary cracks create interla-mellar tensile and shear stresses which separate the lamellae, later resulting in debonding of the osteons.

Forwood and Parker[19] observed some of these effects in their study using whole-bone specimens to examine cortical bone fatigue microdamage in rats. Tibiae harvested from 60 rats were loaded in torsion at a number of different loading cycles. The authors found that lower levels of cyclic loading caused cracks to develop parallel to and traversing the lamellae, whereas higher levels of cyclic loading resulted in cracks through the full thickness of the cortex, invading across and through the Haversian canals or osteons[19].

Li *et al*[20] conducted an *in vivo* experiment where 20 rabbits were induced to run and jump over a period of 60 d by subjecting them to an electrical impulse at various intervals. Using radiographic and histological analyses on this group and a control (non-exercising) group, the authors found osteoclastic reabsorption occurred before the presence of any cracks in the cortical bone. Furthermore, only some rabbits developed cracks in the bone after the period of exercise, suggesting that in the majority of cases, the rabbit tibiae rapidly adapted to changes in the applied stress. Unlike the studies on cortical bone specimens, these *in vivo* tests may account for adaptive remodelling in living cortical bone.

The above research on cortical bone cyclic testing, both *in vitro* and *in vivo* studies, provided invaluable data on the development of fatigue injury in cortical bone. Like TSFs, cortical bone microtrauma occurring in MTSS is likely the result of tensile failure causing osteon debonding at the cement lines as the tibial microstructure is unable to repair quickly enough through adaptive bone remodelling. However, unlike a TSF, this microdamage clearly does not extend beyond the microscopic lamellae structure, at least in many cases, so that crack development is arrested in MTSS before a macroscopic partial fracture transversing the osteons occurs.

THE CAUSES OF MTSS

There are different theories on the exact cause of MTSS, although none of these theories have yet been proven. A number of previous studies have involved linking a specific muscle or muscle groups to MTSS based on the anatomical location in relation to patient symptoms. However, there have been conflicting results from these studies, leading experts to have different opinions to the exact cause of the injury.

Holder and Michael[7] performed TPBS on five male and five female athletes with clinically diagnosed postero-medial tibial pain, where the location of the injury in the ten patients was a combination of the lower, middle and upper thirds of the tibia[7]. Based on a concurrent analysis by the authors where lower leg musculature on cadavers was examined and EMG studies performed, they concluded that the proximal tibia and fibula origins of the soleus was largely responsible for the injury due to the

Figure 1 Anterior and medial views of the tibia with the main features shown, with the larger insert demonstrating the deep fascial attachments (A) and schematic section through the tibia illustrating the four compartments of the leg and their fascial coverings (B). The wide subcutaneous medial surface of the tibia can be seen. Images adapted from Oakes[24].

location of radionuclide uptake[21]. However, there was no data presented showing the results of individual patient nuclear bone scans and the exact location of symptoms in those patients; hence, it is difficult to understand how the authors came to this conclusion.

Beck and Osternig[22] dissected the legs of 50 cadavera and concluded that either the soleus or flexor digitorum longus (FDL) was responsible for MTSS based on muscle attachment sites, but the tibialis posterior was not. In their study, the soleus and FDL both had origins from the posteromedial border of the tibia, which is one of the injury sites of MTSS (48% $\pm$ 11% and 35% $\pm$ 7.9% of the tibial length from the medial malleolus respectively), whereas no fibres from the tibialis posterior did. Based on their work and results of previous studies, they concluded that the soleus was most likely responsible for MTSS, and the cause was a traction-induced longitudinal periostitis at the injury site.

In a later study, Saxena *et al*[23] also conducted a dissection analysis, finding the origin of the tibialis posterior includes a portion of the lower third of the tibia in all cadavera examined. They therefore concluded that the tibialis posterior may be the cause the type of MTSS which occurs in the lower third of the tibia, since this muscle correlates to the location of the symptoms. However, a significant limitation in their study was there were only ten cadavers in their sample. The findings in this study were contradictory to Beck and Osternig, who concluded that the tibialis posterior was probably not involved in MTSS, as few tibialis posterior muscle fibres in their fifty cadavera arose from the tibial posteromedial border.

Matin proposed that the disruption of Sharpey's fibres, which extend from the soleus-muscle-tendon complex to the cortical bone, could result in increased remodelling in the bone, therefore producing a longitudinal elongated pattern of injury[8]. In this hypothesis, the periosteal irritation from the Sharpey's fibres result in an osteoblastic response in the cortical bone[9].

The apparent contrary findings in some of these previous studies, where the injury has been attributed to different muscles or other tissues, may be because there are different types of MTSS, each with their own specific aetiology. One of the current authors (Oakes[24]) first proposed this in 1988, where, based on the bone fatigue studies which had been conducted at the time and his own extensive clinical observations, MTSS could be classified into two main categories, where the first type was associated with external cortical bone microfractures, and both types may also be seen together to form a third type of MTSS. This has been previously described by the authors[24,33], but is also outlined below:

Type I: Distal tibial tenderness which when overt, can result in subcutaneous periostitis or oedema on the anteromedial surface of the mid to distal third of the tibia (Figure 1) due to microtrauma caused by microcracks between the Haversian systems or osteons in the underlying superficial cortical bone. Oakes postulated this was caused by "tibial flexion from contraction of the two heads of the Gastrocnemius and the Soleus muscle causing tibial bending moments during the push-off phase of running"[33].

Type II: Posteromedial linear pain and tenderness, principally from the strong deep fascia of the posterior calf muscle compartment attaching to the linear posteromedial border of the tibia (Figure 1), but also due to the tibial origin of the FDL. Franklyn *et al*[33] proposed this was caused by "tension in the tibial attachment of the deep fascia in conjunction with the origins of the powerful action of the soleus and gastrocnemius muscles proximally".

Type III: A combination of the two types observed in committed middle and long distance runners, or in young immature bone where growth is not complete and BMD is low.

Despite these different theories, clinical and research studies on the cause of MTSS, the fact that the detailed structural cause is still unknown highlights the need for prospective longitudinal investigations.

DOES PERIOSTITIS OR CORTICAL BONE MICROTRAUMA OCCUR FIRST IN MTSS?

It is apparent from the current evidence available that MTSS involves cortical bone microtrauma in the majority of cases. However, it is not clear if cortical bone microcracks cause tibial periostitis or if tibial periostitis results in cortical bone microcracks. In the first instance, it is theorised that underlying cortical bone microtrauma developing over a period of time eventually results in a periosteal soft tissue reaction in the region of the microcracks. In the second case, muscle fibre traction is postulated to cause periostitis which may or may not lead to cortical bone microcracks.

In dissection studies on the human tibia *in situ*, the soleus, FDL and tibialis posterior were all purported to be associated with MTSS. Although the authors of these studies did not specifically discuss the relationship between these muscles and cortical bone microtrauma, it is apparent the general consensus is that muscle fibre traction *via* Sharpey's fibres results in tibial periostitis at the injury site, thus implying that either the periostitis occurs first, or there is a periosteal reaction in the absence of cortical bone microtrauma (since microtrauma was not discussed in these papers).

Matin[8] believed that the radionuclide deposition at the injury site of his patients was due to the periosteal response from the early developing bone abnormality and that Sharpey's fibres were the cause. In other words, the early underlying cortical bone microtrauma initiates periostitis at the injury site through the Sharpey's fibres; thus suggesting the bone response occurs first.

Based on their MRI study of 14 patients with 18 symptomatic legs, Fredericson *et al*[12] postulated that periosteal oedema occurs prior to the formation of cortical bone microcracks, as only periosteal oedema was detected in their patients with the mild injuries, or the MTSS, while those with more severe injuries had both periosteal oedema and either a partial fracture, or marrow oedema indicating bone microtrauma.

While the literature on cadaveric dissection supports muscle fibre traction as a potential cause of MTSS, there is also evidence for cortical bone microtrauma causing the injury, and in fact, it is known that cortical bone microtrauma occurs from impact exercise at the early stages of training. For example, Etherington *et al*[25] studied a cohort of 40 male military recruits over 10 wk of basic training, 26 of whom completed the training, and measured a number of parameters including the velocity of ultrasound in the heel. The authors found there was a mean decrease in the ultrasonic velocity from pre to post training in recruits who completed the training uninjured, signifying that either trabecular thinning due to bone remodelling or loss of trabeculae due to the development of microfractures. However, as the bone markers measured indicated there was an overall reduction in bone turnover, the decrease in ultrasonic velocity was likely due to microfractures

rather than active bone remodelling. Thus, cortical bone microtrauma occurs prior to the development of any clinical injury, and could be a precursor to periostitis.

NUCLEAR MEDICINE AND MRI

Prior to the advent of nuclear medicine techniques, MTSS could only be diagnosed early by a clinical examination and a detailed patient history, as radiographs, if not occult, would not show any visible radiological signs of the injury for at least 3-4 wk. However, this changed in the 1980s, after TPBS had been developed, as a clinical examination could be supplemented by medical imaging to confirm the diagnosis and exclude other conditions with similar symptoms.

Nuclear medicine studies have shown that patients with MTSS have increased uptake of radionuclide in the cortical bone, showing a characteristic longitudinal "double stripe" pattern[10]. Accuracies of 75% or greater have been found for nuclear bone scans[10,26,27], although it has been criticised for resulting in false positives: it has been argued that increased radionuclide uptake is not specific to a particular pathology, but instead due to increased activity of the patient[27-29]. However, nuclear bone scanning indicates there is a bone osteoclastic/osteoblastic response and an uptake of radionuclide may be due to a number of reasons including an increased cortical bone vascularity associated with bone metastases and/or increased physical activity of the patient. Thus, while nuclear bone scanning is an important diagnostic tool, the results need to be considered in conjunction with the patient's clinical symptoms for a correct interpretation of the findings.

MRI has more recently emerged as the preferred imaging modality for the diagnosis of both MTSS and TSFs. This was first reported by Fredericson *et al*[12], who found that MRI was more effective than other imaging modalities for the diagnosis, and also the early diagnosis, of tibial stress injuries. In a study involving 14 runners with 18 symptomatic legs (4 had bilateral symptoms) who sustained either a tibial stress reaction, MTSS or a TSF, the authors compared radiology, nuclear bone scans and MRI, concluding that MRI was anatomically specific and more sensitive in its correlation with the clinical symptoms and signs of bone stress injuries than TPBS.

The primary limitation of the study was the small number of patients analysed: out of 18 tibiae, two were found to have no pathology; thus there were a total of 16 painful tibiae. Also, although all tibial stress reactions were on the posteromedial border, the location along the tibia differed, comprising of patients with proximal, midshaft and distal leg pain. However, from this work, the authors also developed a four-level MRI classification system for tibial stress injuries, where Grades 1 and 2 were diffuse injuries (MTSS) while Grades 3 and 4 were localised injuries (TSFs). Pomeranz[11] (2001) later modified this classification system by separating Group 4 into two different types: Group 4a (partial cortical

Table 1 Clinical features and magnetic resonance imaging findings in the four grades of tibial stress injury		
Grade	Clinical exam	MRI
1	Periosteal tenderness at the distal 1/3 to 1/2 of the anteromedial tibial surface. Requires firm palpation with thumb	Periosteal oedema: mild to moderate on T2-weighted images. Marrow normal on T1 and T2-weighted images
2	Tenderness as above Requires less firm palpation with thumb and may have linear tenderness along the posteromedial tibial border	Periosteal oedema: moderate to severe on T2-weighted images Marrow oedema on STIR or T2-weighted images. T1 normal
3	Tenderness as above Requires less firm palpation and may have linear tenderness as above May have subcutaneous anteromedial tibial oedema	Periosteal oedema: moderate to severe on T2-weighted images. Marrow oedema on T1 and STIR-T2-weighted images
4	Tenderness as above Requires less firm palpation and may have linear tenderness as above A discrete region of maximal tenderness/thickening (early callus formation) over the fracture site will be palpable. Obvious tibial subcutaneous oedema is usually present	Periosteal oedema: moderate to severe on T2-weighted images. Marrow oedema on T1-STIR or T2-weighted images Fracture line clearly visible as low fuzzy incomplete (4a) or complete (4b) line May see oedema in proximal tibial origins of Tibialis Posterior, FDL and Soleus

Modified by Oakes from Fredericson *et al*[12] and Pomeranz[11]. MRI: Magnetic resonance imaging; STIR: Short T1 inversion recovery.

Figure 2 Coronal T2-weighted magnetic resonance imaging images of a 17-year-old female hockey player who was training on a concrete pitch covered with Astro Turf® for approximately 2 mo and was subsequently diagnosed with medial tibial stress syndrome. A white longitudinal line of periosteal oedema on the medial cortex can clearly be seen on the enlarged view (right), which was consistent with the region of pain and tenderness.

fracture) and Group 4b (complete cortical fracture). Table 1 demonstrates the modified grading system, which has been further adapted by Oakes.

In a later study by the Bergman *et al*[30] group it was found that MRI can demonstrate a positive stress reaction in individuals performing intense exercise; this is similar to nuclear bone scans where radionuclide uptake had previously been observed in individuals due to intense exercise. In 21 asymptomatic elite university runners, the authors found nine athletes had Grades 1-3 abnormalities on MRI, indicating a tibial stress reaction was present, yet on follow-up, none of these individuals developed a bone stress injury. This not only highlights the importance of assessing MRI (or nuclear bone scan) findings in conjunction with a detailed clinical examination and patient history, but demonstrates cortical bone microcracks can develop in response to intense impact training and do not always signify a current or subsequent bone stress injury with overt microcracks.

Figure 2 demonstrates T2-weighted images of a 17-year-old patient who sustained MTSS after playing hockey on a synthetic turf surface (Astro Turf®) for approximately 2 mo. Her treating sports physician (Oakes) recommended a series of MRI scans. The periosteal oedema can be visualised on the medial cortex.

BMD AND CORTICAL BONE GEOMETRY CHANGES IN MTSS

Since the studies were published on cortical bone microtrauma and MTSS, there has been more recent research demonstrating MTSS patients have other changes to the cortical bone. This work has involved either BMD measurements or detailed tibial cortical bone geometry studies.

BMD

The initial research on MTSS and BMD was performed by Magnusson *et al*[31], who measured BMD in 18 male professional athletes who sustained chronic MTSS

Table 2 Bone mineral density in male medial tibial stress syndrome patients and an athletic control group[31]			
BMD (g/cm^2)	MTSS	Athletic control	Significance
Proximal	1.29	1.48	< 0.01[b]
33% level (injury site)	1.43	1.85	< 0.001[b]
Distal	1.32	1.33	> 0.05

[b]Statistically significant. Although there are differences in the proximal tibia, the difference is much greater at the injury site. Select data presented for comparison with the two other BMD studies discussed. BMD: Bone mineral density; MTSS: Medial tibial stress syndrome.

Table 3 Bone mineral density in female tibial stress fracture and medial tibial stress syndrome patients[33]			
BMD (g/cm^2)	MTSS (n = 20)	TSF (n = 10)	Significance
Proximal	1.21	1.27	0.136
33% level (injury site)	1.46	1.63	0.013[a]
Distal	0.90	0.94	0.403

[a]Statistically significant. BMD: Bone mineral density; MTSS: Medial tibial stress syndrome; TSF: Tibial stress fracture.

diagnosed both clinically and by nuclear bone scanning, 18 male age and sex matched professional control athletes (exercising 3-15 h/wk) who were not injured, and 16 age and sex matched male control subjects who were recreational athletes (0 to 5 h per week) using Duel Energy X-ray Absorptiometry (DEXA). The MTSS patients were diagnosed both clinically and by a nuclear bone scan, and all had medial diffuse pain at the junction of the middle and distal thirds of the tibia (it was not stated if all patients had posteromedial pain, although this was implied in their introductory discussion).

The authors demonstrated that athletes with chronic MTSS had a localised lower BMD at the injury site than both the athletic control and the control subjects, and the low BMD was bilateral, even when the injury was unilateral. Conversely, in the proximal and distal tibial regions, where the BMD was also measured, it was found that the MTSS subjects had higher BMD than the two groups of control subjects (Table 2); thus, leading the authors to conclude that MTSS is associated with low regional BMD. In a subsequent study, the authors found that after recovery from the injury, the BMD returns to normal[32]. This observation suggests that the low BMD is not inherent, or pre-existing, but develops in conjunction with the symptoms.

The study by Magnusson *et al*[31,32] had significant limitations related to exercise exposure. First, there was considerable variation in the amount of exercise performed per week in the professional athlete control group (3-15 h/wk), while individuals in the recreational exercise control group performed some exercise (0-5 h/wk); hence, they were not a real sedentary control group. Second, the individuals who exercised performed a wide variety of activities including both impact (*e.g.*, running) and non-impact activities (*e.g.*, weightlifting and swimming), which may have affected the BMD results. Last, in both control groups there were individuals with both manual and non-manual occupations, further diversifying exercise exposure of individuals in the groups.

The current authors conducted a preliminary study where BMD was compared between female chronic MTSS and TSF patients[33]. BMD was measured in three locations in the tibia: proximally, distally and at the injury site (the junction of the mid and distal thirds of

the tibia); these locations were similar to three of the five locations BMD was measured in the Magnusson study. Patients were diagnosed both clinically and by a nuclear bone scan. They had been performing impact exercise at least 3-4 times per week with a 2-year minimum training history (although the majority had a much longer training history) prior to the analysis. It was found that at all three sites, the BMD was lower in the MTSS patients than the TSF patients, although it was only statistically significant at the injury site (Table 3). The main limitation with our preliminary study was that the subject numbers were not large: there were only five TSF patients (10 tibiae) and ten MTSS patients (20 tibiae). Nevertheless, the patient numbers were sufficient to demonstrate statistical significance.

In another BMD study on MTSS patients, Ozgürbüz *et al*[34] found that the BMD did not differ between MTSS patients and aerobic controls in several different bones, including the tibia at three different sites. The study contained a total of 22 subjects, where 11 subjects were MTSS patients and 11 subjects were aerobic controls, and each group comprised of both males and females. MTSS was diagnosed clinically by two different physicians and the MTSS patients had a history of the injury from 3-10 wk.

The strength of this study was the control group, which contained subjects who were all performing impact exercise rather than a mix of subjects performing impact and non-impact exercise. However, there were some significant limitations: MTSS patients were only diagnosed clinically and there was no information provided on the assessment criteria used in the diagnosis. More importantly, the patients had only sustained MTSS for a period of 3-10 wk (5 wk on average); therefore, they were not chronic MTSS patients. Thus, it is unlikely that these patients would yet have experienced any changes to the cortical bone in such a short time period, which is the most likely explanation why the authors found that BMD did not differ between the MTSS subjects and the aerobic controls. Interestingly, the BMD values measured by Ozgürbüz were considerably lower than the values found in the other BMD studies, for example, at the injury site (a similar location in the tibia in all the BMD studies), the BMD values were Ozgürbüz 0.315 (MTSS) and 0.323 (aerobic control), Franklyn and Oakes 1.46 (MTSS), and Magnusson 1.43 (MTSS) and 1.85 (aerobic control). This clearly requires further examination.

Figure 3 Comparison of computed tomography with a new generation magnetic resonance imaging image. (A) typical CT image (B) enlarged CT showing the high resolution cortical bone depiction and (C) MRI image for comparison. CT: Computed tomography; MRI: Magnetic resonance imaging.

Thus, it can be concluded that BMD is lower in chronic MTSS patients than in aerobic controls, but this is not the case for other regions of the tibia, while patients with acute MTSS do not appear to have low regional BMD. In addition, BMD is lower in patients with MTSS than TSF patients. It is probable that the low BMD in MTSS patients occurs in conjunction with the symptoms. A longitudinal study, where BMD is measured at periodic intervals in an exercising cohort, and where both male and female subjects are included but analysed as separate groups, is needed to confirm these findings.

Cortical bone geometry
In previous research, low values of various cortical bone geometric factors have been associated with TSFs[35-37], but there is only one previous study where detailed cortical bone geometry has been analysed in MTSS patients[38]. In this research, it was found that the MTSS subjects had lower values of some geometric parameters than aerobic control subjects, but not as low as TSF subjects, and these differences were not the same in males and females[38]. Significant parameters in males included cortical bone cross-sectional area, polar moment of area, second moments of area and section moduli, indicating that males with MTSS are less adapted to axial loads, torsion, maximum and minimum bending and pure bending. Females sustaining MTSS had smaller section moduli than aerobic controls, indicating less adaptation to pure bending, but other geometric parameters did not differ. Although MTSS patients had lower values of geometric bone parameters than aerobic controls, they were not as low as the values in the TSF groups, indicating that there may be some different mechanisms involved in each of these injuries.

Although this research was limited in that it was not a longitudinal study, the aerobic control group in the study had higher values of the significant cortical bone geometric parameters, suggesting these parameters increase in response to impact exercise and in fact, longitudinal studies in the literature on both humans and animals demonstrate that cortical bone geometric

parameters increase in response to exercise[39,40]. Thus, it is probable that bone geometric factors also alter in conjunction with the development of the injury, although a longitudinal study using periodic CT or MRI scans is needed to confirm these findings. While CT has traditionally been the best imaging modality for the calculation of tibial geometric factors due to its superior depiction of cortical bone, new generation MRI scanners now show improved bone resolution (Figure 3); therefore, may be an alternative choice due to the lack of ionising radiation. However, validation studies comparing geometric parameter computations on the same individuals scanned using both CT and MRI would be initially needed to elucidate any significant differences between the two imaging modalities.

BMD and cortical bone geometry
In summary, previous studies on BMD and cortical bone geometric parameters demonstrate that patients with MTSS have lower BMD and lower values of various cortical bone geometric factors than aerobic control subjects. MTSS patients appear to also have lower BMD than TSF individuals, but higher values of cortical bone geometric factors. These findings suggest that both BMD and cortical bone geometry may both contribute to the likelihood of sustaining a TSF or MTSS, but the balance between the two factors may predict an individual's likelihood of developing one of these specific injuries.

IS MTSS A PRECURSOR TO A TSF?

There are conflicting views as to whether MTSS is a precursor to a TSF and thus they are on a continuum of injury[12], or if they are two separate entities with common aetiology and risk factors, but differences in predisposition and development of the injury[8,41].

It can be argued that MTSS and TSFs are on a continuum as MTSS is most commonly found in the same location as TSFs, at the junction of the mid and distal thirds of the tibia, but this is not always the case as MTSS is also observed in other locations in the tibia[12,42], suggesting it is a separate injury. Clinical examination

of patients with TSFs demonstrates that in addition to the small pronounced area of focal pain overlying the fracture location, there is often overt anteromedial subcutaneous pitting oedema on palpation along a region of the tibia, indicating that the diffuse region of microcracks may have progressed to a macrocrack at one location. However, not all cases of MTSS lead to a TSF; if they were one injury on a continuum, all MTSS patients would eventually sustain a TSF with continued exposure to the same impact forces, yet this does not occur.

Both MTSS and TSFs occur from microcracks developing in cortical bone as the anterior cortex of the tibia cycles from overt compression loading on heel-strike to tension loading at push-off, and both injuries involve an alteration in cortical bone geometry[38] and BMD[31-33]. However, cortical bone geometry and BMD also differs between TSF and MTSS patients[33,38], indicating there may be different specific biomechanism involved in each case.

While it is clear that MTSS and TSFs have commonality with regards to the development of microcracks in the cortical bone, changes in BMD and alteration to the cortical bone geometry, it is yet to be proven if they are one injury or two separate entities. Opinions in the literature differ but the issue is unlikely to be resolved until longitudinal studies are performed.

STRAIN GAUGE ANALYSES AND COMPUTER MODELLING

Earlier papers on MTSS predominately focused on defining the injury and describing the most appropriate techniques for diagnosis, with some authors hypothesising potential causes of the injury, while recent research has centred on reviews of the literature[1,43,44], risk factors[42,45-48], interventions[49,50] and treatment options[51,52]. However, studies investigating the aetiology of the injury are limited, and future research should focus on the exact mechanisms of MTSS, which may lead to the development of improved interventions. Some techniques which may be employed in future work are *in vivo* strain gauge experiments and finite element (FE) analysis.

Surgically-bonded strain gauges have been used in previous TSF research in order to examine the relationship between loading conditions and stress or strain in the bone *in vivo*[53-57]. While these studies have provided information on the stress or strain experienced by the tibia under different types of impact exercise, in all these studies, the subjects had no pathology, and the stress or strain experienced by the tibia is likely to differ between these non-injured subjects and individuals with MTSS or a TSF. Conducting this type of experimental work on injured subjects would provide invaluable data pertaining to the injured tibia; however, there are obviously ethical and other considerations in performing this type of analysis which may preclude this type of

study from being conducted, especially on subjects who are injured.

An alternative technique for analysing stress or strain in bone is by the use of computational techniques such as the FE method. FE analysis has a number of advantages over strain gauges in that the entire stress or strain in the bone can be computed; therefore, regions of peak stress or strain can be easily identified. In addition, the loading conditions on the model can easily be altered so the direct relationship between applied load and stress or strain in the bone can be determined, and the model geometry can also be changed.

Several FE models have more recently been developed in order to better understand tibial stress injuries; however, these studies have focused on TSFs rather than MTSS. Sonoda *et al*[58] developed a subject-specific tibiofibula FE model based a on 20-year-old female, 165 cm in height and 52 kg in weight, applying loading conditions from the literature on the model. The subject had no pathology; however, they simulated small tibial fractures in the model to represent TSFs, finding that that the (von Mises) stresses in the anterior border, where the TSF was most severe, ranged from approximately 63 MPa to approximately 75 MPa. Edwards *et al*[59] developed a generic tibial FE model based on a publicly available dataset which they used to develop separate models for each of their 10 male subjects (approximately 24.9-year-old 1.7 m, 70.1 kg) by scaling the tibial length based on the subject's body weight and then using gait data from the subjects to determine the loads to apply to the models. The authors used a probabilistic model for TSFs to determine when failure would occur and found the peak (maximum principal) strain to be approximately 3670 (approximately 68 MPa) on the tibial anterior surface.

The stresses predicted in these FE models are considerably higher than those measured in the strain gauge studies, where values of stress on the anteromedial border ranged from approximately 14 MPa[53] to approximately 28 MPa[54] (by converting the measured strains into stress using a Young's modulus of 18600 MPa), highlighting the fact that the tibial stresses will be higher in injured individuals at the injury site, and the need for more studies examining the stress and strain in the tibia of both TSF and MTSS patients.

More recently, the current authors developed an FE model based on a female athletic patient who sustained chronic MTSS with the input loads to the model derived from gait analysis data from the same patient[33]. The model was used to analyse the relationship between loads while running and stresses in the tibia. While the analysis is still being finalised, the results show the magnitude of stress in the tibia is higher in the MTSS patient than the tibial stresses in the subjects from the strain gauge studies; a similar finding to the FE models representing TSF patients (Figure 4). Additionally, the results indicate the magnitude and position of the high tensile stress region is predominately affected by the

> 1.21e+02
> 1.21e+02
< 9.49e+01
< 6.87e+01
< 4.26e+01
< 1.64e+01
< -9.82e+00
< -3.60e+01
< -6.22e+01
< -8.84e+01

Max = 1.47e+02
Min = -8.84e+01

Figure 4 Preliminary finite element analysis by the current authors. Maximum values of principal stresses in the model were significantly higher than those measured by strain gauge analysis, but similar to some other FE models in the literature. FE: Finite element.

combination of the input loads, while the distribution of the high stresses (diffuse or localised) appear to be more influenced by the specific bone geometry of the subject. However, these preliminary findings require further analysis.

Previous strain gauge studies have provided invaluable data on the stress and strain state of the tibia under loading, but as these were all performed on uninjured subjects, the results are not necessarily transferable to individuals with bone stress injuries; indeed, the FE modelling which has been conducted to date indicates they are not. Performing strain gauge experiments on MTSS patients may provide a critical insight into the strain experienced by the tibia when injured; however, there are obviously ethical considerations in surgically bonding strain gauges to the bone of injured individuals. Hence, further computational modelling might provide the key to better understanding the stresses and strains in the tibia in injured individuals.

