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MINIREVIEWS

Coronaviruses: An overview with special emphasis on COVID-19 outbreak with musculoskeletal manifestations

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Abstract

An acute respiratory illness caused by a novel coronavirus, namely, severe acute respiratory syndrome coronavirus 2, the virus that causes coro-navirus disease 2019 (COVID-19), began spreading across China in late December 2019. The disease gained global attention as it spread worldwide. Since the COVID-19 pandemic began, many studies have focused on the impact of the disease on conditions such as diabetes, cardiovascular disease, pulmonary disorders, and renal malfunction. However, few studies have focused on musculoskeletal disorders related to COVID-19 infection. In this review, we update the current knowledge on the coronavirus with special reference to its effects during and after the pandemic on musculoskeletal aliments, which may inform clinical practice.

Key Words: Coronaviruses; COVID-19; Musculoskeletal; Infection; Pandemic; Orthopaedics

Core Tip: Severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019 (COVID-19), began spreading across China in late December 2019 and became a pandemic. This review focuses on musculoskeletal signs and symptoms of COVID-19 infection. Furthermore, a hypothetical pathway showing factor-induced hypoxic conditions and their downflow changes in the musculoskeletal system during severe COVID-19 infection are discussed.

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INTRODUCTION

Coronaviruses, RNA-positive sensory viruses, are 60–140 nm diameter spheres with spiked projections that make them appear crown-like under an electron microscope [1]. Subsequent to β-coronavirus and pneumonia outbreaks occurring in 2019 in Wuhan, China, the World Health Organization (WHO) named the novel coronavirus 2019-nCoV on January 12, 2020. The WHO formally identified coronavirus disease 2019 as COVID-19, and the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses designated the severe acute respiratory syndrome coronavirus as SARS-CoV-2 on February 11, 2020[2]. The WHO declared that the COVID-19 outbreak was a global pandemic on March 11, 2020.

In more than 210 countries and territories, the virus spread within a brief period. Almost 58699047 cases of COVID-19 have been reported to date, of which 40639477 people have recovered and 1389562 people have died. The numbers are increasing, so these figures are changing every day[3].

The enormous potential of infection and low-to-moderate death rates due to COVID-19 have presented a significant challenge to health care systems worldwide. Furthermore, according to the current information, the novel coronavirus is predominately transmitted through aerosols and direct contact with infected surfaces. Therefore, for any specific prophylactic measures, both of these types of transmission need to be considered.

In this pandemic situation, it is a misconception that COVID-19 affects only specific health care specialties/systems. In fact, all body systems are affected by COVID-19. It has been observed that most developed countries, even those with well-established health care systems, have suffered greatly due to COVID-19. Therefore, it is not difficult to understand the disastrous effect of COVID-19 in low-resource countries with very limited health care . In the present review, we provide information about coronavirus with special reference to musculoskeletal aliments that have been found in COVID-19 patients during the pandemic and may continue to appear after the pandemic is over, thereby affecting clinical practice.

CORONAVIRUSES

Severe acute respiratory syndrome coronavirus (SARS-CoV) first appeared in 2003, and later, in 2012, the Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged, although the first coronavirus was reported even earlier, in 1965[4]. The diverse family of viruses infects mammalian and avian hosts' respiratory and gastrointestinal tracts, and the bat is a natural reservoir for these viruses[5]. The virus belongs to the *Nidovirales* order, which includes four families: *Coronaviridae, Arteriviridae, Roniviridae* and *Mesoniviridae,* in which *Coronaviridae* consists of a vast genome size of 26–32 kb; again, it has a subfamily, *coronavirinae* and *toronavirinae* with four genera, α, β, γ and Δ coronavirus[6].

SARS-CoV-2 is the causative agent of the novel COVID-19 and belongs to the β-genera coronavirus family. The virus consists of positive single-stranded RNA with a single linear RNA fragment[7]. Under an electron microscope, it appears crown-shaped, circular or oval with a diameter of 60–140 nm, and the length of the genome is 30 kb[8].

Types of coronaviruses

According to the U.S. Centers for Disease Control, there are seven varieties of coronaviruses: 229E, NL63 (α coronaviruses), OC43, and HKU1 are beta coronaviruses, MERS-CoV (β coronavirus), SARS-CoV (β coronaviruses), and COVID-19 (SARS-CoV-2)[9].

Differential molecular structure of COVID-19

A study on protein sequences found that there is 94.6% similarity among all seven nonstructural proteins and amino acids as well as the genomes of both COVID-19 and

SARS-CoV. The spikes on the viruses consist of two linked parts; when those halves divide, the spike activates, and only then does the virus reach the host cell. This division happens in SARS-CoV with some difficulty. Nevertheless, in SARS-CoV-2, the bridge that links the two halves can be quickly broken by an enzyme named furin produced by human cells and crucially in several tissues[8]. COVID-19 shares a 79.5% identical genomic structure with SARS CoV[9].

Key virulent factor of COVID-19

According to a report by Wu *et al*[10], nonstructural protein 1 (Nsp1), Nsp3c, and open reading frame 7a (ORF7a) are the three main coronavirus virulence factors that interfere with the host's innate immunity and assist in coronavirus immune escape. Nsp1 interacts with the host's 40S ribosomal subunit, which directly causes mRNA degradation in the host and inhibits interferon development. Nsp3c has the potential to bind ADP ribose from the host to allow coronavirus escape of innate immunity. In addition, bone marrow matrix antigen 2 (BST2) may prevent host cells from releasing newly assembled coronavirus. SARS-CoV ORF7a binds directly to BST2 and inhibits its activity by preventing BST2 glycosylation[10].

What is COVID-19?

COVID-19 is an infectious disease caused by a novel coronavirus that may induce flu-like symptoms, such as fever and dry cough (the two most frequent symptoms), weakness, nausea, and nasal congestion. As the pandemic progresses globally, certain new signs have arisen, such as loss of smell and taste. COVID-19 has a fatality risk of 4.4%, which is significantly lower than that of SARS (10%) and MERS-CoV (approximately 30%). However, the potency of infection with COVID-19 is much greater than that of either SARS or MERS-CoV. In addition, it is crucially undetectable, even asymptomatic patients or patients with minor symptoms are able to transmit the infection[11].

Why is COVID-19 the most virulent form?

A study showed that the virus uses the human angiotensin-converting enzyme-2 (ACE-2) receptor and recognizes it with comparable affinity to SARS-CoV isolates, which indicates that it can spread effectively in humans[12]. Researchers also found that the RBD spike protein of COVID-19 binds with human ACE-2. This is why the COVID-19 spike protein with high affinity (10–20 times) to human ACE-2 is the most contagious and virulent form (Figure 1)[13,14].

IMPACT OF RISK FACTORS AND COMORBIDITIES ON THE CLINICAL OUTCOME OF COVID-19-INFECTED PATIENTS

Previous studies[15-29] have indicated and correlated the risk and severity of COVID-19 illness in patients with comorbidities and compared these patients to those without comorbidities. Therefore, triage is carried out by carefully reviewing the medical history of COVID-19 patients, as this will help to distinguish patients according to their prognoses. Patients with COVID-19 who have any associated comorbidities are at high risk and should be treated with extra caution in an intensive care unit (ICU) facility if needed.

There is an urgent need to consider severe clinical comorbidities to improve risk stratification and strategic planning for COVID-19 patients. Based on the knowledge and clinical experience currently available, older people and people of all ages with severe underlying medical conditions, such as diabetes, cardiovascular disease, pulmonary disorders, and renal malfunction, could be at higher risk of acute disease following COVID-19[15].

In a retrospective study, Zhou *et al*[16] found that advanced age, higher rates of sepsis-related organ failure assessment score, and high d-dimer at enrolment were risk factors for the deaths of COVID-19 adult patients[16]. In the sex-based comparison, there were more male than female patients. This inequality indicates that women have more robust innate and adaptive immune responses[17,18]. However, this observation may also be due to occupational risk factors for men in Huanan's wet market[19].

According to some studies[20-23], the most prominent comorbidity with COVID-19 infections was hypertension (14%-30%) and diabetes (6%-19%), followed by cardiovascular diseases such as acute cardiac injury or failure (4%-8%) and respiratory system diseases such as pulmonary hypertension and chronic obstructive pulmonary