ADVICE FOR THE TREATING PHYSICIAN

In the last few decades, the diagnosis of MTSS has changed, predominately due to the advances in medical imaging technology. In the 1980s and 1990s, physicians were reliant on plain film radiology and nuclear bone scans to verify their clinical findings. Plain radiographs were often normal in the early stages of a suspected TSF (*e.g.*, 3-4 wk post-symptoms or 4-6 wk post-injury), but a nuclear bone scan may be positive, demonstrating early uptake of radionuclide in the region of increased vascularity of the overt fracture not readily seen on plain radiographs, such as a fractured navicular in a running athlete or a fractured scaphoid in a gymnast. Nuclear bone scans were particularly useful to the clinician in that a positive scan with a localised radionuclide uptake (*i.e.*, "hot spot") was objective evidence of a fracture; however, the anatomical specificity was poor, especially with the small bones of the carpus. CT imaging could be used in conjunction with radiography and a nuclear bone scan for cases

where a TSF was suspected, as small overt fractures could often be observed, such as small fracture in the navicular, other tarsal bones, the carpals and the sesamoids of the foot, and avascular necrosis of these bones could also be identified.

Plain radiology was not particularly useful for an early diagnosis of MTSS as the inflammatory reaction associated with the periostitis and cortical microfracture formation could not generally be observed for 4-6 wk post-injury, even though symptoms and signs are usually present at 3-4 wk post-injury.

The advent of MRI and developments in this imaging modality over the last 10-15 years has given the treating physician an alternative option involving no ionising radiation. MRI exams now demonstrate excellent anatomical resolution of both bone and soft tissue. Physicians could use it to follow patients at various points in time, and it was particularly useful for clinical trials, as the long-term response of bone and soft tissues to both normal and excess loading conditions could be determined.

For the practicing physician, the current contemporary diagnosis of both MTSS and a TSF involves a combination of both a clinical examination and medical imaging. The clinical exam should include an assessment of both legs (while the patient is standing) for alignment, length, any deformity and foot stance. Foot pronation, indicating weak invertors, may signify an alignment problem associated with a TSF or MTSS. While the patient is seated, the physician should palpate the tibia for tenderness, especially the anterior border and posteromedial longitudinal borders of the tibia where the deep fascia attaches, as well as the whole of the subcutaneous anteromedial surface. Particular note should be made of regions with more acute tenderness, especially the distal one-third of the tibia, and its distribution (local or diffuse). The leg should also be examined for any subcutaneous oedema, which indicates periostitis is present and probable associated microfractures. The three compartments of the leg (anterior, peroneal and posterior) should be palpated for

tenderness, with "tightness" in the muscle compartment of the leg indicating the patient may have compartment syndrome. A weakness in one or more muscle compartments or in a myotome may indicate lumbar spinal nerve compression or other isolated motor nerve pathologies including rare entrapment syndromes.

A full strength/power assessment of all the muscles of the leg should be performed as well as a full vascular and neural exam. Range of motion in the ankle joint, especially ankle joint dorsiflexion or extension, should be checked to exclude a tight/short gastroc-soleus-tendon complex; if short, it would increase anteromedial tibial loading on running. Similarly, excess forefoot pronation may indicate tibialis anterior/posterior weakness and thus greater tibial torque on running.

Bone pain and tenderness, especially in a non-athletic patient, should be regarded with special care, as bone tumours or infection must be initially excluded. For these patients, plain radiographs of the whole tibia are mandatory.

Where other pathologies have been excluded and the patient has clinical indications of a tibial bone stress injury, an MRI exam should be performed of the whole tibia, where the findings and classification of the injury have presented earlier in this review.

Treatment of the patient with a confirmed MTSS (or a TSF) will vary according to the cause. While non or reduced weight bearing should be generally prescribed, issues such as leg alignment and forefoot pronation need to be addressed in order to facilitate healing and prevent future re-occurrence.

CONCLUSION

MTSS is an overuse fatigue injury involving tibial periostitis in conjunction with cortical bone oedema and microtrauma, although the cortical bone response may not occur in all individuals. The two main mechanisms of injury appear to be a traction-induced periostitis, where the cause is likely to be the soleus and/or the FDL, and microtrauma comprising of oedema and microcracks in the cortical bone which result in debonding of the osteons and subcutaneous periostitis on the surface of the tibia. While there are numerous studies in the literature on risk factors, interventions and treatment for MTSS in addition to a number of review papers, studies examining the aetiology are limited, therefore the exact causal mechanisms are still not understood.

It is apparent that prospective longitudinal studies are required where athletes or military recruits are monitored by CT or MRI and DEXA in order to quantify precise changes in cortical bone geometry and simultaneously monitor both BMD and cortical bone oedema during the development of MTSS. However, this type of research requires a large cohort where a definite minimum number of individuals will reliably sustain the injury, and consent to perform a large number of scans, some with ionising radiation. This may not occur in the near future as the current focus in many universities and research organisations is for shorter research studies which lead to the development of quick clinical outcomes. Surgically-bonded strain gauges on the tibia offer an alternative approach, although there are ethical considerations with conducting these types of experiments. FE analysis is another technique which should be explored for future studies, as it can be used to examine stresses in the whole tibia under different loading conditions.

Contemporary accurate diagnosis of either MTSS or a TSF includes a comprehensive clinical examination to identify signs of bone stress injury and to exclude other pathologies. This should be followed by an MRI study of the whole tibia. The possible cause of the injury should be established and addressed in order to facilitate healing and prevent future long-term re-occurrence.

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REVIEW

Current concepts on osteonecrosis of the femoral head

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Abstract

It is estimated that 20000 to 30000 new patients are diagnosed with osteonecrosis annually accounting for approximately 10% of the 250000 total hip arthroplasties done annually in the United States. The lack of level 1 evidence in the literature makes it difficult to identify optimal treatment protocols to manage patients with pre-collapse avascular necrosis of the femoral head, and early intervention prior to collapse is critical to successful outcomes in joint preserving procedures. There have been a variety of traumatic and atraumatic factors that have been identified as risk factors for osteonecrosis, but the etiology and pathogenesis still remains unclear. Current osteonecrosis diagnosis is dependent upon plain anteroposterior and frog-leg lateral radiographs of the hip, followed by magnetic resonance imaging (MRI). Generally, the first radiographic changes seen by radiograph will be cystic and sclerotic changes in the femoral head. Although the diagnosis may be made by radiograph, plain radiographs are generally insufficient for early diagnosis, therefore MRI is considered the most accurate benchmark. Treatment options include pharmacologic agents such as bisphosphonates and statins, biophysical treatments, as well as joint-preserving and joint-replacing surgeries. the surgical treatment of osteonecrosis of the femoral head can be divided into two major branches: femoral head sparing procedures (FHSP) and femoral head replacement procedures (FHRP). In general, FHSP are indicated at pre-collapse stages with minimal symptoms whereas FHRP are preferred at post-collapse symptomatic stages. It is difficult to know whether any treatment modality changes the natural history of core decompression since the true natural history of core decompression has not been delineated.

Key words: Osteonecrosis; Femoral head; Conservative treatment; Core decompression; Stem cells; Total hip arthroplasty

Core tip: This paper walks the reader through the most current evidence regarding the etiology, pathogenesis, treatment options and prognosis of patients presenting with osteonecrosis of the femoral head. We emphasize early diagnosis with magnetic resonance imaging,

review surgical and non surgical treatment modalities and provide a personalized management algorithm according to the different stages of the disease.

INTRODUCTION

Osteonecrosis (ON) of the femoral head (ONFH) is the final common pathway of a series of derangements that result in a decrease in blood flow to the femoral head (FH) leading to cellular death, fracture, and collapse of the articular surface[1,2]. It typically affects relatively young, active people between 20 and 40 years and regularly follows an unrelenting course resulting in substantial loss of function. It is estimated that 20000 to 30000 new patients are diagnosed with ON annually accounting for approximately 10% of the 250000 total hip arthroplasties (THA) done annually in the United States[3]. Spontaneous regression of avascular necrosis is rare, with the vast majority of untreated patients progressing to THA and a collapse rate of 67% in asymptomatic patients and 85% of symptomatic hips[4]. Although many authors have suggested treatment based on patient age, symptoms, stage, and/or medical status, the orthopedic community has not yet adopted a uniform treatment algorithm[5-11]. The lack of level 1 evidence in the literature makes it difficult to identify optimal treatment protocols to manage patients with pre-collapse AVN of the FH, and early intervention prior to collapse is critical to successful outcomes in joint preserving procedures.

ETIOLOGY AND PATHOGENESIS

There have been a variety of traumatic and atraumatic factors that have been identified as risk factors for ON, but the etiology and pathogenesis still remains unclear. The estimated frequency of the most frequent risk factors for ONFH in the United States is: alcohol (20%-40%), corticosteroid therapy (35%-40%), and idiopathic (20%-40%)[12].

Most studies have attributed the disease process to the combined effects of genetic predisposition, metabolic factors, and local factors affecting blood supply such as vascular damage, increased intraosseous pressure, and mechanical stress[3,13,14]. This results in bone ischemia and infarction leading to bone death. The precipitating mechanism which leads to this pathway is variable though (Figure 1). Ischemia can result from external or internal vascular insult typically caused by direct trauma, vascular occlusion, direct cellular toxicity,

or altered mesenchymal stem cell differentiation[15].

Several mechanisms leading to vascular occlusion have been proposed as possible underlying causes of necrosis. High doses of glucocorticoids prevalent in systemic diseases such as systemic lupus erythematosus as well as excessive alcohol intake have been associated with alterations in circulating lipids with resultant microemboli in the arteries supplying the bone[16]. In addition increased risk of fat emboli has also been attributed to the increase in bone marrow fat cell size which blocks venous flow. Therefore, fat emboli, adipocyte hypertrophy, and venous stasis have all been implicated as etiologic factors in this disease process. Vascular occlusion can also result from disease processes that increase intravascular coagulation and thrombus formation. Antiphospholipid antibodies, inherited thrombophilia, and hypofibrinolysis have all been associated with altered mechanisms in both the coagulation and fibrinolytic pathways. Occlusion can also occur as a result of red blood cell sickling and bone marrow hyperplasia as seen in sickle cell hemoglobinopathies or may be due to an accumulation of cerebroside-filled cells within the bone marrow as seen in Gaucher's disease[17]. Decompression sickness associated with increased pressure can lead to nitrogen bubble formation that can also cause arteriolar occlusion and necrosis. This has also been shown to result in elevated plasma levels of plasminogen activator inhibitors leading to increased coagulation[18]. Trauma due to fracture or dislocation can lead to damage to the extraosseous blood supply. This is especially specific to fractures in the subcapital region of the femoral neck. Trauma at this location interrupts the anastomosis between the lateral epiphyseal vessels, which are branches from the medial femoral circumflex artery supplying, and the artery of the ligamentum teres leading to compromised blood flow to the FH. Lastly, direct cellular insult may result from irradiation, chemotherapy, or oxidative stress and may lead to a reduction in osteogenic differentiation and physiologic diversion of mesenchymal stem cells toward the adipocytic lineage[15].

DIAGNOSIS AND ASSESSMENT

Early diagnosis is crucial for optimal treatment of ON, as treatment success is related to the stage at which the care is initiated[13]. Current diagnostic modalities available include radiography, scintigraphy, functional evaluation of bone, magnetic resonance imaging (MRI), computer-assisted tomography, and histological studies.

Clinical presentation of ON typically is asymptomatic in early stages, although patients may develop groin pain that can radiate to the knee or ipsilateral buttock. On physical examination, patients usually present with a limited range of motion at the hip and complain of pain particularly with forced internal rotation. A detailed history can identify any associated risk factors (Table 1)[13]. ON must be suspected with presentation of pain

Traumatic pathway

Hip fracture	Hip dislocation

Interruption of blood flow

Critical ischemia

Bone necrosis

Inflammatory response

Bone resorption and collapse

Atraumatic pathway

Glucocorticoids	Alcohol
Fat emboli	Gaucher's
Sickle cell hemoglobinapathy	Decompression sickness

Coagulopathy: Antiphospholipid antibodies, inherited thrombophilia, hypofibrinolysis

Drugs, radiation, toxins

Adipocyte hypertrophy, endothelial damage, and thrombus formation

Figure 1 Mechanisms of osteonecrosis.

Table 1	Risk factors for osteonecrosis of the femoral head	
Direct		**Indirect**
Femoral head/neck fracture		Chronic corticosteroid use
Hip dislocation		Excessive alcohol consumption
Slipped capital femora epiphysis		Coagulation disorders
Radiation		Hemoglobinopathies
Sickle cell disease		Dysbaric phenomena
Caisson disease		Autoinmune diseases
Myeloproliferative disorders		Smoking
		Hyperlipidemia

Table 2	Ficat and arlet classification system
Stage	**Features**
0	Normal radiographs (silent hip)
I	Slight abnormality as patchy/opaque areas, minor osteopenia
II	Sclerotic or cystic lesions
	II a: No crescent sign
	II b: Crescent sign without flattening of the femoral head
III	Flattening of the femoral head or femoral head collapse
IV	Femoral head collapse and osteoarthritis of the hip (joint space narrowing, osteophytes and acetabular changes)

in the hips, negative plain radiographs, and any of these risk factors, since plain radiographs may present as normal in the early stages of necrosis. Patients who have had a history of necrosis must be watched for bilateral ON, as bilaterality has been reported in up to 70%[19].

The two most common classifications used in the diagnosis of ON include the Ficat and Arlet and the Steinberg University of Pennsylvania systems (Tables 2 and 3)[20]. Ficat classification consists of four stages, based on standard radiographs. Stage I indicates normal imaging. Stage II indicates normal FH contour, but with evidence of bone-remodeling, such as cystic or osteosclerotic regions. Stage III indicates evidence of subchondral collapse, or flattening of the FH. Stage IV indicates a narrowing of the joint space with secondary degenerative changes in the acetabulum, such as cysts, osteophytes, and cartilage destruction. Hungerford[13] described the stage 0, silent hip (preclinical and preradiologic), in which AVN can be suggested if it has been already diagnosed in the contralateral femoral head. In this case bone marrow pressure and histology studies

would be abnormal. Although the Ficat classification system has been well established, it is dependent on radiographic imaging and does not allow for quantitation of lesion size, making it impossible to measure disease progression[21]. Steinberg expands the Ficat system into six stages and includes quantification of involvement of the FH within each stage. They defined mild (less than 15% radiographic involvement of the head's articular surface), moderate (15%-30% involvement of the head's articular surface), and severe (greater than 30% involvement of the head's articular surface) stages. In addition, the Association Research Circulation Osseous (ARCO) suggested a new classification system based on the combination of radiographic, MRI, bone scan and histologic findings. However, apparently these two classifications systems, Ficat and ARCO are still not enough reliable to assess the status of ONFH alone[22].

Several studies have shown that the size of the necrotic segment in the FH is a fundamental parameter to determine the prognosis and treatment of this condition. Different methods are currently used to measure the size of the lesion. These include, the tradicional

Figure 2 Left hip anteriorposterior and cross leg lateral X-rays showing (arrows) the crescent sing.

Figure 3 Bilateral osteonecrosis of the femoral head with flattening of the surface and early sings of osteoarthritis.

Table 3 Steinberg staging system	
Stage	**Features**
0	Normal radiograph, bone scan and magnetic resonance imaging
I	Normal radiograph, abnormal bone scan and or magnetic resonance imaging
	I A Mild (involves < 15% of femoral head)
	I B Moderate (involves 15% to 30% of femoral head)
	I C Severe (involves > 30% of femoral head)
II	Cystic and sclerotic changes in the femoral head
	II A Mild (involves < 15% of femoral head)
	II B Moderate (involves 15% to 30% of femoral head)
	II C Severe (involves > 30% of femoral head)
III	Subchondral collapse (crescent sign) without flattening of the femoral head
	III A Mild (involves < 15% of femoral head)
	III B Moderate (involves 15% to 30% of femoral head)
	III C Severe (involves > 30% of femoral head)
IV	Flattening of the femoral head/femoral head collapse
	IV A Mild (involves < 15% of femoral head)
	IV B Moderate (involves 15% to 30% of femoral head)
	IV C Severe (involves > 30% of femoral head)
V	Joint space narrowing and/or acetabular changes
	V A Mild
	V B Moderate
	V C Severe
VI	Advance degenerative joint disease

angular measurements methods described by Kerboul and Koo and Kim and the quantitative volumetric measurement performed by quantitative digital analysis[23,24]. A recent study[25] comparing the efficacy of these systems showed more accurate and reliable measurements using the volumetric measurement method[25]. However, simpler measurement systems, though less accurate, are more commonly utilized since volumetric measurements are technically too demanding for general use. In spite of that, the size of the necrotic region must be determined as part of a comprehensive evaluation of this condition.

Current ON diagnosis is dependent upon plain AP and frog-leg lateral radiographs of the hip, followed by MRI. The AP radiographs will usually demonstrate the primary area of involvement once changes can be viewed. Generally, the first radiographic changes

seen by radiograph will be cystic and sclerotic changes in the FH. Subtle osteosclerotic or cystic changes in the subchondral regions may be missed because the anterior and posterior acetabular margins overlap the superior FH, therefore lateral frog-leg radiographs of the FH are necessary. Early delamination of the cartilage from the underlying bone will most likely be demonstrated by the crescent sign (Figures 2 and 3)[15]. Flattening of the FH can also be viewed by radiograph, but may only be visible in one view[15].

Although the diagnosis may be made by radiograph, plain radiographs are generally insufficient for early diagnosis; therefore MRI is considered the most accurate benchmark[5]. A single-density line on T1-weighted images and a high signal intensity line on T2-weighted images represent the early necrotic-viable bone interface and the hypervascular granulation tissue characterizing ON (Figure 4)[13]. However, recently subchondral insufficiency fractures of the FH have been proposed as a new concept regarding FH collapse with a reported incidence of 5%-10% of patients who underwent a hip replacement with a diagnosis of ONFH[26,27]. These entities must be differentiated since AVN represents an irreversible condition, which might lead to permanent joint failure and SIF may either completely resolve or progress toward epiphyseal collapse[28-30]. The characteristic finding of SIF on MRI is a low intensity band on T1 in association with bone marrow edema, however, this finding has also been described in ONFH. A recent study[30] demonstrated that the shape of the low intensity band (on T1-weighted MRI) is helpful for differentiation between the two diagnoses. The low intensity band seen in SIF is generally irregular, serpiginous, discontinuous, and convex to the articular surface, while the band in ONFH tends to be smooth, concave and well circumscribed. However, the shape of the low intensity band is not always diagnostic and further imaging may be required (MRI with gadolinium). Ultimately, both clinical and MRI characteristics need to be evaluated for the critical differentiation of both conditions (Table 4).

Other functional tools for evaluating ON include measuring bone-marrow pressure, venography, and core

Figure 4 Magnetic resonance imaging of the left hip showing extensive avascular necrosis of the femoral head with collapse and a large area of devitalized bone demonstrating fibrocystic change. There is associated severe arthrosis of the left hip joint with a moderate effusion, synovitis and debris and a marked bone marrow edema pattern on both sides of the joint.

Table 4 Clinical and imaging differences between osteonecrosis femoral head and subchondral insufficiency fracture		
	SIF	**ONFH**
Age/sex	Elderly/female	30 s to 40 s
Etiology	Osteoporosis/obese	Steroid/alcohol
Bilateral	Rare	50%-70%
Shape of the band	Iregular, disconnected	Smooth
High signal of the proximal Segment on gadolimium MRI	Yes	No

From Yamamoto T. In: Yamamoto T. Subchondral Insufficiency Fractures of the Femoral Head. *Clinics in Orthopedic Surgery* 2012: **4**: 3. SIF: Subchondral insufficiency fracture; ONFH: Osteonecrosis femoral head; MRI: Magnetic resonance imaging.

biopsy. While these tests are specific and sensitive, they are invasive and only used when MRI, and radiograph reveal negative findings in a patient where ON is highly likely. Although CT scans can aid in distinguishing between late stages of ON before collapse of the FH, this modality is rarely used due to its high doses of radiation. Characteristic features that define the diagnosis of ON include: collapse of the FH, anterolateral sequestrum, or the crescent sign, or when a double-line sign is demonstrated through MRI on T2-weighted images, or there is a positive histologic finding upon bone biopsy.

Non-surgical management
The aim of treatment of AVN of the hip is to prevent collapse of the FH and may vary depending on the underlying etiology and stage of progression. Treatment options include pharmacologic agents, biophysical treatments, as well as joint-preserving and joint-replacing surgeries. Medical management of AVN has been increasingly used in early stages in attempt to delay the progression of the disease.

Pharmacological management of AVN includes lipid lowering agents, anticoagulants, vasoactive substances, and bisphosphonates. Increases in both the number and size of circulating fat cells have been associated with the development of ON of the hip, therefore lipid lowering agents, such as statins, which reduce the rate of adipogenesis, are beneficial. Statins have been shown to provide protective effects for patients receiving steroids. It is still unclear whether statins have the ability to reverse steroid-induced ON once it has already occurred[31,32]. Anticoagulants such as enoxaparin act through the inhibition of platelets aggregation thereby increasing blood flow to ischemic areas of the bone. These agents are primarily beneficial in patients with underlying coagulopathy disorders, such as thrombophilia or hypofrinolysis[9,33]. Prostacyclin is a vasoactive agent that improves blood flow through its vasodilator effects in the terminal vessels. Although prostacyclin has shown significant improvement in both clinical and radiologic outcomes in early stages of AVN, long term benefits have yet to be established[34].

Bisphosphonates significantly reduce the incidence of collapse of the FH in osteonecrotic hips by reducing

osteoclast activity. Alendronate has been shown to prevent early collapse of the FH in Steinberg stages Ⅱ and Ⅲ non-traumatic ON at 24-28 mo follow up and has been reported to diminish the amount of pain at one year follow up when it is compared with placebo treatment[35,36]. Alendronate has been used as an adjunctive therapy with surgical procedures and has been found to reduce pain and the risk of collapse in early stages of ONFH[37]. Evidence for prevention of THR and reduction of AVN progression still remains controversial[38].

Biophysical treatments include extracorporeal shockwave therapy (ESWT), pulse electromagnetic therapy, and hyperbaric oxygen (HBO) therapy. ESWT has been shown to restore tissue oxygenation, reduce edema, and induce angiogenesis and may offer an alternative to the invasive modalities for FH necrosis in the earlier stages[39,40]. ESWT has also been associated with improvement in both pain and function, and has been found to result in a reduction of lesion size and bone marrow edema at 1-year follow up. Long term (8-9 years) improvement in pain and Harris Hip scores has also been demonstrated in the ESWT group treatment when compared with the core decompression group treatment[41]. Although not as commonly used, pulse electromagnetic therapy is believed to function by stimulating osteogenesis and angiogenesis however its role as early stage ON treatment has not yet been established[42]. HBO increases extracellular oxygen concentration and reduces cellular ischemia and edema by inducing vasoconstriction[43]. Studies have reported radiographic improvement in Steinberg stage I-AVN, as well as pain and ROM improvement in Ficat stage-Ⅱ ON[39,44].

Conservative treatment of AVN may be effective in the earlier stages of the disease. Although medical management may improve pain and functional outcomes, randomized clinical trials are necessary with long term follow up to determine effectiveness of therapy.

Surgical treatment
Currently there is no consensus regarding the treatment of the different stages of ONFH in the adult population[7,10,45,46]. A recent survey of 753 members of the American Association of Hip and Knee Surgeons reported that total hip replacement was the most common intervention for treatment of post-collapse stages of ONFH, whereas core decompression was the most common procedure for symptomatic pre-collapse stages of ONFH. Other less frequently performed treatments include conservative management, vascularized and non-vascularized bone grafts, hemi-arthroplasty, osteotomy, and arthrodesis[47]. ONFH tends to affect younger patients, therefore a variety of joint preserving surgical procedures have been developed to delay the progression of the disease and afford pain relief[5,21,48,49].

The surgical treatment of ONFH can be divided into two major branches: FH sparing procedures (FHSP) and FH replacement procedures (FHRP). In general, FHSP are indicated at pre-collapse stages with minimal symptoms whereas FHRP are preferred at post-collapse symptomatic stages.

FHSP: FHSP aim to preserve the FH and include core decompression (CD), CD combined with different grafting procedures and/or biologic agents and rotational osteotomies. Since all these procedures cannot restore the sphericity of the FH their role in the management of post-collapse stages is very limited[50,51].

CD: CD of the FH is the most common procedure currently performed to treat early stages of ONFH with the goal of decompressing the FH pressure in order to restore normal vascular flow and ultimately relieve pain[5,52,53]. The technique of CD has varied in terms of surgical approaches, number of drillings, and trephine diameter. Small diameter drilling has been proposed as an alternative because it has the advantage of reaching the anterior portion of the FH (most frequently involved region in ONFH) (Figure 5). In addition, small diameter drilling has been associated with minimal morbidity, less risk of weakening the FH and the articular cartilage, and less risk of stress risers that ultimately can lead to a subtrochanteric fracture[54]. Although CD has been shown to delay the progression of ON, its role in complete reconstruction of the necrotic area has not yet been established[55].

Bone grafting procedures: Non-vascularized bone grafts from different sources (allograft, autograft or artificial) have been used to fill the necrotic area in the FH. The grafting can be performed through the core decompression tract, which is the most common technique, but also through a window in the FH or in the femoral neck[56]. This latter technique, also referred to as the trapdoor procedure, requires a surgical dislocation of the hip in order to graft the defect through a cartilage window in the FH.

Vascularized bone grafting combines the benefit of core decompression along with an osteoinductive and osteoconductive graft in the devitalized FH. This procedure was popularized in the 1970's coincidently with the emergence of microsurgical techniques[51]. The variability among the surgical techniques to perform this procedure has however confounded the uniformity of the published data.

The free vascularized fibular grafting (FVFG) has been shown to support the subchondral architecture as well as restore local circulation to the necrotic FH in treatment of ONFH. A study on 470 patients with a mean follow-up of 5.0 years showed an average Harris hip score improvement from 65.0 to 86.9, no radiographic changes in 57.3% of patients, improvement in 33.7% of patients, and necrosis progression in 9.0% of patients respectively. These results show that the modified technique of the use of FVFG for treatment of ONFH yields similar postoperative results in comparison

Figure 5 Core decompression of the left femoral head. Preoperative magnetic resonance imaging, above (coronal and axial views) and fluoroscopic imaging during the procedure below.

to the traditional method. Although vascularized fibular grafting has shown promising results, especially in young patients with ONFH, the extensive surgical time, donor-site morbidity, prolonged rehabilitation, and an increased risk of a proximal femoral fracture has limited its use in practice[57-59].

Tantalum implants: Porous tantalum implants in combination with core decompression offers the advantage of providing structural support without the risk of autograft harvest or the infectious complications of bone allograft[60-62]. Veillete *et al*[62] reported an overall survival rate of 91.8% at twenty-four months, and 68.1% at forty-eight months after evaluating fifty-four patients with ONFH treated with core decompression and the insertion of a porous tantalum rod. Although these results appear promising, there are concerns about the origination of metal debris in the joint if a THR becomes necessary as well as a more complicated surgical technique. In addition, previous histologic studies demonstrated little bone ingrowth and insufficient mechanical support of the subchondral bone at the time of conversion from a tantalum rod to THR[63]. Long-term follow up is necessary in order to assess the functional and clinical outcomes of this technique.

Biological agents: There is considerable enthusiasm in the development of biological therapies that can enhance core decompression with osteogenic (mesenchymal stem cells) and/or osteoinductive agents (bone morphogenic protein) that have the potential to produce better results for larger lesions.

It has been hypothesized that there is an insufficient supply of progenitor cells in patients with AVN, which are required to enhance remodeling in areas of ON[64]. For this reason, newer treatment modalities have been developed to introduce stem cells to the areas of necrosis in order to prevent fracture and collapse of the FH. Since 2002, when Hernigou *et al*[65] first described a technique for injecting mesenchymal stem cells into an area of necrosis, four studies have prospectively evaluated the use of stem cells and core decompression. These studies presented consistent findings showing that patients treated with core decompression and stem cells achieved a significantly higher Harris Hip Score at final follow up. Gangji *et al*[66] reported in 2004 the results of a controlled, double blind study comparing core decompression with and without bone marrow aspirate. After 24 mo follow up the survival analysis revealed a significant difference in the time to collapse between both groups and a decreased of 35% of the necrotic lesion in the bone marrow graft group.

The instillation of stem cells into the osteonecrotic region of the FH can be performed through various methods. These include the direct instillation through the core tract, a selective femoral arterial perfusion, or the catheterization of the medial, lateral, or obturator artery. The direct instillation through the core tract is the most commonly performed procedure, however the catheterization of these vessels makes it difficult thereby requiring higher technical skills. However, it is important to maintain the final concentrate of cells

Figure 6 Right femoral head osteonecrosis. Flattening of femoral head progression in 24 mo ending up in a right total hip replacement.