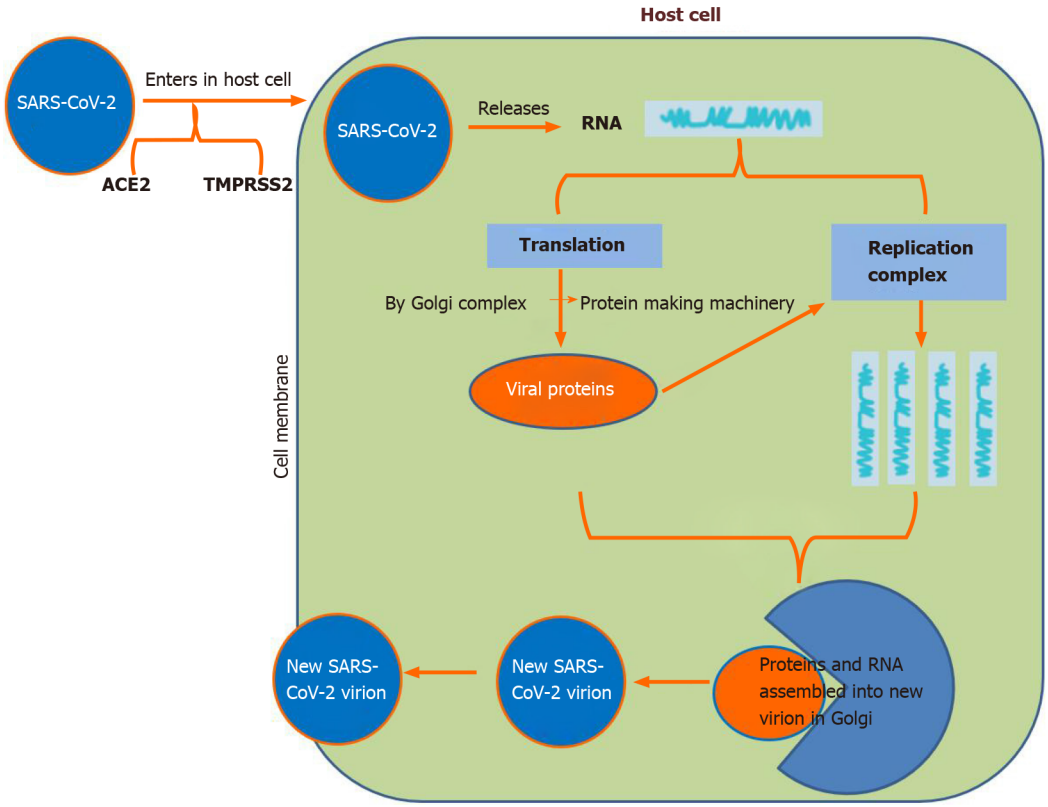

Figure 1 Spike protein on the virion binds to angiotensin-converting enzyme-2 (cell surface protein), transmembrane protease serine-2, an enzyme that helps the virion enter and release virion RNA. Some RNA is translated into proteins by the cell machinery; some of these proteins form replication complexes to make more RNA. The proteins and RNA assemble into a new virion in the Golgi and are finally released. ACE-2: Angiotensin-converting enzyme-2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; TMPRSS-2: Transmembrane protease serine-2.

disease (COPD) (1%-3%)[20-23]. Among these comorbidities, hypertension is associated with an almost 2.5-fold higher risk of severe illness or death with SARS-CoV-2 infections. According to Schiffrin *et al*[24], there is no evidence to date that hypertension is related to COVID-19 outcomes. In COVID-19 patients, people with diabetes present poor outcomes; however, the susceptibility to COVID-19 infection in diabetic patients may not be more significant[25]. Because of a lack of clinical evidence, current guidelines from the European Cardiology Society also strongly recommend that patients use their typical diabetic/antihypertensive medications as usual in the COVID-19 pandemic situation[26]. In a comprehensive meta-analysis, Lippi and Henry[27] showed that COPD is associated with more than a fivefold elevated risk and severity of COVID-19 infection; thus, patients with COPD must be advised to take more effective measures to prevent from becoming infected with COVID-19. Patients with chronic cardiovascular disease are among the individuals at highest risk for severe COVID-19 disease and death from acute cardiac injury or failure[20]. According to Li *et al*[28], patients with prior cardiovascular and metabolic disorders may face a higher risk of COVID-19 infection with a poor prognosis due to sudden morphological and hemodynamic damage to heart tissues.

Similarly, patients with chronic musculoskeletal disorders may also be at high risk of COVID-19 infection. This might be due to impaired immunity because of prolonged use of corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) in daily life.

However, the main limitation to properly assessing the comorbid risk with COVID-19 is self-reporting on admission, mainly due to lack of awareness. Moreover, underreporting of comorbidities might be a significant confounding factor affecting the strength of association with poor prognoses. Thus, more controlled and well-designed studies with large sample sizes are needed to explore their associations in a more reliable way.

MUSCULOSKELETAL ANOMALY DURING SEVERE COVID-19 INFECTION

The number of COVID-19 patients is increasing dramatically worldwide. It is necessary to discriminate between patients with mild and severe cases of COVID-19 to prevent overburdening the ICU and to timely triage severely ill patients. In severely ill patients with COVID-19, due to prolonged pulmonary malfunction, chronic hypoxic conditions develop.

Compared to other body organs, the musculoskeletal system is more adaptive to hypoxic situations due to special muscle fibers (intermediate muscle fibers). However, the WHO recently declared that some musculoskeletal-associated symptoms (14.8%) are related to severe COVID-19 infection, including myalgia or arthralgia[29]. Hypoxia-inducible factor (HIF) studies in skeletal muscles are complicated due to various energy metabolism mechanisms, including various O_2 supplies and homeostasis and varying proportions of oxidative, glycolytic and intermediate fibers [30]. This section discusses the downflow changes of severe COVID-19-infected patients with the initiation of musculoskeletal-associated symptoms.

In severe COVID-19 patients, the low oxygen level in skeletal muscles may lead to the formation of excess lactic acid because of muscle pain (myalgia), a low pH level (cramps) or other related complications. Furthermore, in chronic hypoxic conditions, muscle tissue shows a significant alteration in gene regulation[29]. The HIF family plays a crucial role in the hypoxic response of the musculoskeletal system, similar to other tissues[29]. HIFs are heterodimeric transcriptional regulatory factors comprised of unstable HIF-α and HIF-β subunits. HIF signaling contributes to an adaptive pathway to minimize the oxygen requirement and increase the oxygen supply to achieve a new equilibrium. The cellular level of HIF-α is oxygen-dependent and conditionally balanced by proteasomal degradation (normoxia)[31-34].

As seen in severe COVID-19 patients in chronic hypoxic conditions, the low oxygen level inactivates the prolyl hydroxylase action and constrains HIF-α hydroxylation. Subsequently, stabilized HIF-α binds with HIF-β to form a stable dimer. This dimer enters the nucleus and transactivates target genes by directly stimulating the expression of fibrogenic factors. It affects signaling pathways, including the transforming growth factor-β/Smad, Notch, phosphoinositide 3-kinase/Akt, and nuclear factor kappa B pathways, to further affect various biological and pathological processes, ranging from fibrosis and skeletal muscle wasting angiogenesis, erythropoiesis, cell proliferation, inflammation, and apoptosis[30,32-38]. These hypoxic conditions induce altered gene regulation that may lead to more pronounced initial musculoskeletal symptoms, such as myalgia (which may be due to excess lactic acid production), arthralgia (which may be due to inflammation), and other musculoskeletal abnormalities (such as lower back pain and cervical pain), that ultimately indicate the severity of COVID-19 in patients (Figure 2). Apart from associated symptoms and inadequate peripheral oxygen saturation levels, several laboratory parameters such as low lymphocyte count and elevated C-reactive protein, D-dimers, interleukin 6, ferritin and cardiac troponin may also indicate the severity or poor prognosis of COVID-19 patients. The clinician should consider these parameters in prioritizing risk stratification and admittance to the ICUs of COVID-19 patients[38]. Additionally, these alterations in blood parameters might directly or indirectly affect musculoskeletal physiology. However, further research needs to delineate the possible musculoskeletal pathophysiology mechanism.

COVID-19 IN MUSCULOSKELETAL MANIFESTATIONS

As already discussed, the effect of comorbidities on the outcome of COVID-19 is well observed, but information that highlights the chronic musculoskeletal comorbid condition is not currently available. Many questions remain, such as "Do musculoskeletal comorbidities worsen the prognosis of COVID-19 patients?" Whether these comorbidities are a prominent risk factor for COVID-19 infections remains a dilemma to date. This may alter the natural course of the disease.