Figure 7 Bilateral total hip replacement in a patient with bilateral hip osteonecrosis of the femoral head.

when doing a direct instillation in order to effectively regenerate the osteonecrotic region (optimum effective dosage minimum necessary concentration 5 × 107 and CD 34 + 5 × 107 cells)[45,67]. This is another factor that has been shown to influence healing of necrotic areas in the FH[64,65]. Additionally, the relationship between the injected volume and the lesion volume needs to be studied. Although these previous studies confirm that bone marrow aspirate concentrate has the potential to induce bone repair in ONFH, the data is preliminary and many questions still need to be addressed[45,64-67].

Osteotomies: Two general types of osteotomies, angular intertrochanteric and rotational transtrochanteric, can be performed to remove the segment of necrotic bone away from the weight-bearing region in the hip[68-72].

The transtrochanteric rotational osteotomy (TRO) for treatment of ONFH was introduced by Sugioka[71] in 1972. The aim of this procedure is to rotate the necrotic region of the FH out of the weight bearing area of the acetabulum. Sugiota[71] reported promising clinical results with a success rate of 78% after 3-16 years. However, their results with this technically demanding procedure have not been reproduced[68-70]. Rotational osteotomies can provide a painless, mobile, and stable hip if there is an unloading of the necrotic area of the FH when it is rotated from the acetabular major bearing surface and if the depth of the necrosis is not bigger than one third of the head diameter[71]. Hisatome *et al*[72] reviewed 25 hips in 21 patients six years after Sugioka's transtrochanteric anterior rotational osteotomy for ONFH. They concluded that although the collapse of a new weight-bearing region can be prevented, the progressive collapse of the transposed necrotic area induces anterior joint instability and subsequent arthritic changes.

Despite the promising results, patients who ultimately require conversion to THA after a proximal femoral osteotomy have a 17% intraoperative complication rate and an 82% survival rate of the implant after 10 years. Osteotomies are a reasonable option when they are performed by experienced surgeons in patients younger than 45 years with a Kerboull angle below 200° and no longer taking steroids.

Figure 8 Algorithm for the management and treatment of patients with osteonecrosis of the femoral head. RF: Risk factors; ONFH: Osteonecrosis of the femoral head; FH: Femoral head; MRI: Magnetic resonance imaging; FHCD: Femoral head core decompression; NVBG: Non vascularized bone graft; BA: Biologic agents; VBG: Vascularized bone graft; OA: Osteoarthritis; THA: Total hip arthroplasty.

FHRP

Although FHSP may provide good clinical results in patients with small pre-collapse lesions, these interventions are less predictable in patients with larger lesions or in FH collapse. These patients are therefore better candidates for FHRP.

Hemi-resurfacing arthroplasty and hemipolar/ bipolar hip replacement: Hemi-resurfacing arthroplasty is a significant treatment option when the joint surface is still preserved and the articular cartilage is minimally damaged. Possible indications include a Ficat Ⅲ, early stage Ficat Ⅳ, or early failure of a free vascularized fibula graft. With good patient selection and surgical technique this procedure can restore patient function although pain relief may not be as predictable as after THR[73]. Hemi-resurfacing arthroplasty causes little distortion of the anatomy, preserves bone, and produces minimal particle debris. Accurate evaluation of the acetabular articular cartilage and its longevity with this component poses a difficult challenge.

Hemi-arthroplasty replacements are an alternative treatment strategy as they preserve the acetabular bone stock. The major concerns with this procedure are the incidence of protrusion and polyethylene wear that can lead to particle-induced osteolysis and femoral stem loosening[74,75]. Nevertheless, either hemi-resurfacing arthroplasty or proximal femoral osteotomies are pre-ferred to hemi-arthroplasty.

THA: Arthroplasty is typically reserved for patients with late-stage ONFH, as well as older patients and those with more advanced arthritis (Figures 6 and 7)[47]. Arthroplasty is the only treatment that has been proven to reduce pain and restore mobility. In the United States, it is estimated that approximately 10% of all THRs are done in symptomatic hip ON[6,49].

There have been several studies which have shown poor results of THR for ONFH with failure rates between 37% and 53%, but more recent long term follow up studies have reported improved results compared with earlier reports[76-78]. The advances in the past two decades with the advent of surface bearings with low wear rates present promising results when used in patients with an advance stage of necrosis at mid-term follow up[79-81].

Kim *et al*[82] recently reported a 98% stem survivorship and an 85% cementless cup survivorship at 17.3 years of mean follow up. The most common reason for revision was due to cup wear or loosening. Although longer-term follow up studies are needed, promising stem and cup survivorship seems to be feasible.

Overall patients with ONFH present similar failure rates after THA than the general population. However a few ON risk factors, as renal failure and/or transplant and sickle cell disease, have been associated with

worse outcomes[81]. Fortunately these risk factors are present in a small population of patients with ONFH and even in this high-risk group population the outcomes of THR have improved over time[83-85]. Many studies have also shown that the outcomes of primary THR are not affected by previous hip joint preserving procedures[86-91]. However, THAs performed after rotational or angular osteotomies have shown higher complication rates when compared to those who did not have a previous osteotomy because of the disturbed anatomy of the proximal femur after the TRO[86,92-94].

CONCLUSION

Clinical and MRI characteristics need to be evaluated for the critical diagnosis of ONFH (Table 4). The progression of ONFH has not been well established, therefore it is difficult to evaluate whether a specific treatment modality changes the natural course of the disease. Medical management and surgical intervention has demonstrated to provide symptomatic relief, and early intervention prior to collapse has been shown to be critical to successful outcomes in joint preserving procedures. Future research should be directed at delineating whether one treatment strategy can delay the progression of ONFH of the hip thereby preventing collapse and the need for THA. A proposed algorithm for the diagnosis and management of ONFH is given in Figure 8.

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MINIREVIEWS

Complex ankle arthrodesis: Review of the literature

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Abstract

Complex ankle arthrodesis is defined as an ankle fusion that is at high risk of delayed and nonunion secondary to patient comorbidities and/or local ankle/hindfoot factors. Risk factors that contribute to defining this group of patients can be divided into systemic factors and local factors pertaining to co-existing ankle or hindfoot pathology. Orthopaedic surgeons should be aware of these risk factors and their association with patients' outcomes after complex ankle fusions. Both external and internal fixations have demonstrated positive outcomes with regards to achieving stable fixation and minimizing infection. Recent innovations in the application of biophysical agents and devices have shown promising results as adjuncts for healing. Both osteoconductive and osteoinductive agents have been effectively utilized as biological adjuncts for bone healing with low complication rates. Devices such as pulsed electromagnetic field bone stimulators, internal direct current stimulators and low-intensity pulsed ultrasound bone stimulators have been associated with faster bone healing and improved outcomes scores when compared with controls. The aim of this review article is to present a comprehensive approach to the management of complex ankle fusions, including the use of biophysical adjuncts for healing and a proposed algorithm for their treatment.

Key words: Ankle; Arthrodesis; Ilizarov; Reconstruction; Salvage

Core tip: This research article aims to review the definition, current trends and future direction of complex ankle arthrodesis surgery. To our knowledge, there has not been a review article in the literature on this important and challenging topic. This article discusses the major risk factors that entail this type of ankle fusion surgery. It brings forth the debate in recent literature on how to treat this complex pathology, mainly in regards

INTRODUCTION

Ankle fusion is often a limb salvage procedure in patients with end-stage or complex pathologic conditions of the ankle joint that may warrant a below-knee amputation as the only alternative. Complex ankle fusion is defined by certain risk factors of patients undergoing the procedure and includes individuals with comorbidities associated with poor surgical healing or with local healing problems that predispose to a high rate of delayed and nonunions. In addition to the technical demands of lower extremity surgery, concomitant suboptimal patient profiles impart significant challenges and constraints. The risk factors of patients undergoing complex ankle fusion can be organized into systemic and local factors that pertain to co-existing ankle or hindfoot pathology.

ETIOLOGY AND RISK FACTORS

Systemic factors

Systemic factors including patient comorbidities and global risk factors are frequently associated with failed or complication-ridden ankle arthrodesis. The spectrum of these factors is vast and includes advanced age, smoking, alcohol abuse, worker's compensation, non-compliance, obesity and systemic conditions (*i.e.,* atherosclerosis, immune suppression, diabetes mellitus and connective tissue diseases). Several studies convey the higher association of nonunion in patients who smoke or have a significant smoking history, which is even further heightened as the patient's age increases[1-4]. In a study by Fragomen *et al*[5] more than 50% of the patients who smoked failed to achieve healing of their ankle fusion. Alcohol abuse is another factor associated with nonunion in patients undergoing ankle fusion. Frey *et al*[6] displayed a greater than 85% nonunion rate among patients with major medical problems, which included alcohol abuse. Worker's compensation patients undergoing ankle fusion have been linked to poorer outcomes in comparison to provincial/third-party insured patients[2,3]. Patient compliance is imperative for attaining successful ankle fusion. The importance of restricted weight-bearing following ankle fusion with internal fixation cannot be emphasized enough as well as proper pin-care management in patients managed with external fixation in order to prevent failure and complications after the operation[7]. Although there is little evidence supporting obesity as a direct risk factor

for nonunion, it has been proposed to interfere with the healing process for bony union. Obese patients are faced with several challenges, including adequate cast or brace fitting as well as maintaining non-weight bearing status post-operatively. These circumstances have the potential to compromise the fixation and place increased mechanical load on the implant's fusion site, leading to unwanted motion at the arthrodesis[8]. Major complication rates seem to be relatively higher for smokers, patients with an increased BMI, and diagnosis of diabetes mellitus with rates of 80%, 70% and 65% of these patients, respectively, after ankle arthrodesis with external fixation[9]. The analysis of patients' concomitant diseases show that the incidence of systemic compromises associated with chronic local ischemia and disturbances of proprioception is three times higher in patients who developed nonunions. These chronic circulatory disturbances in combination with multiple operative procedures decreases the local healing potential of bone and soft tissue[10]. Chahal *et al*[3] found that patients who had noninsulin-dependent diabetes mellitus had an 18.7 times higher likelihood of varus malunion than nondiabetic patients. These patients also had poor clinical outcomes when compared with the remainder of the patients. Rheumatoid arthritis also adds a degree of complexity in ankle arthrodesis surgery. Bone stock and ankle deformity are frequently poor and necessitate more difficult and demanding operative treatment than osteoarthritis. In rheumatoid bone, it is typically difficult to achieve adequate purchase of screws and stable fixation. External fixation is more often complicated because of increased risk of pin tract infections and patients often receive high doses of corticosteroids and cytotoxic agents, leading to fragile skin and loss of subcutaneous tissue that impairs wound healing and increases infection. Patients with rheumatoid arthritis who are taking medications known to impede wound and bone healing require a drug-free interval during the perioperative period. Belt *et al*[11] study of rheumatoid patients undergoing the Dowel technique demonstrated a significantly high complication rate of infection and non- and malunion. Although the complication rate can be high, successful fusion can be achieved with a reported fusion rate of 90%[12]. Other systemic factors include major medical problems, such as end-organ failure, immunosuppresion, malnutrition, malignancy and chronic infections. In Frey *et al*[6] review of the predisposing factors leading to nonunion in ankle arthrodesis, patients with major medical problems (including renal failure, a significant smoking history, diabetes, and alcohol abuse) suffered an 85% nonunion rate. Saxena *et al*[13] demonstrated that the need for additional surgery was more likely if two or more of the high-risk designated criteria were met, which included immunosuppression, obesity and diabetes.

Local ankle and hindfoot factors

Local factors that define a complex ankle fusion include bone loss, a compromised soft-tissue envelope,

presence of infection, ankle or hindfoot deformity, and neuropathy. Frey *et al*[6] reviewed 78 patients who underwent ankle fusion and revealed a nonunion rate of 83% in patients who had an open fracture, 89% in patients with AVN and 60% in those with a history of infection.

Bone loss typically manifests as a result of high-energy trauma leading to comminution or bone expulsion, bone resorption secondary to chronic infection and avascular necrosis or bone stock deficiency post-TAR. Bone loss can also create a significant degree of shortening, leading to leg-length discrepancy. Tibial plafond fractures can present with a significant degree of periarticular comminution and metaphyseal bone loss, which makes compression fixation with internal fixation difficult or impossible. This renders neutralization fixation *via* ankle fusion an option to prevent secondary deformities that could result from compression fixation in the presence of bone defects.

In the setting of high-energy trauma, the soft tissue envelope is often significantly compromised by multiple traumatic and surgical scars, edematous, fibrous skin that is not pliable, or by draining sinus tracts if infection develops. This can be a risk when performing surgical approaches for fusion of the ankle[14].

Infection is often chronic and involves septic arthritis or osteomyelitis. Complex ankle arthrodesis success rates are decreased in the presence of infection. To achieve successful fusion in the setting of local infection, radical debridement, bone contact, stable fixation, and minimal compromise of the marginal blood supply are necessary. It is also of vital importance to avoid introducing foreign bodies at the site of infection and thus, external fixation should be highly considered. Antibiotic coated IMN can also be considered if acute shortening and bone contact can be achieved.

Deformity poses another obstacle to ankle fusion, often arising from the nature of the trauma itself, the result of malunion or nonunion from previous ankle fusions, or from co-existing neuropathy, which may lead to a Charcot arthropathy. Instability and progressive deformity in Charcot arthropathy can ultimately result in ulceration in a high percentage of cases. This leads to a high risk for progression to osteomyelitis and subsequent need for amputation[15].

SURGICAL TECHNIQUES

Surgical treatment for complex ankle pathology is often demanding and difficult due to the limitations imposed by the etiology of the patient's condition. There are over forty techniques documented in the literature which range from open crossed screw constructs to plates, intramedullary nails (IMNs), and external fixation devices. Although the most widespread operative strategy for achieving arthrodesis is internal fixation, the role for other methods of fixation and stabilization become more apparent as complexity of ankle pathology increases[16-18].

Both external and internal fixations have demonstrated positive outcomes with regards to achieving rigid fixation, union and minimizing infection. The pitfalls and advantages of each arthrodesis strategy must be considered in deciding the course of management that is most likely to achieve an optimal clinical outcome. Advantages of internal fixation include the ready availability of screws, the relatively low cost, the ease of application, and the documented clinical efficacy under favorable patient conditions[19]. Reduced rates of complications (such as non-union and infection) and neutralization of biomechanical forces have also been reported[20]. Relative to external fixation, it may provide earlier and higher fusion rates, a greater degree of patient satisfaction and decreased complications, especially soft tissue infections.

However, there are situations in which adaptation of the modular circular external fixator for ankle arthrodesis offers significant advantages over screw fixation. The Ilizarov ring system is indicated in difficult cases, especially when additional distal tibial pathologic conditions, bone defects, length discrepancies, or the need for early weight bearing are present[10]. Several of the indications for ring external fixation include: (1) bone quality that is subjectively and radiographically deemed to be insufficient to support internal fixation; (2) a history of infection at the tibiotalar nonunion site; and (3) expected patient compliance with external fixator pin care[7]. The combination of dynamic axial compression and demonstrated ability to resist bending, shear, and torsional forces allows the option of early weight-bearing. These features make it an ideal fixation tool for patients with complex ankle pathology. Unlike screw fixation, external fixation arthrodesis can be performed in poor bone and soft tissue conditions and can be used in the presence of active infection as a one-stage procedure. Typically after debridement of the tibial plafond and talus, flat surfaces are left for apposition. Compression with a circular frame provides excellent mechanical stability in this setting[21]. This allows the surgeon to employ this technique with confidence in patients deemed unsuitable for reliable screw fixation[17]. Another advantage of the Ilizarov method for ankle fusion is its ability to equalize limb length discrepancies through simultaneous tibial lengthening using distraction osteogenesis. Performing a tibial osteotomy in the setting of an ankle fusion has also been thought to enhance healing at the arthrodesis site[22]. In addition to limb lengthening, the principles of distraction osteogenesis can be used to correct malalignment. The ability to correct the position of the hindfoot and forefoot by adjusting the frame as needed during the regeneration phase is a unique advantage of the Ilizarov method. It allows the surgeon to address any intraoperative errors or early postoperative loss of position, ultimately leading to improved success when treating severe malalignment, failed fusion, and septic arthritis[23,24]. Thordarson *et al*[16] reported that screws provided better resistance to torsional

loading in specimens with higher bone quality, whereas external fixation resulted in better resistance to torsion in specimens with lower bone quality. The authors concluded that screw fixation is "essentially useless" in osteopenic bone. When Hoover *et al*[25] compared traditional crossed-screw fixation to bimalleolar external fixation, the bimalleolar external fixator revealed to be the more rigid construct in both bending and torsion as compared to traditional lag-screw technique. External fixation is not without its pitfalls, which may include increased risk of pin tract infections, wire breakage, decreased patient comfort with application of the device and the need for additional surgeries, including removal or repair of the fixator.

From a biomechanical point of view, the choice of combined internal and external fixation is reasonable. Compared with stabilization with external skeletal fixation alone, additional internal osteosynthesis offers the opportunity of early removal of the fixator and consecutive mobilization of the adjacent tarsal and metatarsal joints. With the protection of the internal osteosynthesis, beginning early partial weight bearing of the limb increases further bony healing[10]. Thordarson *et al*[16] demonstrated that the external fixator gives good protection against torsional rotation but lacks good stability against plantar flexion-dorsiflexion movements at the fusion gap. However, these forces can be neutralized by cancellous bone screws. Hybrid techniques such as lengthening and then nailing (LATN) and lengthening and plating (LAP) can reduce the amount of time spent in external fixation and the risk of early regenerate fracture[26,27].

INTERNAL *VS* EXTERNAL FIXATION

Internal fixation
Internal compression or neutralization plating: For many years, the most widely applied techniques for ankle arthrodesis were crossed lag screws and IMN. Recently, the use of compression or neutralization plating has become increasingly more common. This approach, often with the use of proximal humeral and pediatric blade plates, offers another option for stabilization of the arthrodesis, especially in the setting of high-energy trauma or osteoporotic bone. From a biomechanical perspective, internal compression plating has been shown to have similar initial stability when compared with IM nailing (IMN), both in uni-directional[28] and multi-directional loading planes. When comparing the stability of IMN and blade plate constructs in fresh-frozen cadaveric models with reduced bone mineral density, the results were also very similar. The relationship between bone density and plantar/dorsiflexion and torsional stability was not significantly different in either construct; only in inversion/eversion was there a difference between the two, with blade plates exhibiting a reduction in stability as compared to IMNs[29]. Independent studies evaluating union rates in patients with tibiotalocalcaneal (TTC) arthrodesis

via either blade plate fixation or IMN yielded similar fusion rates and clinical findings between the two constructs[30,31]. In a biomechanical study by Nasson *et al*[20] comparing the compression blade plate to crossed screws, crossed screws proved to make a stronger ankle fusion construct than the compression blade plate in valgus and dorsiflexion testing and trended to achieve greater resistance to plantarflexion, varus and torsional loads. However, in the presence of severe metaphyseal comminution and nonreconstructable joint incongruence, screw fixation techniques may be compromised while the blade plate demonstrates an attractive option. Ankle arthrodesis using a cannulated blade plate is a viable option to treat a nonreconstructable articular surface and metaphyseal bone defects in complex tibia pilon fractures. The cannulated blade-plate used in Bozic *et al*'s[32] series offered several advantages over other implants. Its use with a guide-wire allowed for precise placement of the blade, decreasing the likelihood of malposition and successfully maintaining correct foot position. It provided stable fixation with axial and rotational control in comminuted fractures with extensive bone-loss or non-union without requiring compression across the fusion site. Similar results were seen in Morgan *et al*[33] study where tibiotalar arthrodesis and metaphyseal reconstruction was achieved in all patients using a fixed-angle cannulated blade-plate with no mechanical or fixation failure. In comparison to IMN, the blade plate avoids the subtalar joint, preserving motion and decreasing the likelihood of arthrosis of adjacent joints. The use of the cannulated blade-plate allows for direct insertion with its thin leading edge of the blade, decreasing the likelihood of iatrogenic talar fracture. Complications seen with blade plate fixation include breakage of the plate and deep infection, especially in patients with a history of infection, which may require IV antibiotics and removal of the hardware. Disadvantages of the technique are related to prominence of the plate when it is placed anteriorly or laterally, which can lead to local irritation and need for subsequent removal of the plate[33].

Retrograde IMN: Ankle arthrodesis with a retrograde retrograde IMN has been shown to be an effective method for complex reconstructive procedures of the ankle and hindfoot. Recent biomechanical studies have shown superior strength with the use of IMN fixation over that of conventional cross screw techniques for ankle and hindfoot fusion, offering the advantage of being useful in conditions of either distal tibial and talar bone loss or when conventional screw fixation is suboptimal. Upon biomechanical comparison of IMN fixation and lag screw fixation for TTC arthrodesis, the IMN construct was shown to be significantly stiffer than the crossed lag screw construct after cadaveric specimens were subjected to cantilever bending tests in plantarflexion, dorsiflexion, inversion, and eversion as well as in internal and external rotation[34,35]. Thus,

the IMN can be seen as more helpful in aiding the maintenance of hindfoot alignment during union, which ultimately increases the rate of fusion. IMN also allows for immediate stability and alignment with less dependence on external immobilization. Indications for tibiotalar, TTC or TC fusion with the IMN include salvage of failed tibiotalar arthrodesis, globular avascular necrosis of the talus, failed TAR, rheumatoid arthritis, inflammatory arthropathies, Charcot arthropathy, and gross instability presenting as a flail ankle as well as other neuromuscular conditions[36]. Ankle arthrodesis using the retrograde IMN is an effective method of correcting deformity and providing a plantigrade, braceable foot in patients with severe Charcot arthropathy and diabetes mellitus. Dalla Paola *et al*[37] achieved complete bony union of the ankle panarthrodesis with use of the IMN in 14 of 18 patients with Sanders pattern IV Charcot neuroarthropathy with no intra- or perioperative complications. In a similar subset of patients, Pinzur *et al*[38] investigated the use of a longer, femoral nail for ankle arthrodesis and its role in decreasing the risk of tibial stress fractures compared with shorter nails. All 9 patients achieved fusion of their ankle arthrodesis with a longer retrograde femoral nail. There was no evidence of infection, stress fracture or stress concentration at the proximal metaphyseal tip of the nails and all patients were ambulatory without localized pain. Ankle fusion with longer IMNs dissipates the stress along the entire shaft of the tibia and prevents its concentration at the tip. In patients with tibial fractures previously treated with external fixation, there is a greater risk for infection with ankle arthrodesis using the IMN. Pawar *et al*[14] were able to achieve union and eradicate infection with an antibiotic-coated locked IMN in five patients with infected Charcot ankles, 3 of whom had failed treatment with circular external fixation for infected ankle neuroarthropathy. Retrograde IMN is associated with several complications which include wound slough, infection, malunion, delayed union and nonunion, hardware failure, plantar foot pain, stress fractures, cortical hypertrophy, or stress risers at the proximal nail junction. Deep infection with proximal extension often requires removal of the implant, debridement and salvage with an external fixator if arthrodesis is incomplete. Initial treatment for delayed unions and nonunions includes removal of the proximal locking screws and adjunctive use of bone stimulator. If nonunions are symptomatic, reaming and exchange to a larger rod, or alternatively salvage with blade plate and bone grafting augmented with compression screw fixation may be necessary. Plantar foot pain is minimized with placement of the nail flush with the plantar cortex of the calcaneus and avoiding insertion on the weight-bearing heel pad[36].

External fixation
The Ilizarov technique harbors several advantages in the management of patients undergoing complex ankle arthrodesis. Several circumstances, especially settings of infection, bone loss, osteopenia and poor soft tissue coverage, provide an inclination for the use of external fixation. As with any active infection, the introduction of foreign bodies (*i.e.,* internal fixation with plates and screws) poses a major risk for failed fusion and continued infection. External fixation bypasses implant usage and can be used in the presence of active infection as a one-stage procedure. With major bone loss or other defects, the principles of distraction osteogenesis can be used to correct limb length discrepancies and malalignment. It allows the surgeon to address any intraoperative errors or early postoperative loss of position. External fixation provides adequate dynamic axial compression of flat, otherwise unstable surfaces that may be continued in the postoperative period and is able to resist bending, shear, and torsional forces. Thus, the rigid fixation provided, allows for the option of earlier weight bearing than seen with other arthrodesis techniques. The following sections hereunder aim to discuss in further detail the outcomes of external fixation in various clinical scenarios.

SPECIAL SITUATIONS, OUTCOMES AND COMPLICATIONS

External fixation in patients with multiple comorbidities
Achieving arthrodesis in a Type B host presents a reconstructive challenge to the orthopaedic surgeon[5]. A Type B host is a patient with malnutrition, immune deficiency, chronic hypoxia, malignancy, diabetes mellitus, renal/liver failure, tobacco use, chronic lymphedema, major vessel disease, or extensive scarring. These patients have compromised bone healing and have traditionally been treated non-operatively or with amputation. External fixation has been used in the setting of these complex cases as a last resort treatment for limb salvage. Fragomen *et al*[5] achieved a fusion rate of 78% in Type B host patients, compared to a 94% fusion rate in Type A hosts. When smokers were excluded from the Type B hosts there was no difference between host type, demonstrating how smoking is one of the strongest predictors of failure among the factors that define a Type B host. Similarly to Fragomens' study, Cierny *et al*[39] reported success rates of 100% in Type A hosts and 83% in Type B hosts. Additional studies have demonstrated successful results in patients with multiple pathologies undergoing ankle arthrodesis utilizing the Ilizarov method. Kugan *et al*[40] demonstrated an 83% fusion rate with clinical functional improvement and no recurrence of previous deep infection in 48 patients with multiple comorbidities using the Ilizarov technique alone. Despite a few expected complications, most of which can be controlled and treated if recognized early, external fixation serves as a reasonable limb salvage alternative to amputation in this subset of patients.

External fixation in patients with infected and non-infected Charcot arthropathy
Severe foot and ankle deformity frequently arises as a

consequence of peripheral neuropathy, which ultimately leads to Charcot arthropathy. Charcot neuroarthropathy is most serious when the ankle is involved because of the instability and progressive deformity, which often leads to ulceration, osteomyelitis, and amputation. Limb salvage is considered superior to amputation if a stable, well-aligned, lower extremity can be achieved due to the excessive weight-bearing and potential increase in severe diabetic complications the contralateral limb will likely face. Ankle arthrodesis, even in cases before ulcerated lesions appear, is considered a limb salvage treatment for this condition. External fixation has been routinely applied for arthrodesis in patients with Charcot arthropathy. Among patients with complex ankle pathology undergoing arthrodesis *via* the Ilizarov method, the fusion rate for patients with Charcot neuroarthropathy has been shown to be lower than for patients without Charcot neuroarthropathy. These patients exhibit numerous complications, including tibial stress fractures, subtalar joint collapse after frame removal, total collapse of the calcaneal body, and return to the operating room for frame revision and have often ended with a below knee amputation[5]. Utilization of a neutrally applied three-level circular external fixator in diabetic patients affected by Charcot neuroarthropathy with midfoot deformities and open wounds has shown excellent results. Pinzur[41] demonstrated 24 of 26 patients to be ulcer and infection-free and able to ambulate with commercially available depth-inlay shoes and custom accommodative foot orthoses. Although complications such as amputation for persistent infection, stress fractures and recurrence of plantar ulcers were seen, the study concludes that adequate correction and maintenance of the fixed midfoot deformity with a neutrally applied ring external fixator can be achieved in morbidly obese diabetic individuals with multiple co-morbidities complicating severe Charcot foot deformity. Hybrid external fixation has also been used for ankle fusion in patients with Charcot neuroarthropathy complicated by ulcers with isolated tarsal or ankle osteomyelitis[15]. This technique has demonstrated an 87% fusion rate and achievement of a stable, plantigrade foot. The key elements of treatment using this method include: (1) complete debridement of the infected tissue; (2) application of the external fixator with pins and wires not interfering with the infection site; (3) the use of only tensioned thin wires on the foot; (4) 6 to 8 wk of parenteral antibiotics in the postoperative period; (5) strict non-weight bearing post-operatively for 8-12 wk; and (6) the use of negative pressure wound therapy for the postoperative treatment of open wounds.

External fixation in patients with failed total ankle replacement

Total ankle replacement (TAR) is often indicated in patients with end-stage tibio-talar arthritis. Although survivorship of the implant has improved, failure rates still remain elevated with revision arthroplasty being imminent within 10 years of the index procedure[42]. TAR failure results in bone defects, significant limb length discrepancy (LLD) and poor soft tissue envelope quality, limiting many surgical options. In addition to revision arthroplasty, arthrodesis serves as an alternative and is often the preferred salvage procedure. Several approaches to achieve arthrodesis have been reported, ranging from external and internal fixation (plates, screws and retrograde nails) with or without structural bone or trabecular metal graft. Salvaging failed TAR with ankle arthrodesis has the potential to create significant bone deficits. This issue can be addressed in several ways including shoe lifts, placement of auto- or allograft within the bone defect or staged tibial lengthening *via* the Ilizarov method. A retrospective case series by McCoy *et al*[43] investigated the utilization of the Ilizarov method for complex ankle fusion in 7 patients with failed TAR, 5 of whom had undergone prior revisions and re-revisions. External fixation demonstrated an ability to produce an excellent fusion rate in complex, possibly infected, failed TARs with no evidence of fixation failure, re-fracture, or infection in all patients and all achieving a stable, plantigrade foot with minimal limping. In the setting of failed TAR, the Ilizarov method evinces a particular appeal because the staged lengthening modality allows for limb length optimization to be achieved after ankle fusion and bony apposition has already been set in the frame. Optimal bone contact can be achieved at the ankle fusion site and accurate assessment of the postarthrodesis LLD can be done. The patient and surgeon can then make a more informed decision regarding further treatment with limb lengthening or a shoe lift. Both options allow precise adjustment of limb length to patient comfort. Additionally, since the reconstruction does not rely on indwelling hardware or allograft bone, there is less concern when working in an infected field.

External fixation in patients with septic arthropathy and bone loss

Injuries involving bone loss around the ankle are often secondary to high-energy trauma and present a unique challenge for reconstruction and limb salvage efforts. These injuries are frequently compounded by infection, scarring, poor bone quality and shortening, either due to the primary insult or after initial surgery. The ability to achieve a painless, stable limb with eradication of infection using internal fixation is difficult and often contraindicated, setting forth the option of external fixation. The Ilizarov technique has shown to be a viable alternative to amputation in patients with these difficult cases. The rationale is to provide fixed angle stable fixation of the bone fragments, a percutaneous approach that is particularly useful in the presence of poor skin, and avoid the use of internal implants in the presence of infection[44]. Zarutsky *et al*[9] exhibited circular wire external fixation to be a viable treatment for the complex ankle salvage pathology. In a setting where implantable hardware is an absolute

contraindication, only 2 of 12 patients with unilateral septic ankles achieved an unstable nonunion after external fixation. Salem *et al*[45] demonstrated the need for additional surgery and high complication rates despite successful fusion and clinical function using the Ilizarov frame for ankle arthrodesis in patients with significant bone loss and infection. Several patients, nearly all with septic ankle arthritis, needed repeat postoperative wound revisions or resection and renewed frame application to achieve union or to eradicate infection. With infection or AVN of the talus, complete or partial talectomy is often necessary which results in bone loss and LLD. This problem can be resolved with bone transport using the Ilizarov fixator for proximal tibial distraction osteogenesis. Of note, when comparing complex ankle fusion healing time in septic verus aseptic patients, a longer mean time to fusion for the infected cases has been shown[22,41].

External fixation in patients with revision ankle arthrodesis

Malunion and nonunion of an ankle fusion site are frequently complicated by persistent pain, infection, limb-length discrepancy and deformity. Revision surgery with the Ilizarov technique has been used to treat these complex conditions. The ultimate goals of revision ankle arthrodesis are a pain-free ankle, an almost normal gait pattern, and a foot capable of wearing a regular shoe. These goals can be met after obtaining solid union and correcting any deformity or malposition of the ankle, hindfoot, and forefoot. Advantages of external fixation over other methods for revision arthrodesis include rigid immobilization, resistance against shear and torsional stresses, axial loading with the ability for early return to weight bearing status, wound access, and manageability of large soft tissue and bony defects[36]. Excellent results have been achieved for revision ankle arthrodesis using external fixation with successful union being achieved in over 80% of patients and outcomes being comparable to those of primary arthrodesis. These patients who achieved successful fusion exhibited marked improvement in clinical outcomes scores[7,46,47]. The subgroup of patients undergoing revision arthrodesis present a unique challenge because most of them have coexisting pathological conditions and multiple previous operations[23]. Although achieving excellent radiographic and clinical results, the 22 (of 45) patients in Easley *et al*[7] study who had undergone revision tibiotalar arthrodesis with ring external fixation experienced the most complications in comparison to the groups with revision using internal fixation. Most of the complications were minor, not requiring surgical intervention. Although ring external fixation proved to have the highest rate of union among the methods of revision ankle arthrodesis and was effective for achieving union in several re-revision cases, it was associated with the majority of complications. Similarly to patients with other complex ankle pathologies, many patients undergoing revision

ankle arthrodesis with external fixation face major complications such as, persistent nonunion, the need for additional surgical procedures (*e.g.*, frame revisions, re-debridement of residual bone infections), as well as other issues such as pin-site infections, adjacent joint arthrosis and tibial fractures and below knee amputation. Patients undergoing revision arthrodesis with external fixation have also required longer periods of immobilization in comparison to primary arthrodesis surgery[12].

Patients undergoing simultaneous tibial lengthening

Many patients requiring ankle arthrodesis have a significant degree of limb-length discrepancy as a result of severe bone loss; often secondary to trauma or removal due to infection or AVN. Significant LLD presents a major issue in that a greater discrepancy is associated with a higher risk of ankle nonunion[5]. Patients with this issue undergoing ankle fusion using external fixation are at a major advantage in that the limb-length discrepancy can be addressed with either a distal or a proximal corticotomy, followed by distraction osteogenesis and compression at the arthrodesis site[22]. Not only can the external fixator correct limb length inequality, it allows partial weight-bearing during the reconstruction, which enhances rehabilitation and stimulates healing of the arthrodesis and the proximal bone transport[48]. The ideal candidate for tibial lengthening is a nonsmoker, young adult, with a strong family support system, who has greater than 3 cm of shortening[44]. The procedure should be staged several weeks after the index fusion procedure. Abiding to the Ilizarov technique, a seven-day latent period after the corticotomy should be followed by gradual distraction at 1 mm per day. The goal of treatment is for the operatively treated limb to be 0-1 cm shorter than the normal limb. This slight amount of limb shortening is necessary for toe clearance during the swing phase of gait. Several studies have demonstrated excellent results with simultaneous tibial lengthening during complex ankle arthrodesis. Of the 18 patients (with an average LLD of 4 cm) in Katsenis *et al*[23] study, 16 patients' limbs were able to be successfully lengthened to 1.5 cm shorter than the contralateral limb. Among 48 patients with complex ankle pathology that underwent ankle fusion, 11 patients underwent simultaneous tibial lengthening. Bifocal compression-distraction in 10 patients and bone transport in one patient resulted in both fusion and leg length equality. Similarly, eight patients in Rochman *et al*[48] study underwent proximal tibial distraction osteogenesis in the Ilizarov frame to achieve equal limb length. Aside from the common complications associated with external fixation, complications that may arise with bone transport include premature consolidation or delayed maturation of the regenerate bone at the osteotomy site as well as angulation at the site of transport. These complications may require the need for correction with surgical intervention. The advent of the Taylor Spatial Frame

(TSF), which enables correction of residual deformity by computer-generated software and gradual strut adjustments, can negate the need for surgery. Although lengthening adds to the complexity of treatment and prolongs the overall treatment time, it allows limb length equalization after aggressive debridement of all necrotic, infected, and poor quality bone. It also provides a biological stimulus for bone healing, alleviating the need for bone grafts. Studies have demonstrated a 2 to 3-fold increase in blood flow in the bone segment under distraction arthrodesis as compared to the contralateral side. This has been shown to accelerate bone union and control of sepsis[45]. The theory that performing a tibial osteotomy in the setting of an ankle fusion enhances healing at the arthrodesis site by promoting blood flow is, however, of much debate. Fragomen *et al*[5] study disproved the notion of increased fusion rates with osteotomy and simultaneous tibial lengthening. Patients with lengthening had a lower fusion rate, which the authors attributed to compromised healing seen with the increased complexity of patients with LLD that might require lengthening surgery. Simultaneous tibial osteotomy with ankle fusion also exposes the patient to increased swelling, blood loss, and increases the risk of thromboembolism and compartment syndrome.

BIOLOGICAL AND PHYSICAL AUGMENTATION FOR COMPLEX FUSIONS

Biological augmentation
With the progression of technical advances in external and internal fixation, complex ankle fusion outcomes have seen improvement. In addition to better surgical technique, a better understanding of bone healing biology has certainly contributed to these improved outcomes. The manipulation of bone biology to promote healing can be achieved with 2 types of biological agents, osteoconductive and osteoinductive agents. Osteoconductive agents serve as a scaffold matrix for cells to infiltrate, which allows bone to grow across the material. Osteoinductive agents are growth factors that stimulate nondifferentiated mesenchymal cells to differentiate into osteoblasts and other bone or cartilage forming cells. Osteobiologic agents that have been of current research focus include structural allografts, demineralized bone matrix (DBM) and bone morphogenetic proteins (BMPs).

The operative management of complex ankle and hindfoot pathology with large structural bone deficits can be difficult owing significant shortening of the limb. Fortunately, these conditions can be treated with arthrodesis in combination with implantation of bone graft. The foot and ankle is an area of great mechanical stress, rendering corticocancellous (structural) grafts to be frequently used due to the support and rigid fixation they facilitate. The use of frozen femoral head allograft has proven to be useful and safe for the treatment of these complex cases[49]. Although its use is technically demanding because of difficulty maintaining the position of the allograft during preparation and placement of the IM nail, the use of the "cup-and-cone" technique described by Cuttica *et al*[50] has shown to be helpful. After reaming the distal tibia and remaining talus or calcaneus with an acetabular reamer, a concave surface is created for secure placement of the convex interpositional femoral head allograft. The fusion interface leading to increased bone-to-bone contact between the allograft and the residual host bone in combination with the structural strength of the femoral head leads to a stable construct that more readily maintains the alignment and placement of the IMN while preserving the limb length of the patient's affected lower extremity.

A novel substitute to conventional bone graft measures is DBM, a form of allograft bone which preserves the proteinaceous growth factors present in bone that stimulate the induction of non-differentiated bone cells into osteoblasts[51]. It's use as a substitute for other forms of bone graft in complex ankle fusion surgery has demonstrated a mixed array of outcomes in regards to improved union rates[51-53]. Thordarson *et al*[51] was not able to demonstrate fusion rates superior to those observed with historical trials of DMB or standard forms of bone graft (*e.g.*, iliac crest autograft). Although DBM's osteoinductive properties have not exhibited superior results to gold standard autogenous iliac crest bone graft, its use does convey lowered risk of complications such as donor site infection, pain, neurovascular injury, and fracture. In addition, there may be insufficient autograft in cases with large bone defects and operative time is decreased when allograft is used. It is important to be aware of the risks carried with allograft, these include latent infection, decreased mechanical strength following sterilization, and an increased risk of fracture, collapse, or nonunion[43].

BMPs exert a wide range of osteoinductive growth factor functions, with most BMPs (except BMP-1 and 3) promoting cellular proliferation, apoptosis, differentiation, and morphogenesis. They induce bone formation by way of endochondral ossification and in high concentrations may form bone by way of intramembranous ossification[48]. They are key modulators of osteoprogenitor and mesenchymal cells during fracture healing. In a prospective randomized clinical trial of 450 patients who had open tibia fractures, patients who received an IMN in combination with high-dose BMP had significantly fewer hardware failures, shorter time to union, fewer infections, faster wound healing, and fewer nonunions when compared to the patients who only received the IMN[54,55]. Currently, recombinant BMP-2 (INFUSE®) is FDA approved for use in anterior lumbar interbody fusions (with fusion cages) and open tibia fractures treated with IMN fixation. Encouraging results in Liporace *et al*[55] experience with rhBMP-2 in high-risk ankle and hindfoot fusions promotes its clinical use in this spectrum of patients with an excellent safety profile. A case-control

study[56] involving 82 high-risk patients who underwent complex ankle fusion with an Ilizarov frame showed promising results in the patients treated with rhBMP-2. The patients were more likely to obtain fusion after the initial surgery, spent less time wearing the frame and showed more bone bridging on CT scans in comparison to the control group of patients. A reduction in time wearing the frame in patients treated with rhBMP-2 could signify decreased morbidity and complications, particularly superficial and deep infections, pin loosening or failure, and tibial fractures. Recent literature cites unexpected complications such as heterotopic ossification and retrograde ejaculation in patients treated rhBMP for spinal procedures in close proximity to the presacral sympathetic plexus[57,58]. In the case-control study mentioned, there were no differences in the frequency of complications between the groups and no heterotopic ossification, deep vein thrombosis, compartment syndrome, wound breakdown, or focal neurologic deficiency was observed in either patient group. However, another case-control study by DeVries *et al*[59] failed to show significance in the fusion rate and time until radiographic union for rhBMP-2-treated and untreated groups after TTC fusions secondary to failed initial arthrodesis. Even with these encouraging results, it must be stressed that osteobiologic agents, including rhBMP-2, are adjuvant agents; the use of rhBMP-2 alone will not ensure osseous healing and thus it cannot yet be solely relied upon on to bridge bone gaps, especially in high-risk patients.

Physical device augmentation

In addition to the wide array of adjunctive bone grafts and growth factors for complex ankle fusion, various external and internal osteobiologic devices have showed promising results. Three commercially distinct modalities have been of investigation for bone stimulation, which include: pulsed electromagnetic field (PEMF), internal direct current (DC), and low intensity pulsed ultrasound (LIPUS)[55].

PEMF have been approved by the FDA for stimulation of bone growth in the treatment of nonunions following fractures and failed arthrodesis. PEMF seems to stimulate healing of a nonunion through TGF-B-mediated differentiation of fibrocartilage cells and increased expression of BMP-2 and 4, leading to the stimulatory effect on osteoblasts[60,61]. Initial preclinical studies on the application of PEMF treatment on osteotomized rat fibula and canine tibia models demonstrated significant reduction in the amount of time-dependent bone volume loss and osteotomy gap size as well as faster recovery of dynamic load bearing with increased load-bearing capacity compared with the non-PEMF treated controls[62,63]. Use of PEMF devices less than the recommended minimum period of 3 h has been demonstrated to significantly reduce the efficacy of this modality of bone stimulation in union rates, with approximately 2.3 times less union reported compared with when PEMF is used for the recommended

periods[55]. Saltzman *et al*[64] investigated the use of PEMF, immobilization, and limited weight-bearing to treat 19 cases of delayed union after foot and ankle arthrodesis in 334 patients. The treatment protocol was successful in 5 of the 19 cases, with the remainder resulting in nonunion, thereby directing the authors to not recommend their PEMF protocol in treating delayed union in foot and ankle arthrodesis. They attributed the lower success rate, relative to fusion of long bones, to the geometric difficulties in orienting the coils to induce a current through the asymmetric foot and ankle.

The application of implantable DC bone stimulation for the treatment of complex ankle fusion has shown positive outcomes in several studies. Although the implantable DC stimulator may necessitate the need for a secondary procedure to remove the device in light of infection, local irritation, prominent hardware, or pain, it has several distinct advantages, which include increased compliance and constant, DC application to the site of interest with maximal intensity. Despite the absence of controlled studies directly comparing patients with and without implanted DC stimulators, several studies suggest that internal electrical bone stimulation may assist in fusions of the foot and ankle in high-risk patients. Saxena *et al*[13] demonstrated an 86% fusion rate utilizing implantable DC stimulation in conjunction with the standard arthrodesis protocol of bone graft and internal fixation in patients with diabetes, obesity, alcohol abuse, smoking history, previously failed arthrodesis or history of immunosuppressive drug use. Several complications did arise with 2 of the patients sustaining cable breakage of the implanted bone stimulator and 5 needing additional surgery, 4 of whom in order to achieve arthrodesis, which was subsequently successful. On a similar note, Donley *et al*[65] study exhibited a significant decrease in nonunion rate among high-risk patients, with 12 of 13 achieving fusion and improvement in mean pain scores after placement of an implantable DC stimulator during the arthrodesis surgery. Complications included a successfully treated superficial breakdown of a wound and 4 reoperations to remove the implant's batteries. Hockenbury *et al*[66] achieved a 90% fusion rate as well as improved clinical function in 10 patients with severe Charcot neuroarthropathy with the use of rigid internal fixation, autogenous bone graft and an implantable bone growth stimulator. In addition to complex primary arthrodesis procedures, implantable DC bone stimulation was analyzed in 10 consecutive revision arthrodeses for patients who had aseptic nonunion of the ankle. All 10 patients obtained solid fusion with good clinical outcome scale measurements[67].

The concept of LIPUS has also been applied to the arsenal of treatment for foot and ankle fusion. LIPUS has shown to accelerate the fracture healing rate for fresh fractures[68,69] as well as fracture nonunions[70]. It has received more attention for patients or fractures with potentially negative factors for fracture healing,

such as delayed unions and nonunions[71,72]. Jones *et al*[73] were the first to prospectively investigate the use of LIPUS in the treatment of hindfoot nonunions after revision hindfoot arthrodesis. Although the study was not a controlled series and included a variety of hindfoot nonunions and revision surgeries, it demonstrated improved clinical function and only one nonunion from a total of 19 joints (13 patients) that had been revisioned with arthrodesis in combination with LIPUS. An important disadvantage of LIPUS that was mentioned in the study was the high cost of the ultrasound units and reimbursement that varied between carriers and location. Jones *et al*[73] were also the first to complete a prospective comparative study evaluating clinical and radiographic healing of patients undergoing primary subtalar arthrodesis with LIPUS and demonstrated a 100% fusion rate with significantly faster healing rates on plain radiographs and CT in addition to improved clinical function 12 mo post-operatively compared to the control. Although the mentioned studies did not include high-risk nonunion patients, the outcomes demonstrated hold promising results for the treatment of a more complex group of patients. Because of the paucity of literature evaluating electrical and ultrasound bone stimulation with complex hindfoot and ankle arthrodesis, it is difficult to clearly define its role. Sufficient clinical evidence does not exist to support the use of one modality over another. Although the most important aspect in any fusion surgery is meticulous technique, advances in technology with bone stimulators and osteobiologic agents seem to be useful additions in the quest to achieve solid fusions with decreased complications[55].

CONCLUSION

Complex ankle fusion remains a challenging problem, with multiple factors ranging from local ankle and hindfoot pathology to systemic conditions and risk factors. Careful clinical and radiographic assessment, including CT and MRI might be warranted for proper decision making and formulating plan of management. Despite the limitations imposed by the etiology of the patient's condition, both internal and external fixation techniques have shown to be viable limb salvage alternatives, with each having there advantages and disadvantages. Both modalities have demonstrated very good fusion rates in a wide array of conditions including high-energy trauma, significant bone loss, deformity, and Charcot arthropathy. External fixation *via* the Ilizarov method has proved to be invaluable in cases with active infection, significant LLD as well as poor bone quality and soft tissues for adequate coverage. The antibiotic coated locked IM nail can be used in the setting of infection and bone loss if acute bony apposition can be achieved. Lastly, the use of biophysical adjuncts provides a promising field that requires additional randomized controlled trials to further justify their use in light of their expense.

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MINIREVIEWS

Physical activity after total knee arthroplasty: A critical review

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Abstract

Total knee arthroplasty (TKA) is the most commonly performed elective surgery in the United States. TKA typically improves functional performance and reduces pain associated with knee osteoarthritis. Little is known about the influence of TKA on overall physical activity levels. Physical activity, defined as "any bodily movement produced by skeletal muscles that results in energy expenditure", confers many health benefits but typically decreases with endstage osteoarthritis. The purpose of this review is to describe the potential benefits (metabolic, functional, and orthopedic) of physical activity to patients undergoing TKA, present results from recent studies aimed to determine the effect of TKA on physical activity, and discuss potential sources of variability and conflicting results for physical activity outcomes. Several studies utilizing self-reported outcomes indicate that patients perceive themselves to be more physically active after TKA than they were before surgery. Accelerometry-based outcomes indicate that physical activity for patients after TKA remains at or below pre-surgical levels. Several different factors likely contributed to these variable results, including the use of different instruments, duration of follow-up, and characteristics of the subjects studied. Comparison to norms, however, suggests that daily physical activity for patients following TKA may fall short of healthy age-matched controls. We propose that further study of the relationship between TKA and physical activity needs to be performed using accelerometry-based outcome measures at multiple post-surgical time points.

Key words: Physical activity; Knee osteoarthritis; Self-report; Total knee arthroplasty; Accelerometer

Core tip: Little is known about the influence of total knee arthroplasty (TKA) on physical activity levels.

This review describes the potential benefits of physical activity to patients undergoing TKA, presents results from recent studies aimed to determine the effect of TKA on physical activity, and discusses potential sources of variability and conflicting results for physical activity outcomes. Several studies indicate that patients describe themselves to be more physically active after TKA than before surgery. Accelerometry-based outcomes indicate that physical activity for patients after TKA may remain at or below pre-surgical levels. Daily physical activity for patients following TKA may fall short of healthy age-matched controls.

INTRODUCTION

Total knee arthroplasty (TKA) is the most commonly performed elective surgery in the United States for the relief of pain associated with osteoarthritis (OA)[1,2]. A central issue in patients with OA is reduced level of physical activity. TKA is successful for decreasing pain and increasing functional performance, but less is known about the influence of TKA on restoring overall physical activity levels[3-5]. Physical activity, defined as "any bodily movement produced by skeletal muscles that results in energy expenditure", confers many health benefits but typically decreases with endstage OA[6,7]. The purpose of this review is to describe the potential benefits of physical activity to patients undergoing TKA, present results from recent studies aimed to determine the effect of TKA on physical activity, and discuss potential sources of variability and conflicting results for physical activity outcomes.

The positive effects of physical activity are particularly important to patients undergoing TKA, as OA predisposes these individuals to metabolic and functional decline[1,8,9]. This decline may be protected against and/or remediated by physical activity[10-14]. For example, OA confers an increased risk of insulin resistance [odds ratio (OR) = 1.18 normal weight, 1.34 obese] and progression from insulin resistance to type two diabetes mellitus (OR = 2.18)[8,15]. Higher levels of physical activity are associated with reduced risk of metabolic disease, and interventions aimed to increase physical activity may improve metabolic outcomes[15,16]. Healthy metabolic function may be bolstered by physical activity in patients with knee OA, as indicated by higher levels of physical activity conferring an odds ratio of 0.45 for metabolic syndrome[17].

Functional performance strongly influences quality of life and is limited by OA and following TKA[18-20]. Though physical activity does not directly represent functional performance, limitations in functional performance may be improved by increased physical activity. Walking speed, an indicator of functional capacity, has been shown to improve in a population of people with knee OA after exercise aimed at increasing daily physical activity[21]. Little is known about the effect of physical activity on functional performance following TKA, but any potential relationship could be important as functional performance is chronically limited after TKA as compared to healthy adults. In spite of the potential limitations posed by the functional performance deficits present after TKA, treatments aimed to increase physical activity are of particular interest as they may actually ameliorate these functional performance deficits[22].

Physical activity appears to provide a protective effect against OA as demonstrated by a recent systematic review of the literature. This finding is likely related to the positive effect of physical activity on the maintenance of cartilage[23]. More physical activity is not only associated with greater tibial cartilage volume, but also fewer cartilage defects[24]. Although we are unaware of any studies investigating this association in patients with OA, this population could reasonably expect to derive similar benefits from physical activity.

In summary, patients suffering from OA are at increased risk of metabolic, functional, and orthopaedic dysfunction. Overwhelming agreement exists regarding the positive effects of physical activity on these issues. With these benefits in mind, characterization of physical activity levels after TKA is of great importance to promote optimal health and function, but little is known about the relationship of TKA and physical activity.

RESEARCH

This review encompasses results from searches performed in PubMed, Ovid Medline, and Web of Science. Search terms used were: TKA, total knee replacement, and physical activity, daily steps, and activity counts. No delimiters were used regarding date of publication. Studies in which patients undergoing TKA were present as a discrete subgroup were included. Intervention (*i.e.*, not including counseling or encouragement to increase the amount of physical activity performed) studies that determined the effect of TKA on patients' physical activity were excluded *a priori*, as were investigations addressing other types of knee surgery, including revision arthroplasty, and TKA subsequent to conditions other than OA (*e.g.*, hemophilia, acute infection). Since 2002, 18 published studies meeting our selection parameters have examined the relationship between TKA and physical activity (Tables 1 and 2)[25-42]. Five of the studies explicitly note recruiting OA patients undergoing TKA[25,26,29,34,37], while the remaining studies do not indicate the underlying conditions leading to TKA. We assumed that the majority of the individuals

Table 1 Summary of studies

Ref.	Study type	Assessment type	Assessment(s)	Duration of follow-up	Physical activity findings
Bauman *et al*[39]	Cross-sectional	Self-Report Questionnaire	UCLA	1 yr	Engage in moderate to high levels
Bonnin *et al*[41]	Cross-sectional	Self-Report Questionnaire	Perception	Mean = 44 mo	Mixed results
Brandes *et al*[25]	Longitudinal	Accelerometry	Activity Monitor (McRoberts; SAM, OrthoCare Innovations)	12-mo	Increase
Chatterji *et al*[42]	Cross-sectional	Self-Report Questionnaire	Grimby's Scale	1-2 yr	Engage in moderate levels
de Groot *et al*[26]	Longitudinal	Self-Report Questionnaire, Accelerometry	PASIPD, Activity Monitor (IDEEA)	6 mo	Self-report: Increase Accelerometry: No change
Franklin *et al*[27]	Longitudinal	Accelerometry	Activity Monitor (SAM, OrthoCare Innovations)	6 mo	Decrease
Hayes *et al*[28]	Longitudinal	Accelerometry	Activity Monitor (IDEEA)	6 wk, 3 mo, 6 mo, 12 mo	No change
In *et al*[38]	Longitudinal	Self-Report Questionnaire	LEAS	2 yr	Increase
Jones *et al*[29]	Longitudinal	Self-Report Questionnaire	Historical Leisure Activity Questionnaire	12 mo	Increase
Kersten *et al*[30]	Cross-sectional	Self-Report Questionnaire	Short Questionnaire to Assess Health Enhancing Physical Activity	1 to 5 yr	Less than healthy older adults
Krenk *et al*[31]	Longitudinal	Accelerometry	Activity Monitor (Actiwatch, Philips Respironics)	4 d, 6 d	Decrease
Lachiewicz *et al*[32]	Longitudinal	Self-Report Questionnaire	LEAS	1 yr, 2 yr	Increase
Meding *et al*[33]	Cross-sectional	Self-Report Questionnaire	UCLA	20 yr	
Tsonga *et al*[34]	Longitudinal	Self-Report Questionnaire, Accelerometry	PASE, Activity Monitor (Digiwalker, Yamax)	3-6 mo	Increase
Vaidya *et al*[35]	Longitudinal	Self-Report Questionnaire	LEAS	1 yr	Increase
Vissers *et al*[37]	Longitudinal	Accelerometry	Activity Monitor (Rotterdam Activity Monitor, Temec Instruments)	6 mo	No comparison performed
Vissers *et al*[36]	Longitudinal	Accelerometry	Activity Monitor (Rotterdam Activity Monitor, Temec Instruments)	6 mo, 4 yr	No change
Walker *et al*[40]	Longitudinal	Accelerometry	Activity Monitor (Numact)	3 mo, 6 mo	Increase

LEAS: Lower Extremity Activity Scale; PASE: Physical Activity Scale for the Elderly; UCLA: University of California Los angeles Physical Activity Questionnaire; PASIPD: Physical activity scale for individuals with physical disabilities.

Table 2 Outcome measure reliability and validity

Outcome measure	Reliability	Validity
Grimby's Scale	N/A	N/A
Historical Leisure Activity Questionnaire	r = 0.690-0.870[54,59]	r = 0.26[54]
LEAS	r = 0.9147[45]	r = 0.79[45]
PASE	ICC = 0.77[60]	r = 0.06-0.45[51]
PASIPD	r = 0.77[53]	r = 0.30[53]
Perception	N/A	N/A
Short Questionnaire to Assess Health Enhancing Physical Activity	r = 0.77[61]	r = 0.45[30]
UCLA	r = 0.86[49]	r = -0.50 – 0.51[62]
Activity Monitor	r^2 = 0.98[57]	r^2 = 0.91[56]

LEAS: Lower Extremity Activity Scale; PASE: Physical Activity Scale for the Elderly; PASIPD: Physical activity scale for individuals with physical disabilities.

participating in these investigations underwent surgery due to OA, as 95% of all TKAs in the United States are performed secondary to OA[25,29,34-37,43,44].