It is also a matter of concern that most musculoskeletal patients are either middle-aged or elderly persons with a history of taking corticosteroids or NSAIDs for a long time to control pain and relieve localized inflammation[39]. A long-term history of taking these medications may result in a weaker immune system and make these individuals more susceptible to any infection , including COVID-19 infections. Thus, corticosteroids or NSAIDs may alter the clinical picture of these patients. The use of methylprednisolone causes delayed viral shedding in SARS-CoV2 and MERS-CoV and

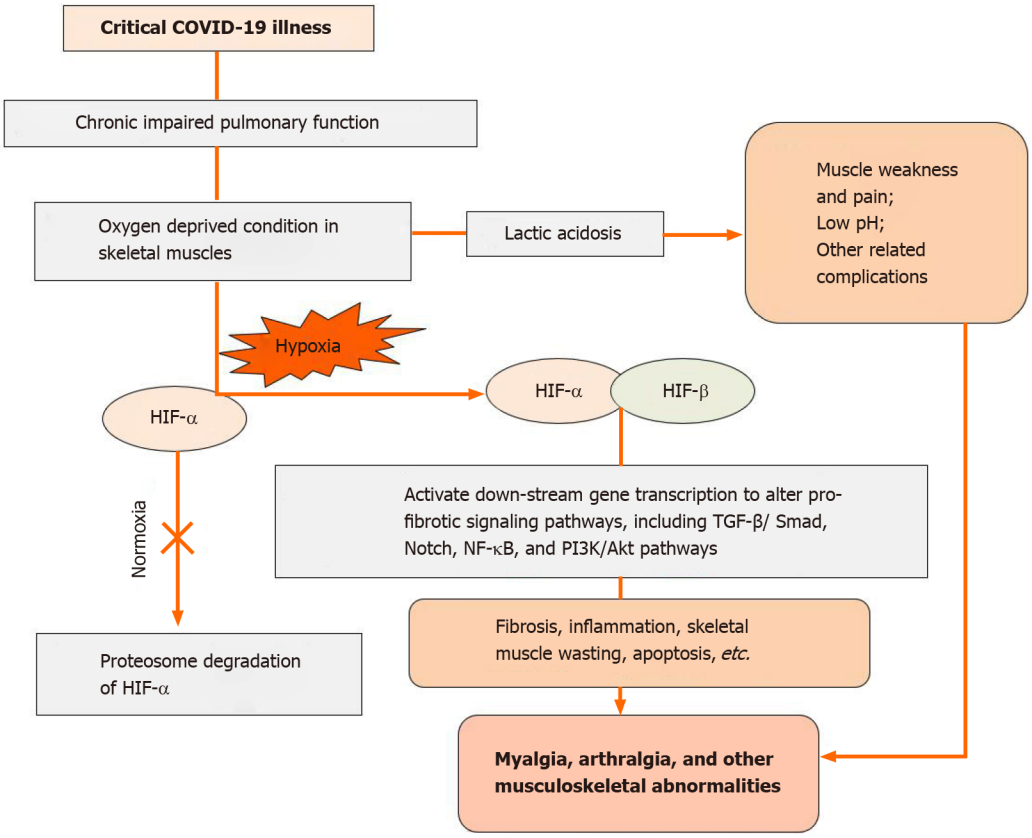

Figure 2 Tentative representation of musculoskeletal anomalies during severe coronavirus disease 2019 infection. COVID-19: Coronavirus disease 2019; HIF: Hypoxia-inducible factors; NF-κβ: Nuclear factor-kappa beta; PI3K: Phosphoinositide 3-kinase; TGF-β: Transforming growth factor β.

avascular necrosis and psychosis related to SARS-CoV. It was also observed that using methylprednisolone can increase mortality in influenza infections[40]. Thus, the WHO currently does not advise the use of any corticosteroids during COVID-19 infection unless they are associated with acute respiratory distress[41]. A previous human study showed that intraarticular steroid application significantly diminished the effectiveness of the influenza vaccine, and patients became more susceptible to viral streaming[42]. However, to date, no research paper explicitly focusing on intraarticular steroid administration in the COVID-19 pandemic situation is available, but the WHO advises not using steroids/NSAIDs unless the patient is in acute respiratory distress syndrome[29].

The current advice is to use mild analgesics and antipyretics such as paracetamol to treat symptoms such as fever and pain[43]. Corticosteroids or NSAIDs may cause significant release of specific cytokines, termed "cytokine storms," and could lead to multiple organ failure. Taking these drugs at the initial stages of COVID-19 may lead to more severe respiratory or cardiac complications with altered disease outcomes.