RESULTS

Longitudinal investigations

Thirteen of the studies in this review used longitudinal study designs. Of these thirteen studies, eight indicate that physical activity level is increased after TKA. However, physical activity level was measured exclusively by self-report questionnaire in four of the eight studies[29,32,35,38]. The Lower Extremity Activity Scale (LEAS), a self-report instrument developed by Saleh *et al*[45] to estimate physical activity in patients with lower limb dysfunction, was used in three of these investigations[32,35,38]. Vaidya *et al*[35] found mean LEAS scores (ranging from a minimally active zero to an extremely active 18) to increase from 6.7 pre-surgically to 11.3 (mean) one year after surgery (P values not provided). Increased LEAS scores were also found two years after TKA by In *et al*[38] [7.7 ± 2.1 to 10.3 ± 1.6 (mean ± SD), P < 0.001] and Lachiewicz and Lachiewicz [8.0 to 9.9 (mean), P < 0.01][32,38]. The final study to focus solely on self-report measures of physical activity used the Historical Leisure Activity Questionnaire (HLAQ)[29]. Median estimated MET-hours per week increased from 2.2 ± 12.4 before surgery to 10.8 ± 2.8 (mean ± SD) 12-mo after TKA (P < 0.0005), thereby exceeding the goal of 7.5 MET-hours per week of physical activity recommended by the United States Department of Health and Human Services[29,46]. Interestingly, this investigation also asked participants to

rate how active they expected to be after surgery, which was significantly greater [23.3 ± 41.1 MET-hours per week (mean ± SD)] than the actual estimated activity levels achieved ($P < 0.05$).

Two longitudinal studies reporting increases in physical activity after TKA used questionnaires in combination with accelerometry-based measures. Tsonga *et al*[34] administered the Physical Activity Scale for the Elderly (PASE) in 52 older women undergoing TKA. The average PASE for healthy individuals aged 65 years or greater is 103 ± 64 (mean ± SD)[47]. In the group of women undergoing TKA, scores increased from a mean of 43.3 before surgery to 67.9 (mean) six months after surgery ($P < 0.01$)[34]. In addition to the PASE, accelerometer-based activity monitors were used to quantify physical activity. However, physical activity monitoring was performed only three (2693 ± 1368 steps/d) and six months after TKA, (3518 ± 1835 steps/d; mean ± SD), and not pre-surgically, so neither alterations in accelerometry-based measures of physical activity, nor their relation to self-assessed measures of physical activity, could be adequately assessed[34]. A comparison can be made to the healthy population, however, as data derived from NHANES suggest the average woman between the ages of 70 and 74 years takes between 2565 and 4250 steps/d[48]. de Groot *et al*[26], performed both self-reported assessments of physical activity in METs per hour per day (METs h/d) using the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) and accelerometry-based measures, before and six months after TKA. Mean PASIPD scores increased from 9.5 at baseline to 17.9 METs h/d (mean) ($P = 0.01$) six months after TKA. However, accelerometry-based physical activity outcomes at three and six months after surgery were not different compared to those collected before surgery[26].

Finally, two investigations found increased physical activity after TKA using only accelerometry-based outcome measures[25,40]. Brandes *et al*[25] found significant increases in daily step count upon comparison of values collected prior to TKA to 12-mo follow-up [4993 ± 2170 to 5932 ± 2111, respectively (mean ± SD), ($P = 0.003$)][25]. Walker *et al*[40], using average amplitude of activity monitor displacement multiplied by steps per day as a surrogate for energy expenditure, found overall physical activity was increased by 79% ($P = 0.02$). This increase could have resulted from increased volume of physical activity, intensity of physical activity, or both.

In contrast to the eight studies that demonstrated increased physical activity subsequent to TKA, three longitudinal studies found no change in physical activity after TKA. These investigations used accelerometry-based measures. Vissers *et al*[36] found no difference in physical activity comparing pre-surgical values [9.4 ± 3.9, movement related physical activity, (% 24 h, mean ± SD)] to those collected six months (10.6 ± 3.5) and four years (9.6 ± 3.8) postoperatively[36]. Hayes *et al*[28] used a system consisting of five accelerometers

(IDEEA, MiniSun, Fresno, CA) attached to patients with TKA to characterize percentage of time spent in various activities including sitting, standing, walk/step/transition, and lie/recline. There were no differences in percentage of time in walk/step/transition between pre-surgical values and those collected six weeks, three months, six months, and Twelve months after TKA, which translated to a lack of significant changes in estimated energy expenditure over time. A second study performed by Vissers *et al*[37] identified percentages of time spent in movement-related activity before and after surgery as 7.6 (3.8, 17.5) and 8.1 (3.2, 17.0) percent [mean (minimum; maximum)] in participant satisfied with their surgical outcomes and 7.3 (2.7, 17.3) and 9.8 (2.8, 18.8) percent in participants less satisfied with their surgical outcomes. No statistical comparison was made between time points[37].

Two studies comparing pre- *vs* post-surgical activity suggest that physical activity may decrease after TKA. These studies used accelerometry-based outcome measures exclusively. Krenk *et al*[31] investigated the short-term (baseline compared to four and six days post-surgery) effect of TKA and found physical activity to be decreased [209861 ± 55077 to 163007 ± 56093 and 186333 ± 71482 activity counts/day, respectively (mean ± SD)], though no formal statistical analysis was performed[31]. Franklin *et al*[27] found similar results [3822 ± 1459 to 2881 ± 1700 steps/d, respectively (mean ± SD)] between pre-surgery and six-months post-surgery, with no statistical comparisons performed.

Cross sectional investigations

Cross-sectional and comparative investigations have also been performed to examine the relationship between TKA and physical activity. Bauman *et al*[39] found the median university of california los angeles (UCLA) Physical Activity Score to be six for 184 participants tested one year after surgery. Meding *et al*[33] demonstrated a mean UCLA Physical Activity Score of 8.3 ± 1.2 (mean ± SD) 20 years after TKA. The results of this investigation using the UCLA Physical Activity Score indicate participation in moderate to high (*e.g.*, bicycling, golf) intensity physical activity in patients having undergone TKA. Another investigation used Grimby's Scale. One to two years after TKA, patients reported a score of 2.8 ± 1.1 (mean ± SD) representing a moderate amount of physical activity. A major limitation of these studies is that PA scores were only assessed post-operatively. No comparisons were made to pre-operative values, nor were comparisons with matched controlled groups performed. Bonnin *et al*[41] used a slightly different approach by asking patients having undergone TKA how active they perceive themselves to be after surgery as compared to before surgery, with 41.5% reporting increased, 29.0% reporting the same, 26.8% reporting decreased, and 2.7% not reporting levels of physical activity.

Comparisons to healthy populations

Comparisons of physical activity performed by patients undergoing TKA to healthy individuals have attempted to characterize potential deviations from physical activity norms. Kersten *et al*[30] investigated physical activity level using the Short Questionnaire to Assess Health Enhancing Physical Activity and found that compared to healthy older adults, patients with TKA engage in significantly fewer minutes of physical activity per week [1433 ± 1313, TKA; 1533 ± 1325, healthy adults (mean ± SD), P = 0.05]. Franklin *et al*[27] found patients with TKA aged 69 years (mean) took 2881 ± 1700 steps/d (mean ± SD) (a value equal to the daily steps taken by the age-matched approximately 25th percentile of men and approximately 35th percentile of women) 6 wk after surgery[27,48]. This finding aligns with the one study that compared physical activity levels of patients receiving TKA to normative age- and sex-matched controls. Mean amounts of physical activity at medium and high intensity were found to be approximately 20% less in patients after TKA than in the healthy population[30]. This finding is absolutely critical as it suggests that even if physical activity increases from pre- to post-TKA, these levels may still be less than healthy individuals. On the other hand, Brandes *et al*[25] found patients having undergone TKA (aged 66 ± 6 years) to take 5496 ± 1969 (mean ± SD) steps/d six months after surgery (approximately 50th percentile for age-matched men; approximately 70th percentile for age-matched women)[25,48]. Walker *et al*[40] assessed the physical activity of patients undergoing TKA as compared to healthy control participants. This study indicates that although physical activity was improved six months after TKA, it was still approximately 20% less than that performed by the control participants.

DISCUSSION

Our review of 18 published studies examining the relationship between TKA and physical activity indicates inconsistent findings. While eight longitudinal investigations (most relying on self-report outcome measures) found improvements in physical activity levels in patients undergoing TKA after surgery, two others found no difference, and three observed a decrease. Several different factors likely contributed to these variable results, including the use of different instruments, duration of follow-up, and characteristics of the subjects studied. Each of these is considered below.

Outcome measures

Variability in outcome measures likely contributed to mixed results. Available reliability and validity values for these outcome measures are presented in Table 2. Not only did outcome measures vary between self-report and accelerometry-based measures of physical activity, but methods of self-report varied by number of questions, timeframe of retrospective self-report, and type of

activity assessed. The LEAS, for example is specifically tailored to patients with lower extremity dysfunction, and involves one question in which participants may rate their level of physical activity. The LEAS is generally deemed valid as reflected by correlation with pedometer measures[45]. Alternately, the PASE requires participants to recall the degree of physical activity in which they were involved during the previous week in 10 different areas. PASE scores take both type and volume of activity into account with possible scores ranging from 0 to 400. Several studies also used the UCLA Physical Activity Score. The UCLA Physical Activity Score is an instrument deemed to be valid in this population[49]. Participants are asked to rate their current activity level on a scale of one (which represents complete inactivity, dependence on others, and the inability to leave one's residence) to ten (which represents regular participation in "impact sports" such as jogging, ballet, and backpacking). Grimby's Scale, a less frequently used measure of physical activity, was also used for one study. In this self-reported scoring system, participation in physical activity ranges from one (hardly any physical activity) to six (regular, hard exercise)[42]. To our knowledge, Grimby's Scale has not been validated. When comparing patients having undergone TKA to healthy individuals, Kersten *et al*[30] utilized the Short Questionnaire to Assess Health Enhancing Physical Activity, which is moderately valid when compared to accelerometry-based measures[30,50]. This questionnaire examines days per week, average time per day, and intensity per session of walking and bicycling for both commuting and leisure. The most extensive self-report measure of physical activity found in these studies is the HLAQ. This assessment asks participants to recall their degree of participation (hours per week) and intensity in 36 leisure activities over the previous month. These results are subsequently translated as an estimate of MET-hours per week as an analog to kilocalories spent in physical activity normalized to body mass. Overall, the variability inherent in the different types of self-report instruments casts doubt on the ability to directly compare their results. Furthermore, all of these instruments rely on participant recall of physical activity participation, which has previously been shown to be problematic in individuals with TKA. For example, Bolszak *et al*[51] found the PASE to be poorly suited to patients undergoing TKA in terms of standard of error of measurement (32%-35%), smallest detectable change (89%-97%), and construct validity.

Concern regarding the validity of self-reported physical activity measures was recently raised by Prince *et al*[52] who performed a systematic review of studies examining both self-reported and direct measures of physical activity in adults. Self-reported measures' correlation to objective measures ranged from strong direct to strong indirect indicating poor overall agreement between recall of physical activity and accelerometry-based measurements of physical activity in a variety

Table 3 Patient characteristics by study

Ref.	N	Age at surgery (mean ± SD)	Body mass index (mean ± SD)	Sex distribution (M/F)	Comorbidities
Bauman *et al*[39]	184	66.4 ± 9.4	30.6 ± 7.9	76/108	Undisclosed
Bonnin *et al*[41]	347	74.8 (28-94)	27.9 ± 4.9	120/227	Undisclosed
Brandes *et al*[25]	53	65.8 ± 5.8	30.7 ± 4.1	19/34	Undisclosed
Chatterji *et al*[42]	144	70.8 ± 10.4	-	64/80	Undisclosed
de Groot *et al*[26]	44	62.1 ± 9.7	32.1 ± 5.3	20/24	Undisclosed
Franklin *et al*[27]	14	-	-	7/14	Undisclosed
Hayes *et al*[28]	65	61.1 ± 2.2	30.3 ± 2.8	5/7	Undisclosed
In *et al*[38]	169	66.7 (49-85)	26.4 ± 4.2	152/17	64 with metabolic syndrome, 40 with hypertension, 36 with diabetes, 13 with hypertension and diabetes
Jones *et al*[29]	90	66.5 ± 9.7	32.6 ± 7.2	36/54	Comorbidity Index of the American Academy of Orthopedic Surgeons Outcomes Data Collection Questionnaires = 0.9 ± 1.2
Kersten *et al*[30]	844	74.4 ± 11.9	29.4 ± 5.0	229/615	Undisclosed
Krenk *et al*[31]	20	70.5 (61-89)	26.4 (19-34)	7/13	Undisclosed
Lachiewicz *et al*[32]	188	71 (41-89)	30.9	49/139	Undisclosed
Meding *et al*[33]	128	63.8 ± 8.9	-	35/93	Undisclosed
Tsonga *et al*[34]	52	72.6 ± 5.9	29.79 ± 5.27	-	Undisclosed
Vaidya *et al*[35]	100	-	-	48/62	55 with diabetes, 65 with hypertension
Vissers *et al*[37]	44	63.5 (42.0-78.0)	30.8 (24.2-44.9)	20/24	Undisclosed
Vissers *et al*[36]	21	63.8 ± 9.4[1]	29.7 ± 5.0[1]	9/12	Undisclosed
Walker *et al*[40]	19	M: 69.1 ± 5, F: 69.0 ± 7.8	-	10/9	Undisclosed

[1]Includes total hip arthroplasty patients.

of adult populations[52]. The PASIPD, for example is somewhat similar to the PASE, but asks a slightly greater volume of questions, yet remains only moderately weakly related to accelerometry-based measures indicating potential validity issues[53]. The validity of the HLAQ may also be an issue with relatively weak relation to activity logs[54]. These concerns are further bolstered by a recent systematic review performed by van Poppel *et al*[55] that found generally poor evidence of adequate validity and reliability in physical activity questionnaires. More extensive validation was deemed to be required even for those that did demonstrate some initial degrees of reliability and validity.

To our knowledge, studies examining the potential impact that an intervention (TKA, in this case) might have on patients' perceptions of their physical activity levels have not been performed. We believe, however, a reasonable argument can be made that decreased pain in combination with enhanced functional performance may lead patients to perceive that they have become more active after TKA. Such an altered perception could explain the apparently dichotomous findings of the majority of self-reported measure compared to several accelerometry-based measures of physical activity. In fact, the only study to compare physical activity values collected prior to and after TKA using both self-report and accelerometry-based measures arrived at divergent results[26]. While patients reported increased levels of physical activity with self-report outcome measures, accelerometry reflected no alterations upon comparison of pre- to post-surgical values.

While self-reported outcome measures are com-

pelling from the perspectives of cost efficiency and ease of administration, they may lack the accuracy required to assess physical activity in an orthopaedic population undergoing a significant intervention such as TKA, and the rehabilitation process typically associated with the surgery[52,53,55]. We suggest that accelerometry-based assessment of physical activity offers greater accuracy than self-reported measures due to validity compared to VO$_2$max, no significant difference in energy expenditure estimation as assessed by doubly labeled water, and the reliability required to assess the outcomes associated with TKA[56,57].

Time to follow-up
Another key difference in the identified studies is time from surgery to follow-up assessment. Time periods ranged from as few as three days to as many as 27 years[31,33]. This may preclude meaningful comparison of studies with different follow-up time points. We suspect that this may be the case as other factors (*e.g.*, functional performance and pain) vary greatly over time[22,58]. Differences/alterations in physical activity between any of these time points may also be altered by both acute chronic health issues as well as the normal course of aging.

Participant characteristics
Participant characteristics (Table 3) of the investigations discussed herein were highly variable. Although mean BMI was similar across studies, all but one study described a predominantly female population[38]. Furthermore, average participant age ranged from 61.1 to

74.8 years[28,41]. This difference may have impacted the ability to compare studies, as age is known to be negatively related to physical activity. This issue is further complicated as the influence of age in combination with an intervention (*e.g.*, TKA) on physical activity is unknown. Another potentially complicating factor is variation in patient comorbidities between studies. Of the articles discussed in this review, only three disclosed patient comorbidities. Of 169 total patients, In *et al*[38] contained 64 with metabolic syndrome, 40 with hypertension, 36 with diabetes, 13 with hypertension and diabetes. Of 90 total patients, Jones *et al*[29], contained patients with a Comorbidity Index of the American Academy of Orthopedic Surgeons Outcomes Data Collection Questionnaires = 0.9 ± 1.2. Of 100 total patients, Vaidya *et al*[35] contained 55 with diabetes, 65 with hypertension. BMI, age, and number/severity of comorbidities are patient characteristics that may have influenced the physical activity of the patients described by these studies.

FUTURE DIRECTIONS

Physical activity is critically important to both short- and long-term health in the population at large, but is of particular importance for patients undergoing TKA to maintain overall health and improve functional performance deficits commonly related to OA. To this end, we propose that further study of the relationship between TKA and physical activity needs to be performed using accelerometry-based outcome measures at multiple post-surgical time points. Potential predictors of physical activity performance after TKA, such as demographic and lifestyle characteristics, should also be investigated. Furthermore, to our knowledge intervention studies aimed to increase physical activity in patients after TKA have not been performed.

CONCLUSION

The investigation of physical activity following TKA is important for the understanding of overall health maintenance and identifying potential targets for improving physiological and functional outcomes. Physical activity (particularly walking) is an attractive intervention as it can be self-managed and performed on a daily basis with low cost and minimal equipment. Several recent investigations have examined physical activity following TKA, using a variety of outcome measures and time-points. On the one hand, some studies indicate that patients perceive themselves to be more physically active after TKA than they were before surgery. On the other hand, several studies using accelerometry-based outcomes indicate that physical activity for patients after TKA remains at or below pre-surgical levels. In addition, daily physical activity for patients following TKA may fall short of healthy age-matched controls and does not meet recommended daily amounts for

health maintenance and/or improvement. More rigorous studies need to be performed investigating the effect of TKA on physical activity. Furthermore, future research should seek to create and refine interventions aimed to increase the amount of physical activity engaged in by patients having undergone TKA.

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Recent biological trends in management of fracture non-union

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Abstract

Bone regeneration is a complex, well-orchestrated physiological process of bone formation, which can be seen during normal fracture healing, and is involved in continuous remodelling throughout adult life. Currently, there is a plethora of different strategies to augment the impaired or "insufficient" bone-regeneration process, including the "gold standard" autologous bone graft, free fibula vascularised graft, allograft implantation, and use of growth factors, osteoconductive scaffolds, osteoprogenitor cells and distraction osteogenesis. Improved "local" strategies in terms of tissue engineering and gene therapy, or even "systemic" enhancement of bone repair, are under intense investigation, in an effort to overcome the limitations of the current methods, to produce bone-graft substitutes with biomechanical properties that are as identical to normal bone as possible, to accelerate the overall regeneration process, or even to address systemic conditions, such as skeletal disorders and osteoporosis. An improved understanding of the molecular and cellular events that occur during bone repair and remodeling has led to the development of biologic agents that can augment the biological microenvironment and enhance bone repair. Orthobiologics, including stem cells, osteoinductive growth factors, osteoconductive matrices, and anabolic agents, are available clinically for accelerating fracture repair and treatment of compromised bone repair situations like delayed unions and nonunions. A lack of standardized outcome measures for comparison of biologic agents in clinical fracture repair trials, frequent off-label use, and a limited understanding of the biological activity of these agents at the bone repair site have limited their efficacy in clinical applications.

Core tip: Successful fracture healing requires mechanical stability and a viable biologic microenvironment. Fractures with compromised biology will benefit from treatment options that can augment the biologic potential at the site of bone repair. An ideal bone graft

should be osteoinductive, osteoconductive, osteogenic, angiogenic and should provide mechanical support and promote physiologic healing without any significant adverse effects. Regenerative strategies like the use of bone morphogenic proteins, platelet rich plasma, stem cells and anabolic agents are promising in the treatment of fractures either acute or fracture non-union.

INTRODUCTION

Healing of the fracture is a multifactorial metabolic process. If these factors impaired, healing process is interrupted resulting in fracture nonunion[1]. The majority of fractures heal without any complications, but literature reported non-union of all fractures ranged between 5% to 10%[2].

Biological stimuli for regeneration of bone involve the interplay of four critical elements, namely: (1) osteoinductive growth factors (induce differentiation of stem cells to osteoblasts); (2) stem cells that respond to osteoinductive signals (osteogenic); (3) an intact vascular supply, and, finally; and (4) a scaffold that supports cellular attachment, proliferation, and ingrowth (osteoconductive matrix)[3].

This article provides a review of the biologic agents that can enhance bone healing either clinically available or are still under trials.

BIOLOGIC ENHANCERS OF BONE REPAIR

Bone grafting, scaffolds and bone substitutes

Autologus bone graft is a commonly performed surgical maneuver to enhance bone healing and being considered as the "gold standard" as it contains all properties required in a bone graft material: osteoinductive [bone morphogenetic proteins (BMPs) and other growth factors], osteoconductive (scaffold) and osteogenesis (osteoprogenitor cells) and has a success rate of 50%-80%[4].

The iliac crest is the commonly used donor sites. But harvesting has its complications and needs an additional surgical procedure[5].

Allogeneic bone graft bypasses the harvesting problems and graft quantity. It is available in many forms, such as demineralised bone matrix, cancellous and cortical, corticocancellous, osteochondral and whole-bone segments[6]. But They have decreased osteoinductive properties and with no cellular component, their main drawbacks are the issues of rejection, immunogenicity, transmission of infection, and cost[7].

Bone-graft substitutes are alternatives to autolo-gous or allogeneic bone grafts. They are composed of scaffolds, such as collagen, hydroxyapatite, b-tricalcium phosphate[8] that enhance the proliferation of bone cells for bone regeneration[6].

Aspiration concentrate of the bone marrow

It contains stem cells that could differentiate into osteoblasts in response to osteoinductive signals[7]. Classically, the iliac crest is the main donor for bone marrow aspiration, but alternative sites, including the vertebral body, proximal humerus, proximal tibia, have also been described[9].

Connolly *et al*[10] were among the first to demonstrate the efficacy of percutaneous bone marrow injection in the treatment of nonunited fracture tibia. In a cohort of 20 tibial nonunions, 90% healed in aveaged 6 mo after injection. In a retrospective study involving 60 atrophic tibial nonunions Hernigou *et al*[11] demonstrated complete healing in 88.3% that were treated with a single injection of bone marrow aspirate.

Percutaneous bone marrow grafting is a minimally invasive treatment. It avoids the complications associated with the open graft harvest procedure. However, this technique, if used alone, may not be sufficient to induce healing of complex fractures with large bone gaps[12].

Platelet rich plasma

Platelet concentration counts in a healthy individual between $1.5\text{-}4.5 \times 10^5/\mu L$. To be labeled as platelet rich plasma (PRP), a platelet count of 4-5 times of the baseline should be present in the platelet concentrate[13].

Platelets contain granules which contain multiple growth factors and cytokines that play an important role in the early responses of bone repair and also help the regeneration of tissues with low healing potential[13].

PRP preparation includes drawing of blood into a tube containing an anticoagulant followed by centrifugation then treated with calcium chloride and bovine thrombin which forms a gel-like substance for direct application[14].

Hakimi *et al*[15] compared combined PRP with autologous cancellous graft and isolated autologous cancellous graft in long bones of minipigs. There was a significantly better bone regeneration in case of combined PRP and graft. Yamada *et al*[16] combined mesenchymal stem cells with PRP in a canine model that resulted in a higher maturation of bone.

PRP is autologous and nontoxic, with no risks of immunogenic reactions. However, the use of bovine thrombin leads to the development of auto-antibodies against factors V and XI, and thus the risk of life-threatening coagulopathies[17].

BMPs

They are involved in early limb development and enhance maturation and function of differentiated cells (chondrocyte and osteoblast)[18]. They bind to their

receptors (serine/threonine kinase receptors) which are responsible for modulating gene transcription[19].

BMP-2 and BMP-7 are the most intensively studied BMPs in the recombinant technology. Their role in the treatment of fractures nonunion has been evaluated in multiple trials and small case series[20].

Adult patients with a diaphyseal fracture tibia with a residual bone defect were randomly received either an autogenous bone graft or a combination of an allograft and rhBMP-2 on a collagen sponge. Healing rates in the autograft group was 66.6% and in the rhBMP-2 group was 86.6%[21].

In a prospective randomized trial, tibial nonunions that required internal fixation and supplemental bone grafting were randomly received either rhBMP-7 or fresh autograft bone, rhBMP-7 (81% healing rate) demonstrated clinical equivalence with respect to fracture union compared with the autograft group (85% healing rate) at 9 mo ($P = 0.0524$) and 2 years ($P = 0.93$)[22].

However, in a prospective study, Ekrol *et al*[23] reported conflicting results with the use of rhBMP-7, Thirty patients with a distal radius malunion were stabilized with a fixator or a plate and were randomly received either rhBMP-7 or autogenous bone graft. The autogenous bone graft group had higher healing rates and shorter time to union ($P = 0.02$). However, the study sample size was small and there was no power analysis presented in the study for sample size calculation. The rhBMP-7 treatment group had higher rates of inflammatory swelling and osteolysis at the site of malunion site.

RhBMPs are among the most common biologic agents used for enhancing bone repair. However, there are certain hurdles limiting their efficacious use in humans. First, rhBMPs have a short half-life and complete healing large bone defects need more than single dose[24]. Second, the ideal carrier matrix for rhBMPs is yet to be identified[25]. Third, supraphysiologic doses (in milligrams) of rhBMPs are being used in humans, and its long-term effects are not clearly known. Consequently, rhBMPs are not FDA-approved in the pediatric age group, in pregnant patients, or in the presence of tumors. Finally, there are complications associated with rhBMPs that are either related to the initial inflammatory response induced by the proteins (neck swelling, seroma, neuritis) or are an extension of their osteoinductive function (heterotopic ossification, paraplegia, transient osteopenia)[26].

Fibroblast growth factor

Fibroblast growth factor (FGF) receptor promotes expression of multiple genes that are involved in all stages of osteogenesis. FGF signaling also controls osteoblast gene expression and apoptosis[27].

A study on the safety and efficacy of rhFGF-2 in fracture, suggested a beneficial effect of rhFGF-2 on bone repair. However, none of the clinical studies has demonstrated any significant improvement in the healing rates compared with the controls[28].

Stem cells

A stem cell is a cell that has two essential characters: and ability to differentiate into a particular cell type and self-renewal[29]. Adult stem cells are pluripotent. They participate in physiologic remodeling/turnover of normal tissues and repair of the injured tissue[30].

Bone marrow is the most intensively studied source of stem cells for bone repair. However, stem cells have been harvested from other tissues, including muscle, periosteum, adipose tissue, vascular pericytes, dermis, and peripheral blood[7]. Fat-derived stem cells still on debate[31].

Quarto *et al*[32] demonstrated successful healing of large bone defects (average of 5 cm) in three patients with bone marrow-derived mesenchymal stem cells (MSCs) seeded on a ceramic scaffold.

Marcacci *et al*[33] used bone marrow-derived MSCs seeded on a ceramic scaffold to treat four diaphyseal bone defects which were stabilized with external fixators. All bone defects demonstrated complete healing at an average of 6 mo with no recorded complications.

Novel techniques of MSCs harvesting, *in vitro* expansion are encouraging[34]. MSCs *in vitro* expansion done by growing them in an osteogenic differentiation media prior to transplantation in the host[35]. But these approaches add costs and risks of viral or bacterial contamination, besides time consuming since they require a two-stage surgery[36].

The use of MSCs in fracture healing is still in the beginnings, mainly due to a lack of studies into the MSCs *in vivo* biology in the fracture environment[37].

Tissue engineering

Bone tissue-engineering is a strategy combines the principles of orthopaedics with biology, physics, materials science and engineering, to generate cell-driven, functional tissues[38].

It combines progenitor cells which are seeded in biocompatible scaffolds with appropriate growth factors, in order to form hybrid constructs to generate and maintain bone, especially for the management of large bone defects[39].

Seven human studies have been done using these hybrid constructs for bone defects healing[40]. They are heterogeneous studies and drawing conclusive evidence from them is complicated[41].

Bone-tissue engineering is still starting, and there are many concerns of efficacy, safety and cost should be addressed before being clinically applied[42].

Gene therapy

It involves the transfer of genetic material into the target cell genome. Genetic material can be done using viral (transfection) or non-viral (transduction) vectors, and by either an *in vivo* or *ex vivo* gene-transfer strategy[43].

Delivery of growth factors, particularly BMPs, using

this technique for bone healing produced encouraging results in animal studies but the issues of cost, efficacy and safety still under concern[44,45].

Systemic enhancement of bone regeneration

The use of systemic agents, including growth hormone[46] and parathyroid hormone (PTH)[47] for acceleration of bone-regeneration process is under extensive research.

There are multiple trials conducted that these biologic agents can be administered systemically to enhance bone repair[48]. The major advantage of these systemic drugs is that healing can be stimulated for a prolonged period of time besides being non-invasive procedures. Recombinant PTH is available clinically, but two more agents; sclerostin antibody and anti-Dkk-1 (anti-Dickopff antibody), are currently being developed for enhancing bone repair in humans. In preclinical fracture studies, sclerostin antibody systemic administration significantly increases the bone mass and callus[49].

Future directions

A strong need of clinical results is required to further progress in cell therapy. Launched trials will hopefully provide this information in the near future. If clinical results are positive, far greater challenges may be raised by the development of more complex tissue engineering techniques, and this may allow the treatment of large bone defects and unsolved situations. A multidisciplinary approach will be required to improve implanted cell survival and to ensure prompt vessel ingrowth into the biomaterial *via* careful selection of structure and shape. The development of new combinations (hydrogel-based, bioceramic-based, or other) that could eventually craft solutions for supplying cells and biomaterials percutaneously is expected in the near future. The immunosuppressive properties of MSCs may allow the transplantation of allogeneic MSCs in various orthopedic conditions, with the establishment of cell banks for regenerative medicine. Early trials evaluating allogeneic MSCs in delayed unions are already under way. And last but not least, a future step that may help to further define and spread these therapies is a careful cost–benefit assessment and a broad economic evaluation to clarify the best indications of bone repair cell therapy as a standard procedure, if confirmation of safety and efficacy is clearly derived from current trials[50].

CONCLUSION

Successful fracture healing requires mechanical stability and a viable biologic microenvironment. Fractures with compromised biology will benefit from treatment options that can augment the biologic potential at the site of bone repair. An ideal bone graft should be osteoinductive, osteoconductive, osteogenic, and angiogenic. Furthermore, an ideal bone graft should provide mechanical support and promote physiologic healing without any significant adverse effects.

Regenerative strategies like the use of bone morphogenic proteins, platelet rich plasma, stem cells and anabolic agents are promising in the treatment of fractures either acute or fracture non-union.

However, large bone defects with compromised biology may not be amenable to simple regenerative strategies and will require polytherapy, which incorporates all of the critical components that are required for bone regenneration.

In future, use of these therapies in the bone regeneration under specific indications and with safety roles will simulates the normal bone formation cascade with reduced morbidity and cost in the long term.

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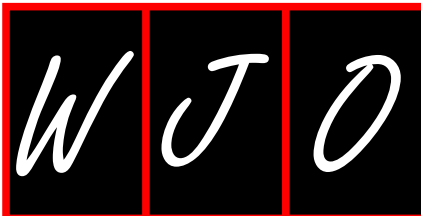
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ORIGINAL ARTICLE

Retrospective Study

Isolated sacral injuries: Postoperative length of stay, complications, and readmission

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Author contributions: Sathiyakumar V, Joyce D, Obremskey WT and Sethi MK designed research; Sathiyakumar V, Shi H and Thakore RV performed research; Lee YM, Ehrenfeld J, Obremskey WT and Sethi MK contributed analytic tools; Lee YM analyzed data; Sathiyakumar V, Shi H and Thakore RV wrote the paper.

Institutional review board statement: This retrospective study was approved by the Vanderbilt University Institutional Review Board, with all data from human subjects appropriately reviewed by the study personnel.

Informed consent statement: This retrospective study was in accordance with the Vanderbilt IRB and required no active informed consent from patients. All the patients information was used in an de-identified manner.

Conflict-of-interest statement: Author William T Obremskey has previously consulted for biometrics and done expert testimony in legal matters. The institution of WTO has received a grant from the Department of Defense. For the remaining authors, none were declared.

Data sharing statement: Statistical output and dataset are available upon request.

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Abstract

AIM: To investigate inpatient length of stay (LOS), complication rates, and readmission rates for sacral fracture patients based on operative approach.

METHODS: All patients who presented to a large tertiary care center with isolated sacral fractures in an 11-year period were included in a retrospective chart review. Operative approach (open reduction internal fixation *vs* percutaneous) was noted, as well as age, gender, race, and American Society of Anesthesiologists' score. Complications included infection, nonunion and malunion, deep venous thrombosis, and hardware problems; 90-d readmissions were broken down into infection, surgical revision of the sacral fracture, and medical complications. LOS was collected for the initial admission and readmission visits if applicable. Fisher's exact and non-parametric *t*-tests (Mann-Whitney *U* tests) were employed to compare LOS, complications, and readmissions between open and percutaneous approaches.

RESULTS: Ninety-four patients with isolated sacral fractures were identified: 31 (30.4%) who underwent

open reduction and internal fixation (ORIF) *vs* 63 (67.0%) who underwent percutaneous fixation. There was a significant difference in LOS based on operative approach: 9.1 d for ORIF patients *vs* 6.1 d for percutaneous patients (P = 0.043), amounting to a difference in cost of $13590. Ten patients in the study developed complications, with no significant difference in complication rates or reasons for complications between the two groups (19.4% for ORIF patients *vs* 6.3% for percutaneous patients). Eight patients were readmitted, with no significant difference in readmission rates or reasons for readmission between the two groups (9.5% percutaneous *vs* 6.5% ORIF).

CONCLUSION: There is a significant difference in LOS based on operative approach for sacral fracture patients. Given similar complications and readmission rates, we recommend a percutaneous approach.

Key words: Sacral fractures; Open reduction and internal fixation; Percutaneous complications; Readmissions; Length of stay

Core tip: Few studies in orthopaedics have investigated complication rates, readmission rates, and length of stay differences with respect to surgical approach for patients with sacral fractures. Investigating these issues in an era of rising healthcare costs will help determine cost-effective care. We reviewed patients presenting with isolated sacral fractures at a large, level-I trauma center, and found those treated with open reduction internal fixation stayed nearly 3 d longer compared to patients treated with percutaneous approaches. With similar complication and readmission rates between the two groups, we recommend a percutaneous approach to help lower total hospital costs for more value-based practice.

INTRODUCTION

Forty-five percent of all pelvic fractures include sacral involvement[1,2]. These fractures often occur in the secondary to high-energy mechanisms, with motor vehicle accidents causing up to 57% of these injuries[2]. Traumatic force may also lead to nearby neurovascular compression, which can precipitate adverse neurological events[3]. For these reasons, sacral fractures are musculoskeletal injuries requiring emergent action at trauma centers to reduce the risk of complications.

While open reduction and internal fixation (ORIF) methods allow for broad visualization of the sacrum and surrounding structures, highly variable wound complication rates range from 3.9% to 27% of study populations[4]. ORIF specifically has been linked to high rates of infection, which can complicate 18% to 27% of sacral fractures treated early and late, respectively[5]. Given these high complication rates, it is therefore reasonable to consider a more minimally invasive technique such as percutaneous fixation to stabilize the sacrum[6]. Percutaneous fixation with iliosacral screws, for example, have led to decreases in overall operative time and soft-tissue disruption, thereby providing avenues to prevent complications[7].

With the recent focus on healthcare cuts due to escalating costs in the United States, it is important to investigate postoperative length of stay (LOS), 90-d readmissions, and complication rates with respect to operative approach for sacral fracture patients. Although sacral fractures constitute a large component of pelvic fractures, little data exists exploring these issues with the most available knowledge regarding stress fractures secondary to osteoporosis[8]. This study therefore seeks to explore differences in LOS, complications, and readmissions based on operative technique to determine the most value-based approach in treating this patient cohort.

MATERIALS AND METHODS

After obtaining approval from our institutional review board, we identified all patients who sustained operative sacral fractures at a major academic level I trauma center from January 1, 2000 to December 31, 2011 through a Current Procedural Terminology code search (Supplementary Table 1). Two hundred and fifty patients were identified, and 102 of those patients were found to have isolated sacral injuries without other concomitant orthopaedic or medical injuries. Ninety-four patients were identified out of these 102 for analysis with isolated sacral fractures fitting the criteria for the operative approach (ORIF *vs* percutaneous).

Data extrapolated from patient chart review included demographics such as age, gender, and race; verification of operative approach (percutaneous *vs* open), American Society of Anesthesiologists' (ASA) classification, complication rates, and readmission rates. Complications included infection, nonunion and malunion, deep venous thrombosis, and hardware problems. Ninety-day readmissions were broken down into three different categories: infection, surgical revision of the fracture, and medical complications such as urinary tract infections, pneumonia, hypotension, and anemia among others.

The LOS in days was collected for the initial admission and for 90-d readmissions if any existed. Additional data concerning the days from discharge

Table 1 Demographic characteristics of patients

	ORIF (*n* = 31)	Percutaneous (*n* = 63)	Total
Average age (yr)	44	37.1	39.3
Gender (*n*)			
Male	19	22	41
Female	12	41	53
Average BMI (kg/m^2)	26.1	24.8	25.5

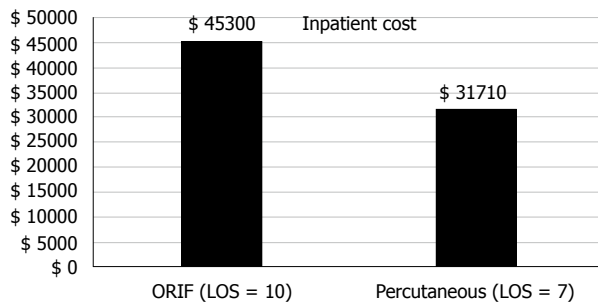ORIF: Open reduction and internal fixation; BMI: Body mass index.

Figure 1 Differences in inpatient costs based on operative approach. ORIF: Open reduction and internal fixation; LOS: Length of stay.

Figure 2 Differences in complication and readmission rates based on operative approach. ORIF: Open reduction and internal fixation.

to readmission were also collected for each patient, including the number of emergency room visits and clinic visits before a patient was admitted or readmitted to the hospital. The average cost per inpatient day ($4530/d) as well as all costs associated with anesthesia, surgery, and ancillary support (*i.e.,* postoperative lab tests, radiography, consults, *etc.*) was obtained from the institution's patient financial services department.

Fisher's exact, student's *t*-tests (for parametric variables such as LOS), and Mann-Whitney *U* tests (for non-parametric variables such as number of clinic visits) were employed to compare patients undergoing ORIF to those undergoing percutaneous fixation to note differences in hospital LOS and subsequent inpatient costs, complication rates, and readmission rates.

RESULTS

Ninety-four patients with isolated sacral injuries were identified for analysis: 31 patients (30.4%) underwent ORIF *vs* 63 patients (67.0%) who underwent percutaneous fixation (Table 1). The average age of all patients was 39.3 years, with ORIF patients older than percutaneous patients. There were 53 females and 41 males included in the study, with more men in the ORIF group and more women in the percutaneous group. The average BMI of all patients was 25.5. There were no significant differences in any baseline demographic between the ORIF and percutaneous groups. The majority of patients (51.1%) had an ASA score of 2, with similar distributions of ASA scores between the ORIF and percutaneous groups.

Table 2 lists hospital LOS, inpatient costs, and average number of emergency room and clinic visits
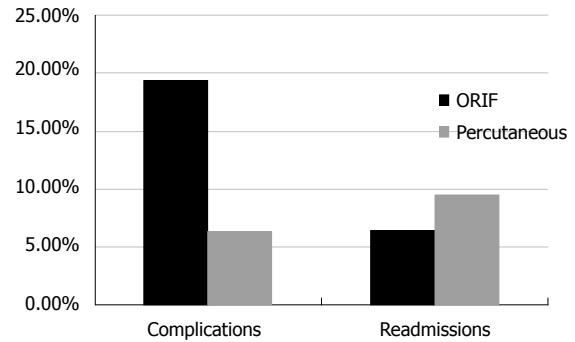
based on operative approach. The mean LOS in the hospital for all patients was 7.1 d, with ORIF patients staying significantly longer (9.1 d) than percutaneous patients (6.1 d) (*P* = 0.043). There was no significant difference in the amount of time from admission to surgery for both groups, but ORIF patients stayed significantly longer after surgery (6.6 d) compared to percutaneous patients (4.6 d, *P* = 0.045). Using an average cost of $4530/d, this corresponds to average inpatient costs of $45300 for ORIF patients and $31710 for percutaneous patients - a difference of $13590 (Figure 1). Furthermore, when breaking down total costs for the patients based on operative approach, anesthesia costs were on average $1769 more for ORIF patients compared to percutaneous patients (*P* = 0.001), and surgical costs were on average $4401 more for ORIF patients (*P* < 0.001). Ancillary costs were statistically similar between the groups.

ORIF patients and percutaneous patients had similar numbers of ER and clinic visits before initial hospitalization. Readmissions were rare, with ORIF patients spending an average of 13.5 d between discharge and readmission compared to 16.5 d for percutaneous patients. There were similar numbers of ER and clinic visits occurring in this period for the two groups. The average LOS (about 5.6 d) for readmissions was similar for the two groups (*P* = 0.954).

Table 3 lists the reasons for complications and readmissions for the two surgical groups. Overall, 10 (10.6%) patients developed complications. While there was a difference in complications between the two groups as shown in Figure 2 (19.4% for ORIF *vs* 6.3% for percutaneous), this was not statistically significant. The distributions of the complications were similar for the ORIF and percutaneous groups (Figure 3). Similarly, 8 (8.5%) patients had readmissions within 90-d, with a difference in readmission rates based on operative approach (9.5% for percutaneous *vs* 6.5% for ORIF) that did not reach statistical significance. The distributions of readmissions was also similar between the two groups (Figure 4). When comparing those who sustained complications to those who did not in the ORIF and percutaneous groups, there were no significant differences with respect to age or BMI.

Table 2 Hospital length of stay, costs, and emergency room and clinic visits based on operative approach			
	ORIF (*n* = 31)	Percutaneous (*n* = 63)	*P* value
Initial hospitalization			
Average LOS (d)	9.1	6.1	0.043
Average time (admission-surgery)	2.4	1.5	0.062
Average time (surgery-discharge)	6.6	4.6	0.045
Average LOS costs	$45300	$31710	0.043
Average anesthesia costs	$4265	$2496	0.001
Average surgical costs	$13490	$9089	< 0.001
Average ancillary costs	$27811	$18476	0.239
Average clinic visits	4.1	3.5	0.123
Average ER visits	1.1	1.0	0.465
Readmissions			
Average LOS (d)	5.5	5.7	0.954
Average days to readmission	13.5	16.5	0.552
Average ER visits	0.0	0.5	0.267
Average clinic visits	5.0	3.5	0.323

LOS: Length of stay.

Figure 3 Reasons for complications based on operative approach. ORIF: Open reduction and internal fixation; DVT: Deep venous thrombosis.

Table 3 Differences in complications and readmissions based on operative approach			
	ORIF (*n* = 31)	Percutaneous (*n* = 63)	*P* value
Complications			
Infection	1 (3.2)	1 (1.6)	
Nonunion	1 (3.2)	1 (1.6)	
Hardware failure	2 (6.4)	2 (3.2)	
DVT	2 (6.4)	0 (0)	
Total	6 (19.4)	4 (6.3)	0.062
Readmission			
Infection	0 (0)	1 (1.6)	
Surgical	2 (6.4)	1 (1.6)	
Medical	0 (0)	4 (6.3)	
Total	2 (6.4)	6 (9.5)	0.473

ORIF: Open reduction and internal fixation; DVT: Deep venous thrombosis.

DISCUSSION

LOS during initial hospital admissions has been shown to affect readmission rates, thereby affecting overall quality of care delivered to patients[9]. Based on our study, we have demonstrated a significant difference in the LOS in patients undergoing ORIF *vs* percutaneous fixation of sacral injuries, with ORIF patients on average staying 3 d longer in the hospital. This amounts to, on average, a difference in LOS costs of close to $14000 for ORIF patients.

The average LOS we obtained for all patients (7.05 d) is within range of similar studies in Level I trauma centers. Vallier *et al*[10] calculated a LOS of 9.2 d for patients undergoing operative fixation of pelvic and acetabular fractures; in comparison, Dechert *et al* found an average LOS of 11.5 ± 14.1 d in patients under 65 years of age with pelvic trauma[10,11]. With regards to operative approach, our difference in LOS of 3 d is similar to other orthopaedic studies which show minimally invasive surgical techniques decrease LOS compared to open approaches. For example, decreases up to 3.8 d in LOS due to minimally invasive techniques
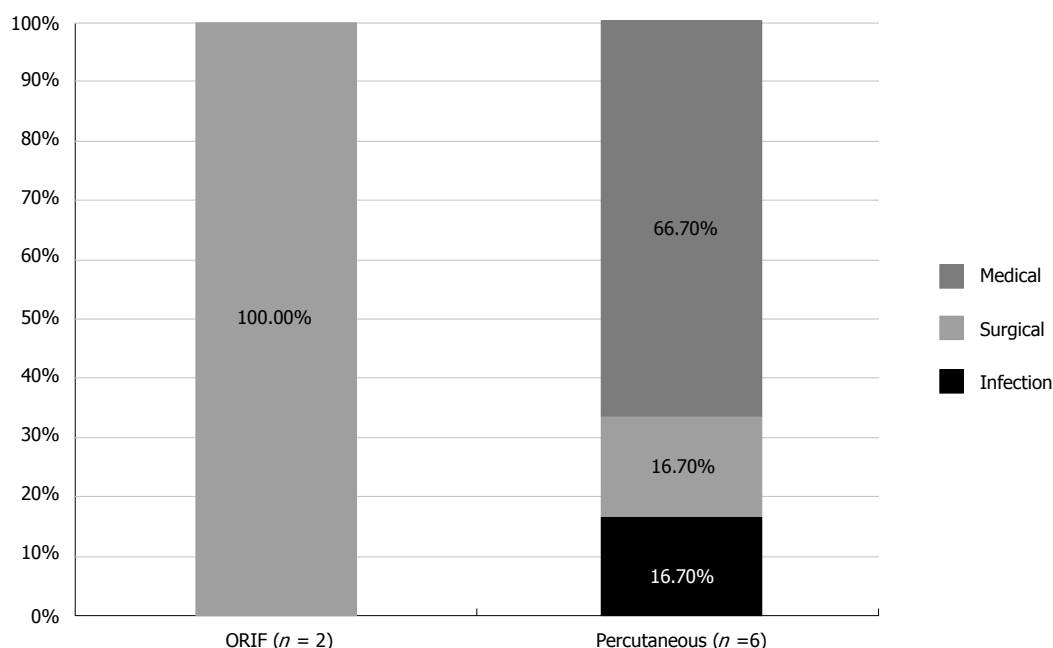
Figure 4 Reasons for readmission based on operative approach. ORIF: Open reduction and internal fixation.

have been demonstrated in sacroiliac joint fusions[12,13]. Similar decreases in LOS up to 3.2 d have been shown for patients undergoing minimally invasive lumbar fusions compared to open approaches[14-16]. Finally, open dynamic hip screw (DHS) fixation of the femur increases LOS by 4.5 d compared to a minimally invasive DHS[17].

LOS is particularly important as it can also have consequences with respect to rehabilitation[18]. It is also a reliable tool for cost analysis of facility charges. For example, the cost of inpatient rooms are included in total facility charges, which are on average almost 4 times greater than orthopaedic professional charges[19]. An important factor affecting LOS with regard to operative approach reflects how orthopaedic surgeons may postpone surgical fixation. For example, open surgical approaches are often delayed for days for patients with pelvic ring fractures to prevent disruption of tamponade and clot formation[7]. Although percutaneous approaches for sacral fractures may also occur days after admission, with one study finding a delay of 4.2 d prior to fixation, definitive fixation may occur much sooner after admission[20]. Given a decreased delay to fixation coupled with fewer bleeding episodes and other complications, a percutaneous approach for sacral fractures may be a more time-effective procedure leading to savings in LOS costs.

Our study further demonstrated surprisingly high overall readmission (8.5%) and complication (10.6%) rates. Although there were trends toward higher rates of readmissions (9.5%) in the percutaneous group and complications (19.4%) in the ORIF group, these did not reach statistical significance. Nevertheless, our overall complication rate (10.6%) falls within the range of pelvic and acetabular complications reported by Vallier *et al*[10] study, which found a 12% (58/465 patients

with 95 complications) rate of post-operative adverse events.

When comparing complication rates for the two approaches, ORIF treatment outcomes differ across various fracture types. For example, reconstruction plate internal fixation of type C unstable sacral fractures can have a 12.5% infection rate and 15.6% complication rate secondary to urological problems[21]. Conversely, Hsu *et al*[22] found a low complication rate (1/19 patients) when following-up two post-operatively a patient cohort with displaced sacral fractures treated with open reductions and internal. Other studies showed 2.8% infections in internal fixation[23]. Based on our results for ORIF patients, hardware failure and infection are the top two causes of complications, similar to published results[21-23]. In comparison, percutaneous screw fixation complications can result from poor visualization of relevant anatomy, incomplete fluoroscopy, unexpected anatomic variations, and malreduction[4]. Most common complications, based on our results, include implant failure and infection. Routt *et al*[24] described fixation failure in 4.5% of patients using a percutaneous iliosacral screw technique, which is close to our 3.17% hardware failure in patients treated percutaneously. Avoidance of deep tissue exposure to the environment in percutaneous approaches is one main reason that is postulated to result in theoretically fewer complications with this approach compared to open techniques[25], although this was not seen in our results. Nevertheless, our results suggest that the percutaneous approach may be just as safe as ORIF in preventing surgical complications. This early data may serve in the future as a quantitative factor for the surgical team to plan and decide whether an open or percutaneous approach is the most efficient manner to approach a fracture. Given that a percutaneous

approach is less invasive and faster, allowing for less pain and early post-operative mobilization, our data may implicate that a percutaneous approach is a better "value" approach given shorter LOS and ultimately lower hospital costs. Our results have even demonstrated lower costs associated with anesthesia and surgery for percutaneous patients, highlighting the added value of a percutaneous approach.

Limitations of our study include the retrospective nature of our methodology, which could not account if surgeons may be driven to favor a certain operative approach for specific patient populations. Although the ASA classification was taken into account as a risk-stratifying mechanism, many patient risk factors were not accounted for during data collection. For example, patients referred to our tertiary care center could be held at other centers prior to transportation. Some research suggests a delay to ORIF that may be upwards of 7 d due to delays in transfer[26]. In some cases, ORIF is actually preferred after 7 d because soft-tissue fibrosis may prevent a successful approach with percutaneous fixation[7]. The longer nature of the ORIF approach may therefore confound LOS when compared to the immediacy of a percutaneous approach, with inherent differential risk stratification for the two approaches. In our study, there was no difference in time to surgery once patients were admitted, but ORIF patients did stay significantly longer after surgery, perhaps highlighting more extensive recovery following an open approach. Furthermore, our study only involved patients treated at a single, level-Ⅰ tertiary care trauma center. These patients may not be representative of the general population, with some bias in the severity of traumatic fractures that may bias our results. High-volume centers like ours often have patients with more medical comorbidities, which factor into LOS calculations due to more hospital days necessary to address these other medical concerns[27]. In our cost analyses, we used a fixed-cost calculation based on total inpatient duration. In this analysis, the use of fluoroscopy or electromyographic monitoring in percutaneous operations was not specifically studied. Yet, the use of these technologies has been shown to impact both safety and cost[28,29]. In addition, hospital legal procedures, insurance status, and the variations in surgeon-specific complication and readmission rates may affect discharge planning, LOS, and ultimately total cost.

The results presented in this study suggest an avenue for quality improvement for patients presenting with sacral fractures. Many health systems have tried to improve patient satisfaction, LOS, complication rates with better discharge planning and education[30,31]. Our study is the first of its kind to demonstrate a significant difference in LOS between ORIF *vs* percutaneous fixation of sacral injuries, with an average difference of $13590 based on difference in LOS. With similar complication and 90-d readmission rates compared to ORIF, we recommend a percutaneous approach when

possible. Our results will provide orthopaedic surgeons with some predictive information as a risk stratification tool to potentially reduce postoperative costs related to sacral fractures.

<div style="background:#E07820;color:white;padding:4px;">COMMENTS</div>

Background
In an era with rising healthcare costs, avenues to reduce expenses must be explored including costs associated with length of stay (LOS), complications, and readmissions. Despite sacral fractures constituting a majority of all pelvic trauma, relatively little data exists exploring differences in these areas based on operative approach. The aim of this study is to investigate inpatient LOS, complication rates, and readmission rates for sacral fracture patients based on surgical technique to determine the most cost-effective approach in treating these patients.

Research frontiers
No study to date has investigated LOS, complication, and readmission differences for patients sustaining sacral fracture based on operative approach.

Innovations and breakthroughs
The authors' study is the first of its kind to show a significant difference in LOS for open reduction and internal fixation (ORIF) *vs* percutaneous patients, with ORIF patients on average staying 3 more days in the hospital amounting to a cost of approximately $14000 more when compared to percutaneous patients.

Applications
Given similar rates of complications and readmissions, yet an overall decreased LOS and subsequent hospital-related costs when compared percutaneous patients to ORIF patients, patients with sacral fractures should be treated with a percutaneous approach. Percutaneous approaches are common techniques now for most major orthopaedic fractures and can be implemented in any major hospital system, providing an avenue for benchmarking quality based on costs.

Terminology
Open reduction internal fixation is a surgical approach used by orthopaedic surgeons in which a fracture is placed in normal, anatomic position with the aid of implants, often necessitating a large incision. Percutaneous fixation is another surgical approach used by orthopaedic surgeons where a fracture is placed in a normal, anatomic position with pins or other stabilizing devices through the use of X-rays, thereby avoiding the need for large incisions.

Peer-review
The authors have performed a good study, the manuscript is interesting.

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ORIGINAL ARTICLE

Retrospective Study

Total hip replacement for arthritis following tuberculosis of hip

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Abstract

AIM: To present the results of total hip arthroplasty (THA) for post tubercular arthritis of the hip joint.

METHODS: Sixty-five patients (45 male, 20 female) with previously treated tuberculosis of the hip joint underwent cementless THA for post tubercular arthritis. The average age at the time of THA was 48 years (range 29 to 65 years). Erythrocyte sedimentation rate, C reactive protein, chest X-ray and contrast enhanced magnetic resonance imaging were done preoperatively to confirm resolution of the disease and to rule out any residual disease. Intra-operative samples were taken for microbiological examination, polymerase chain reaction (PCR) and histological examination. Patients were started on anti-tubercular drugs one week before the operation and continued for 6 mo post operatively. The patients were followed up clinically using the Harris hip score as well as radiologically for any loosening of the implants, osteolysis and any recurrence of tuberculosis. Any complications especially the recurrence of the infection was also recorded.

RESULTS: The mean interval from completion of antitubercular therapy for tuberculosis to surgery was 4.2 years (range, 2-6 years). Preoperatively, 17 patients had ankylosis whereas 48 patients had functional but painful range of motion. The mean surgical time was 97 min (range, 65-125) whereas the mean blood loss was 600 mL (range, 400-900 mL). The average follow up was 8.3 years (range 6-11 years). The average Harris Hip score improved from 27 preoperatively to 91 at the final follow up. Seventeen patients had acetabular

protrusion which was managed with impaction grafting and cementless acetabular cup. The bone graft had consolidated in all these 17 patients at the follow up. Two patients developed discharging sinuses at 9 and 11 mo postoperatively respectively. The discharge tested positive for tuberculosis on the PCR. Both these patients were put on antitubercular therapy for another year. Both of them recovered and had no evidence of any loosening or osteolysis on X-rays. There were no other complications recorded.

CONCLUSION: Total hip replacement restores good function to patients suffering from post tubercular arthritis of the hip.

Key words: Total hip replacement; Cementless hip replacement; Tuberculosis hip; Post-tubercular arthritis hip; Total hip arthroplasty

Core tip: Total hip replacement restores good function to patients suffering from post tubercular arthritis of the hip. A good preoperative work up to rule out any residual disease as well as perioperative chemotherapy are recommended to ensure success. Any recurrence of the disease can be managed by chemotherapy.