Again, the problem is not limited to the current COVID-19 pandemic. It is assumed that musculoskeletal disorders will worsen during the post-pandemic situation. According to the WHO[30], musculoskeletal disorders are the world's most significant contributor to disabilities, with low back pain being the single most significant global cause of disabilities. Severe COVID-19 infection affects muscle tissue (proposed pathway given in the previous section), leading to pain, muscle weakness, myalgia, arthralgia and other musculoskeletal issues. In recovered COVID-19 patients, these musculoskeletal disorders may persist for a longer duration and significantly affect their mental health and socioeconomic loss, as well as place an extra burden on treatment centers. The altered musculoskeletal physiology induced due to severe COVID-19 infection may also increase the chance of many bony pathologies or fractures. Therefore, it is clear that in post-pandemic circumstances, apart from patients with regular musculoskeletal disorders, recovered COVID-19 patients with musculoskeletal anomalies will dramatically increase.

CONCLUSION

This COVID-19 outbreak has challenged the health care infrastructure and socio-economic balance worldwide. In addition, it was assumed that the severity of COVID-19 infection significantly affects many associated musculoskeletal disorders. Therefore, it is necessary to improve the overall health care system and revise related comprehensive guidelines for every specialty to better prepare providers, especially those in orthopedics, to cope with the effects of post-pandemic COVID-19 and future pandemics.

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MINIREVIEWS

Hip prosthetic loosening: A very personal review

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Abstract

Hip prosthetic loosening is often difficult to detect at an early stage, and there has been uncertainty for a long time as to when the loosening occurs and thus to the basic causes. By comparing different diagnostic methods, we found that loosening is best defined as prosthetic migration and measured by radiostereometric analysis. Convincing evidence indicates that poor interlock, poor bone quality, and resorption of a necrotic bone bed may initiate loosening during or shortly after surgery; this forms the basis of the theory of early loosening. Biomechanical factors do affect the subsequent progression of loosening, which may increase subclinically during a long period of time. Eventually, the loosening may be detected on standard radiographs and may be interpreted as late loosening but should to be interpreted as late detection of loosening. The theory of early loosening explains the rapid early migration, the development of periprosthetic osteolysis and granulomas, the causality between wear and loosening, and largely the epidemiology of clinical failure of hip prostheses. Aspects discussed are definition of loosening, the pattern of early migration, the choice of migration threshold, the current understanding of loosening, a less exothermic bone cement, cemented taper-slip stems, a new exciting computed tomography-based technique for simpler implant migration studies, and research suggestions.

Key Words: Hip prosthesis; Prosthesis failure; Radiostereometric analysis; Bone resorption; Bone cements; Radionuclide imaging

Core Tip: Much evidence indicates that prosthetic loosening is initiated during or shortly after surgery. The prosthetic micromovements may increase subclinically during a long period of time. Eventually, the loosening may be detected on standard radiographs and may be interpreted as late loosening but should to be interpreted as late detection of loosening. The discussion includes the definition of loosening, the pattern of early migration, the choice of migration threshold, the current understanding of loosening, a less exothermic bone cement, cemented taper-slip stems, a new exciting

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INTRODUCTION

Hip arthroplasty is one of the most successful of all orthopedic operations, but the results do deteriorate with time because of loosening. Radiographic changes indicating loosening are often difficult to detect at an early stage, and there has been uncertainty for a long time as to when the loosening occurs and thus to the basic causes. Confusion also arose because some hips with obviously loose prosthetic components are not painful[1-3]. To solve these issues, a few steps are required. First, the definition of loosening must be clarified. Second, the loosening must be carefully followed from its earliest detection. Third, the most important triggering factors must be identified, as well as other factors that affect the subsequent progression of loosening. Then the simplest scientific explanation that fits the evidence should be chosen.

DEFINITION OF LOOSENING

When I, as a newly graduated orthopedic surgeon in the early 1980s, started studying hip prosthetic loosening in Lund (in Southern Sweden), the diagnosis of loosening was based on insensitive radiographic criteria (periprosthetic radiolucent lines wider than 2 mm, prosthetic migration exceeding 4 mm, cement fracture, *etc*.). Several poorly defined terms were used, such as allergic loosening, aseptic loosening, mechanical loosening, progressive loosening, and reactive loosening – all without clear distinctions between each other.