INTRODUCTION

Tuberculosis of the hip accounts for a significant proportion of cases of osteo-articular tuberculosis, being next to only tuberculosis of spine[1]. Tuberculosis of hip constitutes 10%-15% of all patients with osteoarticular tuberculosis[1,2]. The patients in developing countries usually present late with advanced joint destruction as a result of the disease. Moreover, many of these patients are young and have several decades of active life ahead of them once the infection has healed with destruction of the affected hip joint. The surgical options for such patients suffering from arthritis of hip due to tuberculosis include excision arthroplasty, arthrodesis, and, total hip replacement. Excision arthroplasty results in an unstable joint with shortening and an abnormal gait[3,4]. An arthrodesis produces a stable painless immobile joint with poor function and is often associated with non union, pain in the adjacent joints and a slow abnormal gait[5]. Total hip arthroplasty (THA) provides a painless stable joint with a normal gait. Although THA has been recommended in patients with post tubercular arthritis[6-10], recurrence of the disease[11-13], fear of high complication rates and the long term survival of the reconstruction remain major concerns. THA, nonetheless, still is reported to be associated with a good outcome in these patients[6-10].

The aim of this study is to present the results of THA done at our center for post tubercular arthritis or ankylosis of hip joint.

MATERIALS AND METHODS

This study was performed at the All India Institute of Medical Sciences, New Delhi. We retrospectively reviewed 65 patients who underwent a total hip replacement for advanced arthritis of the hip due to tuberculosis following treatment. The Institute Ethics committee approved this study. All patients who had arthritis following tuberculosis of hip were included in the study. All patients had successfully completed full course of 18 mo of Anti tubercular drugs previously with documented complete resolution of the disease. The patients who had clinical and/radiological evidence of tuberculosis and those who had not completed the full course of anti tubercular therapy were excluded from the study. Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), chest X-ray and contrast enhanced magnetic resonance imaging (MRI) were done to confirm resolution of the disease and to rule out any residual disease.

All patients were given Antitubercular drugs (Isoniazid, Pyrazinamide, Ethambutol and Rifampicin) starting one week before until 2 mo following surgery. At 2 mo following the hip replacement, Ethambutol and Pyrazinamide were stopped and Isoniazid and Rifamipicin continued for another 4 mo.

All patients were operated under Spinal or General Anesthesia using the posterior approach in lateral decubitus position. Intravenous 1 g cefazolin was used as antibiotic prophylaxis for 5 d. A Cementless Total hip Replacement was performed in all the patients. The tissue and fluid samples obtained at the time of surgery were sent for Gram staining, acid fast bacilli staining, polymerase chain reaction (PCR), culture and sensitivity for mycobacteria and histopathological examination.

Low molecular weight heparin and compression stockings were used for antithrombotic prophylaxis in all the patients.

A retrospective review of all the case records was done. The data was collected from hospital records and follow up records All the patients are routinely assessed at two weeks, one, three, six and twelve months postoperatively and yearly thereafter. The patients were evaluated clinically using the Harris Hip Score[14] and radiologically for bone ingrowth, stability and fixation using the stability - fixation score[15]. The radiographs were also scrutinized for any evidence of loosening or osteolysis in the 7 Gruen zones[16] around the femoral component and 3 zones around the acetabulum as described by DeLee and Charnley[17]. Any complications especially the recurrence of the infection were recorded.
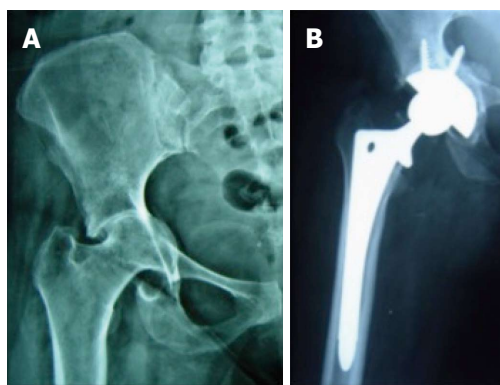
Figure 1 Preoperative X-rays of a patient suffering from Post-tubercular arthritis of hip with protrusion (A) and post-operative X-rays following a cementless total hip replacement along with autogenous impaction grafting for protrusion hip (B).

RESULTS

There were 45 male and 20 female patients. The average age at the time of successful hip replacement was 48 years (29-65 years). Forty-three patients were less than 45 years of age at the time of hip replacement. Twenty-nine patients had right hip involved whereas 36 patients had involvement of the left hip joint.

The implants used were Versys-Trilogy (Zimmer) in 33 patients, Corail -Duraloc (Depuy, Johnson and Johnson) in 27 patients and S ROM -Pinnacle cup (Depuy, Johnson and Johnson) in 5 patients.

Preoperatively, none of the patients had any evidence of residual disease on contrast enhanced MRI. The ESR and CRP were within normal limits in all the patients. On examination of the tissue samples obtained during surgery, no patient had positive tissue culture or histopathological evidence of tuberculosis.

The mean interval from completion of antitubercular therapy for tuberculosis to surgery was 4.2 years (range, 2-6 years). Preoperatively, 17 patients had ankylosis whereas 48 patients had functional but painful range of motion. The preoperative mean limb length discrepancy was 3.8 cm (range 3-5.5 cm).

The mean surgical time was 97 min (range, 65-125) whereas the mean blood loss was 600 mL (range, 400-900 mL).

The average follow up was 8.3 years (range 6-11 years). A fibrous ankylosis was seen in 17 hips. The acetabular defects were classified according to Paprosky classification[18]. There were 17 hips with type I defect, 8 hips with Type IIa defect, and 4 hips with type IIb defects. No major defects were seen on the femoral side. There was a difficulty in dislocating the hip and an *in-situ* osteotomy of the femoral neck was done in 10 cases that presented with ankylosis of the hip joint.

Twenty-five patients had acetabular protrusion (Type I and II Paprosky defect) for which impaction grafting from the femoral head was done was done (Figure 1). The bone grafts consolidated in all the patients at 3 mo. The mean Harris Hip Score improved

from 27 (range, 20-36) to 91 (range, 88-94) at the latest follow up. The improvement in Harris Score was similar in both males and females.

All femoral stems had evidence of osteointegration at 1 year and were stable at the latest follow up with no signs of osteolysis or loosening. No patient had any evidence of osteolysis or loosening on the acetabular side.

There was no dislocation or heterotopic bone formation.

There were 2 patients who developed a discharging sinus at 9 and 11 mo postoperatively respectively. The discharge was positive for tuberculosis on PCR. Both these patients were treated with 4-drug chemotherapy for another one year. Both of them recovered and had no evidence of any loosening or osteolysis on X-rays at the latest follow up of 6.2 and 6.5 years respectively.

DISCUSSION

The patients with tuberculosis of the hip joint often have advanced arthritis with severe deformities and limb length discrepancy. Total hip replacement has been used successfully for the treatment of post tubercular arthritis[6,8,12,19-21]. One of the major concerns is the risk of reactivation of cured or quiescent disease following surgery[8,11-13,22,23].

As tubercular bacilli do not adhere to metal surface and have little or no biofilm formation[24-26], spinal instrumentation has been used successfully in the treatment of active tuberculosis of spine[27]. The early results of Total hip replacement in active tuberculosis are encouraging[10,26,28]. Tuberculosis is a chronic disease and reactivation of disease occurs in 2%-5% of patients as late as 20 years after apparent healing[29]. Systemic Corticosteroid therapy, Malnutrition, diabetes, surgical procedure or injury to previously infected area may cause the dormant bacilli persisting in tissue to start multiplying resulting in reactivation[29]. It has also been observed that the risk of reactivation is more in patients who either had an overlooked tubercular lesion, were on long term steroid treatment, were not given chemotherapy or were non compliant with antitubercular treatment (ATT), had chronic discharging tract, and, in those with positive tissue culture during surgery[8-10,21,26,28].

In patients undergoing THA for tubercular arthritis, the recommended periods of quiescence before THR varies from immediate to 10 years[6,8,9,12,19,20,26,28]. However reactivation has been reported even in cases operated even after a quiescent period of 37-40 years[22]. Hence as a part of preoperative assessment, only patients who had completed full course of antitubercular therapy were considered for THA in the current series. Moreover, any residual disease was ruled out on MRI. In order to prevent any reactivation of disease due to the immune suppression which occurs at the time of surgery, it is recommended to start ATT preoperatively and continue ATT post operatively for 3-6 mo[19-21]. The benefits of ATT in such cases outweigh its possible side effects. In spite

of careful patient selection and ATT, there was recurrence in form of a discharging sinus in 2 patients in the current series. It implies that the complete resolution of disease on imaging and limited perioperative chemotherapy for the infection does not guarantee recurrence free follow up. However, we did not see any recurrence after one year of surgery in the current series.

The gold standard for the diagnosis of tuberculosis is the presence of caseating or non-caseating granulomas with or without positive smears or cultures for Acid fast bacilli on histopathological examination of biopsy specimens from synovial tissues[8,30,31]. The histopathological examination of operative specimens in this study did not yield any evidence of tuberculosis, even in the two cases who had recurrence of infection. It is possible that the specimens taken from the femur, acetabulum and capsule were not extensive enough to pick up the dormant bacilli in the joint. Kim *et al*[8] in their series of THA done for tuberculosis hip had negative histopathological findings in 3 cases at the time of operation which later on developed recurrence. It can be concluded that the negative findings on the intraoperative histopathological specimens and cultures do not necessarily prove the absence of tuberculous infection.

Both the patients who experienced recurrence of the tubercular infection were managed with antitubercular drugs for one year, which led to the complete healing. It has been seen that the tubercular sinuses and ulcers heal within 6-12 wk of systemic antitubercular chemotherapy[29]. Only less than 1% of patients with sinuses require debridement and complete excision of sinuses is often not possible as the sinus ramification is often greater than what is apparent[29].

The treatment of reactivation remains controversial. Johnson *et al*[22] recommended the removal of the prosthesis for control of reactivation whereas McCullough[13] treated recurrent draining sinus with chemotherapy alone without the removal of prosthesis. Kim *et al*[8] also treated 6 cases of recurrence in their series with chemotherapy alone in 5 patients and debridement with chemotherapy in one case. They did not have to remove the prosthesis to control the disease. Hence reactivation of disease can be managed with retention of prosthesis with chemotherapy alone as was also done in this series or in combination with debridement as reported in literature.

Both cemented and cementless implants have been used successfully for patients with post-tubercular arthritis. The reactivation rates for both cemented and Cementless THRs in patients with quiescent tuberculosis are similar[8,10] thereby indicating that ostensible mycobactericidal action of thermal reaction from cement is not relevant to reactivation[8,26].

We have seen in that patients with post tubercular arthritis often have destroyed femoral heads but no major defects in the femur. The femoral reconstruction therefore is straightforward. However, there are defects on the acetabular side ranging from segmental to protrusion defects. The presence of these defects on the acetabular side often necessitates the use of a cementless shell along with bone graft. The current series affirms the success of this technique for post tubercular arthritis.

The patients suffering from tuberculosis of hip are young. These patients present with hip arthritis at a relatively young age and therefore a cementless hip replacement is a good option. The current series confirms the mid term survival of cementless implants in this cohort as there were no failures due to the osteolysis at an average follow up of 8.3 years. We conclude that cementless hip replacement can be used successfully for patients with post tubercular arthritis of hip.

The limitations to this study are its retrospective nature, a relatively short follow up considering young patient cohort and heterogeneity of the implants used. Also in view of the recurrence of infection in 2 patients, we are unable to endorse the current recommended regime and duration of recommended perioperative chemotherapy.

To conclude, total hip replacement under ATT cover restores good function to the patients suffering from tuberculosis provided a good preoperative work up is done to rule out any residual disease and postoperatively patients are followed up for any recurrence. A recurrence is possible especially during the first year after surgery despite complete radiological resolution and perioperative antitubercular chemotherapy but is amenable to treatment with chemotherapy.

COMMENTS

Background
Tuberculosis of hip often results in arthritis of hip joint warranting a total hip replacement. This study aims to present the results of total hip replacement in patients suffering from hip arthritis as a result of tuberculosis of hip.

Research frontiers
The patients suffering from post tubercular arthritis in developing countries are usually young. Total hip replacement in patients with post tubercular arthritis has concerns of recurrence of the disease, fear of high complication rates and the long term survival of the reconstruction.

Innovations and breakthroughs
In this study, cementless total hip replacement restored good function in patients suffering from post tubercular arthritis of hip. A recurrence of disease in form of discharging sinus seen in 2 patients was successfully managed with antitubercular therapy with no surgical intervention.

Applications
Cementless total hip replacement done under cover of antitubercular therapy is a safe and durable treatment option for patients suffering from post tubercular arthritis of hip.

Peer-review
This clinical paper analyses the patient response data to tuberculosis of the hip and varying therapies applied. The paper content is a novel comparison of data to a niche area that will be of interest.

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ORIGINAL ARTICLE

Observational Study

Standardized quantitative measurements of wrist cartilage in healthy humans using 3T magnetic resonance imaging

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Author contributions: Zink JV, Souteyrand P, Guis S, Chagnaud C and Bendahan D designed the study and took part to the data acquisition; Statistical analyses were conducted by Zink JV, Fur YL, Mattei JP and Bendahan D; Fur YL, Militianu D, Rozenbaum M, Rosner I, Guye M and Bernard M made substantial contribution to analysis and interpretation of the data; Zink JV, Souteyrand P and Guis S drafted sections of the manuscript; all authors revised it critically for important intellectual content and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by Aix-Marseille Université - CRMBM-CNRS Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: None.

Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at drgargpankaj@yahoo.com. No cosent was obtained but the presented data ara anonymized and risk of identification is low.

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Abstract

AIM: To quantify the wrist cartilage cross-sectional area in humans from a 3D magnetic resonance imaging (MRI) dataset and to assess the corresponding reproducibility.

METHODS: The study was conducted in 14 healthy volunteers (6 females and 8 males) between 30 and 58 years old and devoid of articular pain. Subjects

were asked to lie down in the supine position with the right hand positioned above the pelvic region on top of a home-built rigid platform attached to the scanner bed. The wrist was wrapped with a flexible surface coil. MRI investigations were performed at 3T (Verio-Siemens) using volume interpolated breath hold examination (VIBE) and dual echo steady state (DESS) MRI sequences. Cartilage cross sectional area (CSA) was measured on a slice of interest selected from a 3D dataset of the entire carpus and metacarpal-phalangeal areas on the basis of anatomical criteria using conventional image processing radiology software. Cartilage cross-sectional areas between opposite bones in the carpal region were manually selected and quantified using a thresholding method.

RESULTS: Cartilage CSA measurements performed on a selected predefined slice were 292.4 ± 39 mm^2 using the VIBE sequence and slightly lower, 270.4 ± 50.6 mm^2, with the DESS sequence. The inter (14.1%) and intra (2.4%) subject variability was similar for both MRI methods. The coefficients of variation computed for the repeated measurements were also comparable for the VIBE (2.4%) and the DESS (4.8%) sequences. The carpus length averaged over the group was 37.5 ± 2.8 mm with a 7.45% between-subjects coefficient of variation. Of note, wrist cartilage CSA measured with either the VIBE or the DESS sequences was linearly related to the carpal bone length. The variability between subjects was significantly reduced to 8.4% when the CSA was normalized with respect to the carpal bone length.

CONCLUSION: The ratio between wrist cartilage CSA and carpal bone length is a highly reproducible standardized measurement which normalizes the natural diversity between individuals.

Key words: Cartilage; Magnetic resonance imaging; Wrist; Quantification

Core tip: Wrist cartilage cross-sectional area has been quantified in wrists of healthy subjects using 3T magnetic resonance imaging. Based on a semi-automatic segmentation method, the reproducibility of the measurements is high as compared to previous studies. A standardized quantitative index has been proposed. This standardized index can be used for future follow-up studies. The measurements performed in a small group of subjects should be further confirmed in a larger group.

INTRODUCTION

Progressive damage to articular cartilage has been appreciated in a variety of pathological situations including rheumatoid arthritis (RA)[1] and osteoarthritis (OA)[2]. In addition, early detection of such damage has important implications for both grading disease severity and for the assessment of therapeutic efficacy of interventions, underlying the need for reliable and accurate imaging methods. Magnetic resonance imaging (MRI) is well suited to this application as it can provide a 3D dataset of joint anatomy as a whole and not indirectly as a space between opposite cartilage cortices as with conventional radiography. Considering the relatively large amount of cartilage at the knee, MRI investigations have provided interesting information relating to cartilage loss in OA[2-4]. In contrast, for the wrist, a site commonly affected in RA, the obvious limitation related to the corresponding cartilage size has made the investigation much more challenging. Initial investigations performed at a conventional magnetic field of 1.5T have been inconclusive in measuring early degenerative changes[5]. Accordingly, the initial evaluation score of RA using MRI (RA-MRIS), proposed by the Outcome Measures in Rheumatology (OMERACT) group, has been mainly based on the detection of bone erosions, bone edema and synovial thickening[6,7] whereas cartilage lesion criteria were ignored. Due to technological advances in MRI and corresponding improvement in image quality, the last OMERACT conference suggested taking cartilage criteria into account for the RA-MRIS score[8]. On the basis of a comparative analysis of joint space narrowing (JSN) using conventional radiography and MRI, the OMERACT group proposed to include the criterion of cartilage lesion in the new RA-MRI score using grading of JSN[8]. Using the same kind of approach, Peterfy *et al*[9] further confirmed that MRI JSN scoring may offer a viable alternative to conventional JSN radiographic scoring. However, the qualitative approach described requires highly-trained observers and provides a gross score which may not be sensitive enough to detect early cartilage alteration.

Besides this qualitative approach, other MRI techniques allowing for the indirect investigation of the chemical composition of cartilage (collagen and proteo-glycans) have been developed. They are mainly related to T1 and T2 relaxation times mapping, magnetisation transfer, diffusion MRI or sodium MRI[10,11]. Among those techniques, the delayed gadolinium (Gd) enhanced MRI of cartilage (dGEMRIC) has provided promising results[12]. The potential drawbacks of this technique are that it is time consuming and requires repeated investigations prior to, and then an hour after, contrast

Table 1 Variables of the magnetic resonance imaging sequences							
Sequence	FOV (mm)	ST (mm)	RT (ms)	ET (ms)	AT (S)	Matrix size	Resolution (mm)
3D DESS	130 × 130	0.5	14	5.2	330	256 × 256	0.5 × 0.5
3D VIBE	130 × 130	0.5	10	3.38	290	256 × 256	0.5 × 0.5

FOV: Field of view; ST: Slice thickness; ET: Echo-time; RT: Repetition time; AT: Acquisition time; VIBE: Volume interpolated breath hold examination; DESS: Dual echo steady state.

agent injection.

Again and likely for the above reasons, this kind of MRI investigation has been mainly performed in knees of OA patients[13-15] with no data reported for wrist cartilage.

It is noteworthy that most of the MRI studies reported so far have been conducted using a conventional magnetic field, *i.e.,* 1.5T but a few studies have clearly indicated that MRI investigations at higher field, *e.g*., 3T could provide a better signal/noise ratio and a more accurate identification of certain anatomical structures[16-19].

In the present study, taking advantage of high-field MRI, we sought to determine whether cartilage cross-sectional area could be quantified at the wrist level in healthy volunteers. Additionally, we aimed to define the normal range for this quantitative index and the reproducibility of the corresponding measurements.

MATERIALS AND METHODS

Subjects

The fourteen healthy subjects (6 females and 8 males) included in the study provided written informed consent for the protocol which had received the approval of the local ethics committee (Aix-Marseille University ethics committee). Their ages ranged between 30 and 58 years (mean ± SD = 47.4 ± 8.9). None of them reported any joint pain, past wrist trauma or other rheumatologic pathologies.

MRI

MRI investigations were performed at 3 T using a Siemens VERIO 3 T scanner (Siemens, Erlangen, Germany). Subjects were asked to lie down in a supine position inside the scanner. To ensure a comfortable position, a home-built rigid platform was attached to the scanner bed so that the right hand was positioned above the pelvic region. The wrist was then wrapped with a flexible surface coil. This position was not only comfortable for the subjects but also allowed us to localize the wrist at the magnet center, a place where magnetic field homogeneity is optimal.

After a localization procedure using scout images, two 3D MRI sequences of the entire carpus and metacarpal-phalangeal area were performed, *i.e.,* the volumetric interpolated breath-hold examination (VIBE) sequence, mainly used for abdominal investigations[20,21] and the double-echo steady-state (DESS) sequence

previously used for knee cartilage imaging[22-25]. The corresponding sequence parameters are summarized in Table 1.

Cartilage segmentation and measurements

The entire segmentation protocol was performed on a slice of interest selected from each 3D dataset on the basis of anatomical criteria (described below). Cartilage cross-sectional areas (CSA) between opposite bones in the carpal region were manually selected. Then a thresholding process was applied on the corresponding region so that only the voxels within the proper signal intensity setting[26,27] were kept and counted. The cartilage CSA was automatically computed considering the image resolution, the slice thickness and the number of voxels. This strategy was similar to what has been previously described for knee and metacarpophalangeal joints[2-4].

The different steps leading to the selection of the slice of interest are illustrated in Figure 1.

We initially looked at the anterior flat border of the radius in the axial plane and drew a line parallel to it through the middle part of the distal forearm. In the corresponding perpendicular sagittal view, we then selected the slice passing through the distal radius, lunate, capitate and the third metacarpal base. The corresponding coronal section was located through the middle of the bones mentioned above. As illustrated in Figure 1A, various joint spaces were visible on this slice and we manually selected the area of interest (Figure 1B), including the cartilage in the radio-carpal joint, the intercarpal joints and the carpo-metarcarpal joints (joints # 2; 3 and 4 in Figure 2A). At this stage, we used a thresholding process allowing to maintain the signal related to the cartilage alone. The same threshold was applied for each subject. In addition to those measurements, the carpus length was measured as indicated in Figure 1C from the proximal aspect of the lunate to the distal aspect of the capitate.

This segmentation process and the corresponding measurements were performed twice by the same experienced radiologist (JVZ, 3-mo interval) and once by two senior radiologists (JVZ and PS). The measurements' reliability was evaluated, comparing between the two operators' measurements. Measurement reproducibility was assessed *via* repeated measurements performed by the same operator.

Comparisons of measurements were performed using Wilcoxon tests. Test-retest reliability was analyzed using
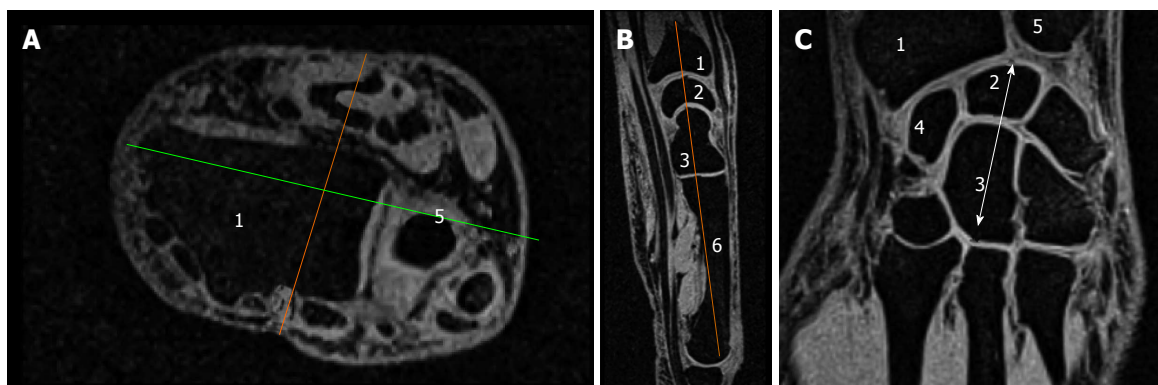
Figure 1 Standardized selection of a slice of interest. A: Axial slice of the wrist in which we initially determined the axis of the anterior part of the Radius (1) (green line) and then the perpendicular sagittal axis (orange line); B: Corresponding sagittal slice in which, we chose the slice going through the proximal part of the capitate (3) and the metacarpal basis (6); C: Corresponding coronal slice showing the radius (1), ulna (5), navicular (4), semi-lunar (2) and capitate bones (3). Arrow indicates the carpal bone length measurement from the lowest point of the capitate to the highest point of the semi-lunar bone.
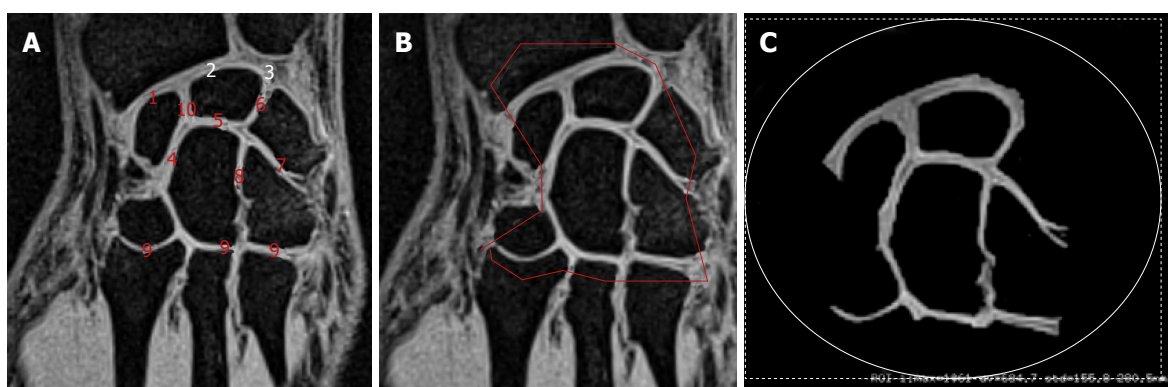

Figure 2 Manual segmentation of the cartilage cross-sectional area. A: Coronal slice (as in Figure 1C) showing different joints between radius and scaphoid (1), radius and lunate (2), lunate and ulna (3), scaphoid and capitate (4), lunate and ulna (5), lunate and triquetrum (6), triquetrum and hamate (7) hamate and capitate (8), carpals bones and metacarpal bones (9) scaphoid and lunate (10); B: Coronal slice illustrating the manual segmentation of the cartilage area of interest and the corresponding result (C).

coefficient of variation (CV) and intra-class correlation coefficients (ICC). Relative reliability is related to an individual maintaining his/her position within a sample with repeated measurements[28]. We assessed this type of reliability with the ICC, a two-way random effects model with single measurement reliability in which variance over the repeated sessions is considered. The ICC indicates the error in measurements as a proportion of the total variance in scores. Absolute reliability is the degree to which repeated measurements vary for individuals[28]. This was performed by calculating the CV for each subject, and then reporting the mean CV for the respective dependent variables. Accordingly, the CV was initially calculated as the SD of measurements recorded for repeated measures and was then divided by the mean of both measurements. Spearman's rank correlation coefficient was calculated to investigate the relationship between measurements obtained with both MR sequences. Statistical analyses were performed using Statistical software for Windows (Statsoft, version 5.5; Statistica, Tulsa, OK, United States). ICC analysis was done using a downloadable excel spreadsheet[29]. A *P* value of 0.05 was chosen as the significant threshold.

RESULTS

As illustrated in Figures 1 and 2, the MR sequences we used generated images of the carpal joint in which articular cartilage appeared as a high signal intensity contrasting with the low signal-intensity subchondral bone.

The carpus length averaged over the group was 37.5 ± 2.8 mm with a 7.45% between-subjects coefficient of variation. Cartilage cross-sectional area (in mm^2) measured on the selected slices from images recorded with both VIBE and DESS sequences are summarized in Table 2.

The averaged cartilage cross-sectional area obtained with the VIBE sequence was 292.4 ± 39 mm^2 whereas the corresponding value with the DESS sequence was significantly lower (270.4 ± 50.6 mm^2, P = 5.6 × 10^{-7}). Interestingly, the between-subjects coefficients of variation were similar for both MRI sequences (14.1% and 16.8% for the VIBE and DESS sequences respectively). The coefficients of variation computed for the repeated measurements were also comparable for the VIBE (2.4%) and the DESS (4.8%) sequences (Table

Table 2 Quantitative measurements of cartilage

	VIBE	DESS
M1	292.4 ± 39	270.4 ± 50.6[1]
M2	292.3 ± 43.8	274.1 ± 37.4[1]
M3	295.9 ± 41.2	272.9 ± 49.1[1]
CVb	14.1	16.8
CVw	2.4	4.8
ICC1	0.96 (0.88-0.98)	0.93 (0.78-0.98)
ICC2	0.98 (0.92-0.99)	0.92 (0.76-0.97)

[1]Significantly different than the corresponding measurement using the VIBE sequence. Values are presented as means ± SD. M1 and M2 refer to both measurements performed by the same operator. M3 refers to the measurement performed by the second operator. CVb and CVw refer to Between-subject and within subject coefficients of variation considering the measurements performed by the first operator. ICC1 and ICC2: Intraclass coefficient with 95%CI calculated considering both measurements performed by the same operator and measurements performed by both operators. CV: Coefficient of variation; ICC: Intraclass correlation coefficients; VIBE: Volume interpolated breath hold examination; DESS: Dual echo steady state.