Radiostereometric analysis (RSA) was introduced in Lund in 1974 by Göran Selvik (1938–1990). It is a technique for obtaining reliable three-dimensional measurements from radiographs and is based on implantation of tantalum bone markers, roentgen calibration equipment, and rigid-body kinematic analysis[4,5]. RSA was mainly used for studies of various bone growth disorders but was also found feasible for the study of hip prostheses[6,7].

My tutor, Lars Ingvar Hansson (1937–1987), advised me to use RSA to look for any pattern in loosening. We used analog films measured with a photogrammetric instrument and assessed (by double examinations) the limit for significant migration along the longitudinal axis to be 0.2 mm. However, later RSA studies have reached a detection limit of 0.08 mm when using fully digital technology[8,9]. By comparing contrast arthrography[10,11], radionuclide arthrography[12,13], bone scintigraphy (^{99m}Tc-MDP)[14,15], and RSA (comprising both instability under load and migration with time) in 14 painful hip arthroplasties, we found that loosening is best defined as migration[16]: All prosthetic components unstable by RSA, or with abnormal arthrogram, or with increased bone scintigraphic activity, or loose at revision were migrating, but no non-migrating components demonstrated any of these signs of loosening. Interestingly, increased activity at the tip of the femoral component by bone scintigraphy (Figure 1) had high sensitivity and specificity in detecting loosening, which was also pointed out earlier[14,15].

PATTERN OF EARLY MIGRATION

To study early prosthetic migration, RSA was performed prospectively on cemented primary hip arthroplasties in two series followed for 2–3 years after surgery[17,18]. Taking these two studies together, we found that 19 of the 36 acetabular components migrated cranially and seven of the 34 femoral components migrated distally during

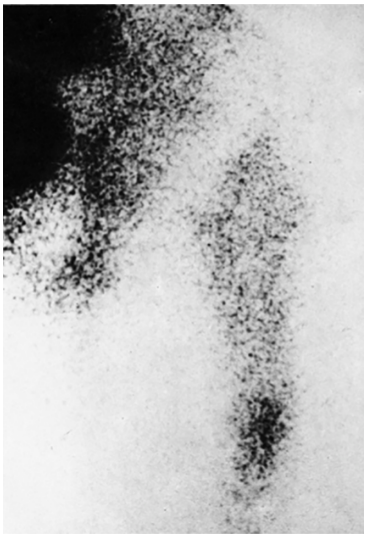

Figure 1 Focally increased activity at the tip of a migrating femoral component at ^{99m}Tc-MDP scan. From Mjöberg *et al*[16] with permission.

the observation period (two femoral components in the latter series[18] were excluded due to insufficient tantalum bone markers); and that in all the cases, but three (two acetabular and one femoral), migration was detected within 4 mo after surgery (Figure 2). We also did not find any correlation between wear and early migration of either prosthetic component[19]. We concluded: (1) That RSA may distinguish between a migrating and a non-migrating prosthetic component within 4 mo after surgery; (2) That the initial migration may be caused by insufficient initial fixation or by resorption of a necrotic bone bed formed due to the heat from curing cement but not by wear products; and (3) That "late loosening" may be the result of late detection rather than of genuine late onset of loosening.

HIGH OR LOW MIGRATION THRESHOLD?

Many RSA studies of hip prostheses have now shown that early migration poses a risk of future failure[9,20-24]. This does not mean that all early migrating components will fail in the foreseeable future. Indeed, certain early migrating uncemented femoral components appear to achieve stability during the healing period[25-27], but it does mean that the failing prosthetic components are recruited from the group of early migrating components.

Some authors have determined a high migration threshold to predict an unacceptably high risk of future clinical failure, *e.g.*, 1.2 mm and 2.6 mm distal migration after 2 years for cemented composite-beam femoral components to predict a revision rate exceeding of 50% and 95%, respectively, within 7 years[20]. As far as I know, no migration threshold values have yet been published for either cemented taper-slip or uncemented femoral components[23].

Others have determined a low migration threshold below which an early migration poses no or almost no risk of future failure, *e.g.*, 0.2 mm cranial migration after 2 years for acetabular components[22] and 0.15 mm distal migration after 2 years for cemented composite-beam femoral components[23] to predict a revision rate of less than 5% within 10 years. Between these extremes (2.6 mm and 0.15 mm), of course, there is a large gray zone. The choice of migration threshold depends on the purpose. In my opinion, a high probability of permanent prosthetic fixation is a more advantageous prediction.