2). As illustrated in Table 2, measurements performed twice by the same operator and by an additional operator were very similar. The corresponding intra-class coefficients were higher than 0.9 in each case (Table 2). Interestingly, cartilage cross-sectional area measurements were significantly and linearly related to carpal bone length measurements (Figures 3A and B). As compared to the CSA values, the corresponding standardized measurements, *i.e.*, the cartilage cross-sectional area scaled to the carpal bone length displayed smaller coefficients of variation, *i.e.*, 8.4% and 10.6% for the measurements obtained from the VIBE and the DESS sequences respectively.

This positive linear relationship was found for measurements performed from MR images obtained with both MRI sequences, *i.e.*, VIBE (R^2 = 0.82) and DESS (R^2 = 0.75).

In addition, as illustrated in Figure 3C, these measurements were linearly and significantly related (R^2 = 0.79) to each other. However, the cartilage CSA values quantified on the basis of the VIBE sequence were consistently larger than those obtained with the DESS sequence.

DISCUSSION

In the present study, we demonstrated that use of high-field MRI combined with a semi-automatic segmentation process can be utilized to measure cartilage cross-sectional area at the wrist, a site commonly affected in RA, accurately. On that basis, we investigated the normal range of the carpal cartilage cross-sectional area of healthy adults, the physiological inter-individual heterogeneity and a potential way of normalizing the corresponding measurements.

It is noteworthy that the initial scoring system devised in the field of MRI investigations of rheumatoid arthritis (RAMRIS) disregarded cartilage MRI quantification due to

its low sensitivity[6,7]. On the basis of MRI investigations performed at higher-field, *i.e.*, 3T, cartilage thickness has been recently introduced as a potential surrogate marker for RA[8] severity. In the current situation, however, we are still lacking quantitative information related to the normal range of cartilage cross-sectional area in healthy human wrists and the reproducibility of the corresponding measurements has never been assessed.

From a methodological point of view, we showed that high-field 3D MR imaging using both VIBE and DESS sequences provides adequate spatial resolution and signal to noise ratio allowing accurate and reproducible quantification of the articular cartilage area in the carpal joints. The results of the present study clearly indicate that measurements obtained from both MRI sequences are largely reproducible. On the basis of repeated measurements performed by the same and by two different operators, we calculated intra-class coefficients which were higher than 0.9. These values can be compared to the ICC of 0.18 initially reported by the OMERACT initiative[30]. Significantly, they are similar to those reported using the recent MRI scoring system related to cartilage narrowing in the wrist of patients with RA[1], indicating that the reproducibility of our quantitative approach is similar to what has been obtained for a scoring system, a qualitative approach by definition[1]. The corresponding coefficients of variation were also similar using both techniques.

Of importance, the natural variability of wrist cartilage cross-sectional area was related to the measured carpal bone length. The highly significant relationships depicted in Figures 3A and B suggested that cartilage CSA would vary in the same way as the carpal bone length and that the corresponding ratio might be used as a normalized index. This normalization procedure is comparable to what has been previously reported for the knee cartilage volume using tibial head diameter[31] or the tibial plateau area[32] as normalization indices. In both cases, the normalization procedure led to a reduction of the coefficient of variation from 19% to 13% which is comparable to the reduction we reported for our normalized measurements, *i.e.*, from 14% to 8% and from 16% to 10% for the VIBE and the DESS sequences respectively. In addition, these results indicate that cartilage cross-sectional area or volume measurements cannot stand alone as a diagnostic criterion of cartilage loss. On the other hand, the highly linear relationship between cartilage area and carpal bone length provides a standardized measurement which might be helpful in future studies conducted in wrist of patients with rheumatologic diseases.

With an eye toward practicality, and in consideration of protocol duration constraints imposed on MRI with Gd injection[33], we deliberately chose in the present study to avoid gadolinium injection and used conventional MRI sequences, *i.e.*, two ultra-fast gradient echo pulse MRI sequences. These sequences provide high spatial resolution within an acceptable acquisition time, *i.e.*, about 5 min. This type of sequence has already proved its
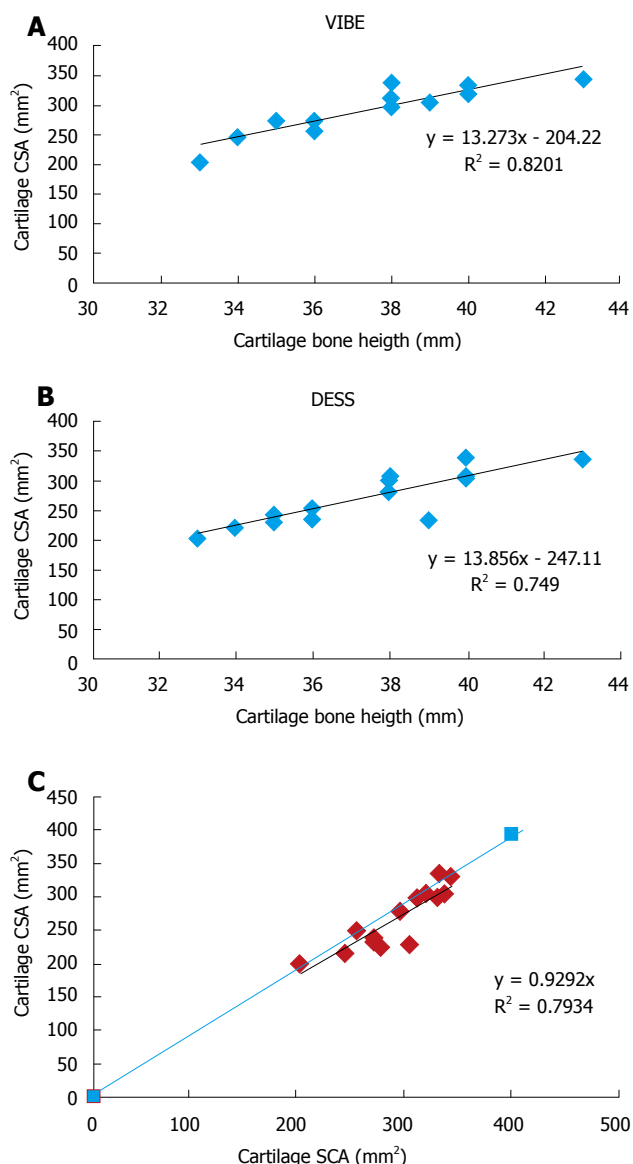
Figure 3 Relationships between wrist cartilage cross-sectional area measurements. Relationship between wrist cartilage CSA (mm^2) and carpal bone length (mm) measured. The cartilage CSA was measured using the VIBE (A) and the DESS (B) MRI sequence; C: Relationship between cartilage CSA measured using the VIBE (x-axis) and the DESS (y-axis) MRI sequences. The continuous line crossing the both axes represents the identity line. VIBE: Volume interpolated breath hold examination; DESS: Dual echo steady state; CSA: Cartilage cross-sectional area; MRI: Magnetic resonance imaging.

utility for the detection of focal cartilage abnormality[11]. Contrary to most of the fast gradient echo pulse sequences providing a T1-based contrast, the DESS sequence offered a T2-weighted contrast. This sequence is actually a combination of fast imaging in the steady precession (FISP) and PSIF (backward-running FISP) and allows T2 weighted imaging with a fast gradient echo technique which has proven its usefulness for the detection of cartilage abnormalities[22-25]. In contrast, the VIBE sequence has not been used very much in the field of musculo-skeletal investigations but rather for head and neck or abdominal imaging[21]. It provides a T1-based contrast. While current guidelines in RA recommend the use of T1 weighted imaging, we demonstrated in the present study that images with both T1 and T2 contrast can be used for quantitative investigation of cartilage. In addition, the three-dimensional nature of the MRI sequences used herein, permit investigation not only of cartilage but also of bone erosions, an index in the RAMRIS score. Further, in that configuration, one is able to choose a well-defined segment in 3 dimensional space and investigate parallel joint spaces for each subject. Such an opportunity would not have been possible using a 2D scheme, given the slightly different orientations of wrist within the flexible coil. The different contrasts related to the VIBE and the DESS sequences may explain the slightly different cartilage area measurements we obtained. However, the highly significant linear relationship between measurements obtained with both methods on the one hand, and with the carpal bone length measurements on the other hand strongly suggest that both methods can be used.

Both operators in the present study were experienced radiologists and processed the MR images after a training period. Considering the multiple steps of the semi-automatic procedure, one may have expected a large operator dependency of the results. And yet, the corresponding ICC were not appreciably different when data were examined by both readers or repeatedly by the same reader, indicating the high reliability of this approach and suggesting that such a reliability can be achieved by any trained reader using similar MRI scans. Automatic segmentation tools have been developed for the measurement of cartilage volume and thickness in the knee[34,35]. Considering the low contrast between cartilage and adjacent structures in the wrist, with its far smaller cartilage thickness, it seems unlikely that such automatic tools could be used for the quantitative investigation of cartilage in the wrist.

The limitations of the current study arise from the modest sample size and the limited age range of the subjects. Of relevance, no marked changes in knee cartilage volume have been identified in healthy subjects with ages ranging from 24 to 82 years[31]. In contrast, a linear decrease of cartilage thickness has been reported in the weight-bearing areas of the femur in healthy subjects[32]. Further studies should be performed in a larger group of subjects in order to determine whether carpal cartilage cross-sectional area remains stable with respect to age.

In conclusion, we report herein for the first time the normal range of wrist cartilage cross-sectional area in healthy subjects. We demonstrated that reproducible measurements of carpal cartilage cross-sectional area can be performed using high-field MRI and that there exists a wide variation in cartilage cross-sectional area in the normal human wrist. We also showed that a standardized index of cartilage cross-sectional area can be calculated taking into account carpal bone length. The corresponding normalized measurement may be helpful for future studies aiming at investigating wrist cartilage in patients with rheumatologic diseases. Technical issues

related to the occurrence of joint effusion might be problematic in differentiating fluid from cartilage and likely be a substantial source of error in inflammatory arthritis. Future studies addressing these questions will possibly benefit from technical evolutions allowing the suppression of MRI signal from fluid[36]. These findings encourage further efforts towards quantitative standardized MRI of cartilage at high field. Additional studies are warranted in order to determine the sensitivity of such normalized indices with respect to the RAMRIS index[37].

ACKNOWLEDGMENTS

COMMENTS

Background
Although magnetic resonance imaging (MRI) has been recently recognized as a potentially useful tool for appreciating and characterizing cartilage loss at the wrist, the corresponding data are few and qualitative in nature.

Research frontiers
There is a need for reproducible quantitative measurements of cartilage cross sectional area (CSA) at the wrist which could be used as surrogate marker of disease progression in rheumatoid arthritis (RA) and other rheumatologic diseases.

Innovations and breakthroughs
In the present study the authors used a semi-automatic method in order to quantify CSA at the wrist level from a 3D MRI dataset. The corresponding measurement was highly reproducible and linearly linked to the carpal bone length. The corresponding standardized ratio, *i.e.,* CSA/carpal bone length captures the natural diversity between subjects and allows a substantial reduction of the coefficient of variation calculated between the subjects.

Applications
The standardized ratio between cartilage CSA and the carpal bone length captures the natural diversity between subjects and might be a helpful surrogate marker of disease progression in RA and other rheumatologic diseases.

Peer-review
The authors have performed a good study, the manuscript is interesting.

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SYSTEMATIC REVIEWS

Systematic review of periprosthetic tibia fracture after total knee arthroplasties

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Abstract

AIM: To investigate the known incidences, treatment options, and related outcomes of periprosthetic tibia fractures after total knee arthroplasty (TKA).

METHODS: A literature search was done to identify studies that fit the inclusion criteria. The database search yielded 185 results, which were further reduced by the exclusion criteria to 13 papers, totaling 157 patients that met these criteria. Incidence rates of the different types of periprosthetic tibia fractures were determined and their treatments were subsequently analyzed based on the fracture's subclass, with patient outcomes being overall favorable.

RESULTS: Of the 144 documented patients, 54 (37.5%) had a subclass C fracture, which are frequently seen in revision arthroplasties or when using cement intraoperatively. The fractures of subclasses A and B occur postoperatively. There were 90 subclass A and B fractures with incidences of 18.75% and 43.75% respectively. When broken down by type, 62 (55.36%) were type 1, 24 (21.4%) were type 2, 24 (21.4%) were type 3, and 2 (1.8%) were type 4. Furthermore, from the studies that included origin of injury, the types were further classified as having non-traumatic or traumatic origins. Type 1 had 78% (40/51) non-traumatic origin and 22% (11/51) traumatic origin. Fifteen fractures were type 2, but 5 were falls and 1 through a motor vehicle accident, giving a trauma causation of 40% (6/15). Of the 24 type 3 fractures, 12 were falls and 2 vehicular accidents, leading to a trauma causation of 58% (14/24).

CONCLUSION: Type 1 fractures were the most common. Subclass A was treated with locking plates, B required a revision TKA, and C was treated intraoperatively or nonoperatively.

Key words: Periprosthetic fractures; Literature review; Tibia fractures

Core tip: A literature search of the PubMed and Web of Science databases was done to compile the known incidences and treatments of periprosthetic tibia fractures after total knee arthroplasties (TKA). Among the relatively uncommon periprosthetic tibia fracture, type 1 fractures were the most common among documented types. Subclass A fractures were treated with locking plates, subclass B fractures first required a revision TKA, and subclass C fractures were either treated intraoperatively when they occurred or were treated nonoperatively.

INTRODUCTION

As of 2010, there were approximately 500000 total knee arthroplastys (TKAs) being performed annually in the United States, with that number increasing each year[1]. After such a procedure, subsequent complications can no longer be treated with the same initial methodology that would be used for non-TKA patients, and so surgeons must approach each case with new treatments. One such complication is the occurrence of periprosthetic tibial fractures.

The incidence rate of periprosthetic tibial fractures after TKA is less than 1%[2], but with the increasing quantity of TKAs being performed each year, the absolute number of periprosthetic tibial fractures is also increasing[3]. However, due to its relatively scarce occurrence, very little research has been done on the subject. A meta-analysis of periprosthetic tibia fractures has not yet been done and so the purpose of this review is to compile the studies done on periprosthetic tibial fractures after TKA and analyze the procedures used for treatment. The focus will be on treatment method for the particular classification of fracture and the anatomical and functional outcome.

MATERIALS AND METHODS

To locate the publications used in this review, PubMed and Web of Science databases were searched for the key term "periprosthetic tibia fracture". From the given results, studies were individually either included or excluded. Criteria for inclusion were the following: (1) Patient must have a fracture of the tibia; and (2) Patient must have undergone a TKA.

Multiple fractures and intraoperative fractures were included. Results that appeared in multiple searches, were not from a human, or were simply a documentation of treatment methods were excluded.

Preliminary data from these studies was organized into an excel spreadsheet for analysis. Important information included study dates, fracture classifications, number of patients, treatment methods, anatomical outcomes, functional outcomes, and any complications encountered during the process. This data was qualitatively and quantitatively analyzed for successful and unsuccessful patterns as well as novel techniques that require further attention.

RESULTS

The database searches yielded 185 results, which were then further reduced based on the inclusion and exclusion criteria from Section 2.65 of the results. Those studies that were eliminated included redundant studies, 8 results that focused on a unicompartmental arthroplasty, 1 result that was of a canine tibia, 59 results that did not actually have a tibia fracture, and 39 results that did not have any patient data. After the exclusion of these papers, only 13 papers were left that fit the inclusion criteria. This breakdown is graphically shown in Figure 1. The papers are shown in Table 1.

Classification

The majority of the papers used the Felix classification system to identify the fracture type associated with the periprosthetic tibia fracture. Simply, there are 4 fracture categories: type 1 are those that extend partially across the tibial plateau, type 2 fully cross the tibial plateau, type 3 are across the tibial shaft past the tibial stem of the prosthesis, and type 4 involve the tibial tuberosity. Each of these types can be further categorized into subclasses: (1) having a stable prosthesis; (2) having an unstable prosthesis; or (3) occurring intraoperatively[10]. This breakdown can be seen in Table 2.

Causes of fractures

Many of the studies did not provide a direct cause for the fractures, instead focusing on the fracture itself and the treatment used. However, a limited number of studies did include this information and, therefore, will be the only studies included here.

Of the 144 documented patients, 54 had a subclass C fracture. These fractures, by definition, occur intraoperatively. A variety of sources can cause subclass C fractures, but they are frequently seen in revision arthroplasties or when using cement.

The fractures of subclasses A and B occur postoperatively. There were 90 subclass A and B fractures. Fifty-one were type 1 and mainly occurred non-traumatically: 8 were through a fall and only 3 were caused by a more major traumatic event. This means only 22% (11/51) of type 1 fractures were caused through trauma. Fifteen fractures were type 2, but only 5 were through falls and 1 through a motor vehicle accident, giving a trauma causation of 40% (6/15). Of the 24 type 3 fractures, 12

Table 1 Studies included in this review

Ref.	Number of patients	Fracture type	Treatment method
Agarwal *et al*[2]	2	Type 2	Revision TKA and locking plate
Cipriano *et al*[4]	16	Subclass C	13 were nonoperative and 3 were braced
Alden *et al*[5]	18	Subclass C	Observation
Thompson *et al*[6]	7	Not stated	Not stated
Jeong *et al*[7]	1	3A	Reduction and revision of tibial stem component
Beharrie *et al*[8]	1	3B	Revision TKA with long stemmed tibial component and bone grafting
Ruchholtz *et al*[9]	NA	NA	No patients, only offered treatment methods for various fracture classifications
Felix *et al*[10]	102	All types	Many different methods were used depending on the fracture type
Watanabe *et al*[11]	1	Not stated	Revision TKA with long stemmed tibial component
Cordeiro *et al*[12]	1	Not Stated	Revision TKA
Fonseca *et al*[13]	1	1B	Revision TKA
Tabutin *et al*[14]	6	3A	Intramedullary nailing
Banim *et al*[15]	1	3C	Cables and plate, with reduction

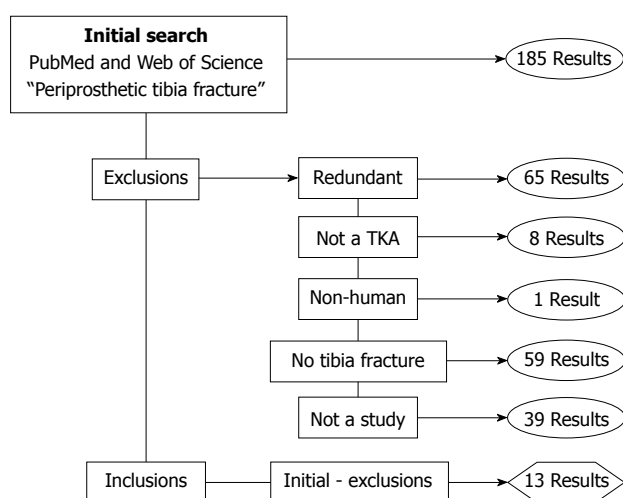TKA: Total knee arthroplasty; NA: Not available.

Table 2 Breakdown of the types and subclass for diagnosing periprosthetic tibia fractures, as described by Felix *et al*[10] in her 1997 study

Type	Description	Subclass	Description
1	Partial tibial plateau	A	Stable prosthesis
2	Full tibial plateau	B	Unstable prosthesis
3	Distal tibial shaft	C	Intraoperatively
4	Tibial tuberosity		

Table 3 Breakdown of the incidents of types and subclasses of fractures

Type	Incidents	Subclass	Incidents
1	62	A	27
2	24	B	63
3	24	C	54
4	2		
Total	112	Total	144

The total number of patients in the review was 154, but not every patient was classified fully.

Figure 1 Flowchart of article exclusion from the PubMed and Web of Science database searches. TKA: Total knee arthroplasty.

occurred through falls and 2 through vehicular accidents, leading to a trauma causation of 58% (14/24).

Diagnosis

As stated before, the incidence rate of periprosthetic tibia fractures is very low, and so diagnostic methods have yet to be standardized. Frequently, a periprosthetic tibia fracture can be clinically diagnosed using the same methods that would be utilized to diagnose a typical tibia fracture. In order to classify the fracture according to the Felix system, however, a radiological evaluation is

required. This is important as treatment methods, to be described in section 4D, differ based upon the fracture classification.

From the studies, not every patient's fracture was fully classified according to the Felix system - several only stated the type or the subclass. Taking this into account, the sum of the breakdown of the types will not add up to the total number of patients in the study. This data is shown in Table 3.

As for incidence rate, of the 144 categorized by subclass, 18.75% (27/144) were subclass A, 43.75% (63/144) were subclass B, and 37.5% (54/144) were subclass C. The large portion of subclass C fractures is misleading due to the fact that many of them did not require any treatment. The subclass B fractures, however, are important as these fractures typically require additional surgery and because they are the most prominent. When broken down by type, of the 112 classified, 55.36% (62/112) were type 1, 21.4% (24/112) were type 2, 21.4% (24/112) were type 3, and 1.8% (2/112) were type 4. A vast majority of the cases were type 1, which is the smallest of the possible fractures as it does not span the width of the bone. Type 2 and 3 fractures were equally prominent. Type 4 fractures, however, appear very rare and an analysis of them is hard to obtain with such a small sample size.

Treatment

Treatment of the various fractures seemed to follow a

pattern based on the subclass for the fracture. Patients with a subclass A fracture typically were treated as normal, that is, as one would be treated without a periprosthetic tibial fracture. This could encompass anything from weight bearing restrictions to nails, depending on the severity of the fracture. Of the 27 cases of subclass A fractures: 6 were treated with intramedullary nailing, all of which were type 3; 2 were treated with extension immobilization and screw fixation, both were type 4; and the rest were treated with either a cast or weight bearing restrictions. Furthermore, these fractures tended to heal as typical fractures and showed little complications.

Patients with subclass B fractures were initially treated in either one of two ways: either they had a revision TKA or they did not. Besides the revision TKA, the fracture itself was treated as normal. There were 63 subclass B fractures, of which only 28 did not immediately undergo revision TKA. For the 40 that underwent revision TKAs, the fractures healed without complications. For those that were simply treated without a revision TKA; however, complications arose in 23 and a revision TKA needed to be done later in order to resolve those issues. Another article did not provide numbers of patients diagnosed with subclass B fractures, but all of them were said to have undergone revision TKA[9]. From the data gathered, it seems that an unstable prosthesis requires a revision TKA before one can address the periprosthetic tibia fracture.

Subclass C fractures tended to be the least severe. Of the 54 type C fractures, none required additional surgery. Those that are noticed intraoperatively can be treated immediately, if necessary. Twelve of the fractures required additional attention during the surgery, while the others were treated nonoperatively. Of these 12, 9 were type 1C and were either fixed with screws or wires, 2 were type 2C and were fixed with bone grafting, lastly, 1 was type 3C, which required cables and a plate after reduction. There were 42 nonoperatively treated subclass C fractures that only required weight-bearing restrictions and, occasionally, casting. Of the 54 patients, only 1 had pain after treatment and 1 passed away before fully healing. The other 52 patients saw full recovery of their subclass C fracture. Overall, subclass C fractures required the least amount of attention.

DISCUSSION

TKAs alone have a low rate of failure, only 20% after 20 years[1], and so the incidence rate of periprosthetic tibia fractures seems to follow that same trend. Data was not gathered on the number of TKAs performed each year, but the small quantity of studies and case reports found on periprosthetic tibia fractures supports the notion that they are very uncommon. Furthermore, many of the more serious fractures, types 2 and 3, are much more common after a traumatic event. It seems as if the design of the prosthesis itself, as well as the procedure used to implant it, is not a major factor in the incidence of periprosthetic tibia fractures. The one obvious exception are subclass C fractures, which have basically no other causation factors.

Nonetheless, periprosthetic tibia fractures do occur and thus are a pertinent issue that needs addressing. Of the different types of periprosthetic tibial fractures, type 1 appeared the most often making up over half of the cases. Type 1 fractures also tended to be the least severe since these fractures do not span the width of the bone. Though not explicitly documented, these fractures can frequently be described as a collapse of the tibial head, where one side of the tibia caves under pressure. These collapses are infrequent in persons with a normal knee, and so their incidence in TKAs begs the question as to what causes these fractures to arise. Firstly, when undergoing a TKA, the removal of the original knee requires cutting of the bone. If too much of the bone is cut, the remaining bone is weaker and more susceptible to fractures. These most prominently result in type 1 fractures as they are closer to the tibial head and less severe. Furthermore, altering the surface of the tibia through cutting can affect the biomechanics of the knee where the tibia contacts the prosthesis. This change in the biomechanics of the joint can redirect the forces of the knee onto different parts of the tibia, which can result in fractures of those respective parts if they cannot support the new load.

In addition to the bone loss from a TKA, muscles are also cut or moved during the procedure. Since the knee initially does not have much muscle support, altering these muscles will have a larger impact on the performance of the knee. With less muscle support, there is more force being exerted from the knee onto the surrounding bone, which can cause the collapse fractures seen in type 1 periprosthetic tibia fractures. These pressure induced fractures are much more likely to cause type 1 fractures than type 2 or 3.

As noted before, type 2 and 3 fractures are seen less frequently than type 1 fractures, but are much more likely to be the result of a traumatic incident. This lends more support to the idea that the procedure or prosthesis has less of an effect on these fractures than they do in type 1. What makes these fractures notable is that they typically require more serious treatment than their non-TKA counterparts. By already having a TKA, the tibia is weaker, and so more cautious care must be given to the healing of these fractures. This is why reduction and internal fixation, using mainly locking plates and screws, was the most common form of treatment for these fractures.

Due to the variety of treatment methods for the different fracture types, it often becomes a difficult decision for the surgeon to decide on a treatment method. It has been shown that, in cases with a subclass B fracture, a revision TKA is required for full recovery over an extended period of time. However, in subclass A cases, the surgeon must decide whether to treat operatively or not. On one hand, nonoperative treatments are often preferred by the patient and

are at less risk for other complications. However, operative treatments are often more direct and can reduce the complications that arise from the prolonged immobilization of nonoperative treatment[16]. In the end, there is not a standardized method to date and the decision is still a judgment call between the patient and surgeon.

Even 17 years after the study by Felix that established the classification system for periprosthetic tibia fractures, very little research has been done on the subject. Of the 13 studies used in this review, there were only 157 patients. Furthermore, of these 157, 102 were from the Felix study done at the Mayo clinic in Rochester, Minnesota. This limits the scope of this review to mostly that specific clinic. Of the remaining 52 patients, 34 came from 2 studies specifically on intraoperative fractures. This leaves only 18 patients from novel studies, many of which were case reports. While the data gathered in this review is still relevant, it is limited in scope by the scarcity of studies on the injury.

This systematic review showed, most importantly, that there is very little data on periprosthetic tibia fractures, but with the rise in occurrence of TKA, periprosthetic tibia fracture incidence will also rise. To this end, more studying needs to be done on the topic to standardize treatment methods so the patient can be given the best treatment.

In conclusion, periprosthetic tibia fractures are relatively uncommon. Type 1 fractures were the most common among documented types. Subclass A fractures were treated with locking plates, subclass B fractures first required a revision TKA, and subclass C fractures were either treated intraoperatively when they occurred or were treated nonoperatively.

COMMENTS

Background

Periprosthetic tibia fractures are relatively uncommon and there are no systemic reviews on this topic thus far. Since total knee arthroplasties are increasing, the incidence of periprosthetic tibia fractures will likely also be following the same trend.

Research frontiers

Periprosthetic tibia fractures are not very common, however, total knee arthroplasties are. Since the incidence of these fractures is low after a total knee arthroplasty (TKA), the design and material used in the implants is being reflected as good. Additionally, there has yet to be an establishment of a standardized protocol for the periprosthetic tibia fracture after TKA.

Innovations and breakthroughs

The authors have summarized the available data on periprosthetic tibia fractures and have found that periprosthetic tibia fractures are relatively uncommon. Type 1 fractures were the most common among documented types. Subclass A fractures were treated with locking plates, subclass B fractures first required a revision TKA, and subclass C fractures were either treated intraoperatively when they occurred or were treated nonoperatively.

Applications

This study can hopefully guide physicians on the periprosthetic tibia fracture

and allow them to provide information to their patients. However, further investigation is still necessary.

Terminology

Periprosthetic fractures are fractures that occur around implants associated with arthroplasty, particularly after TKA in the proximal tibia in this study.

Peer-review

This systematic review showed, most importantly, that there is very little data on periprosthetic fractures. This summarization of literature with regards to incidence and treatment can help physicians treat this situation and will improve patient outcomes.

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