CURRENT UNDERSTANDING OF LOOSENING

Inadequate preparation and cementing technique were probably the main causes of loosening during the pioneering years and greatly reduced rates of loosening were demonstrated after improved technique[3,28-30]. Convincing evidence from both clinical and experimental research indicates that the initial fixation may be insufficient

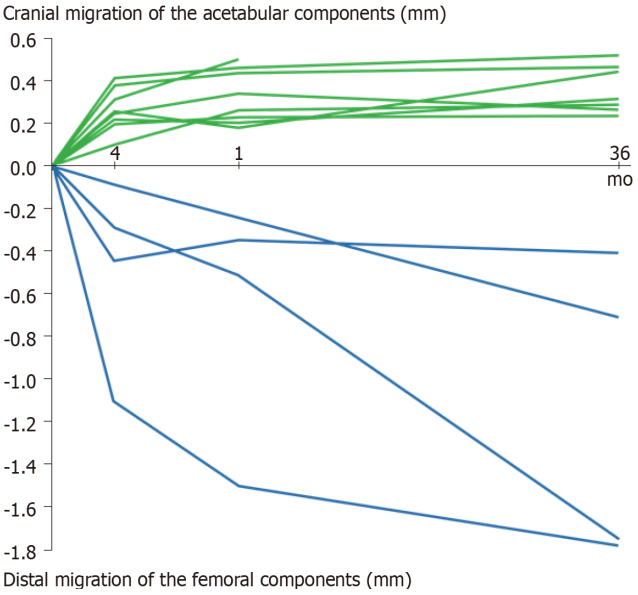

Figure 2 Prosthetic migration along the longitudinal axis. Migration of the migrating eight acetabular (green) and four femoral components (blue) in the series followed by radiostereometric analysis for 3 years [eight acetabular and ten femoral components did not pass the limit (0.2 mm) for significant migration]. From Mjöberg *et al*[18] with permission.

due to poor interlock (inadequate cement filling, interposition of tissue debris, *etc.*)[31-34] or because of poor bone quality (osteoporosis, rheumatoid arthritis, *etc.*)[35-38]. Adequate initial fixation does, however, not eliminate the risk of loosening; resorption of a layer of a necrotic bone bed may result in early loss of otherwise optimal fixation [39,40].

The theory of early loosening[41,42] postulates (the hypothetico-deductive method) that loosening is initiated during or shortly after surgery by these factors alone: Insufficient initial fixation (poor interlock or poor bone quality) or early loss of fixation (resorption of a layer of a necrotic bone). Interestingly, the resorption of necrotic bone can be inhibited with a bisphosphonate during the healing period, which reduces early migration[43] and consequently increases the mean prosthetic survival time[44].

If initiated, the progression of loosening is affected by the degree of early instability, the bone quality, and by the magnitude of the mechanical stresses to which the prosthetic components are exposed during normal daily activity. Thus, femoral components with a high offset[24] or in a varus position[3,34] can be expected to be over-represented among prosthetic failures due to faster increase in the micro-movements of the components in which loosening has been initiated. Similarly, acetabular components that are eccentric (due to design[45] or wear[46]) or have high frictional torque (*e.g.*, metal-on-polyacetal[46] or metal-on-metal articulations[47,48]) can for purely biomechanical reasons be expected to be overrepresented among prosthetic failures. However, such individual components (*e.g.*, femoral components with a high offset or in a varus position) can, if loosening has not been initiated, be well-fixed[3].

The micromovements of a loosened prosthetic component may cause devitalizing spikes of high fluid pressure in the periprosthetic interstice, which can induce osteolysis[49-51] by a complex series of inflammatory responses to the damage-associated molecular patterns of the generated necrotic cells and cell fragments[52]. The periprosthetic fluid may be forced further into the bone (Figure 3), devitalizing the bone tissue that is resorbed, and form a focal osteolysis that is invaded by granulation tissue[54]. The prosthetic micromovements and the subsequent periprosthetic osteolysis may increase subclinically during a long period of time.

The theory of early loosening explains the rapid early migration (Figure 2), the development of periprosthetic osteolysis and granulomas (Figure 3), the bone loss commonly seen in the proximal femur of distally apparently well-fixed stems, the causality between wear and loosening, and largely the epidemiology of clinical failure of hip prostheses[41,42]. But as always, if new data emerge that contradicts the predictions of the theory, the theory must be supplemented or replaced with a more complete theory.

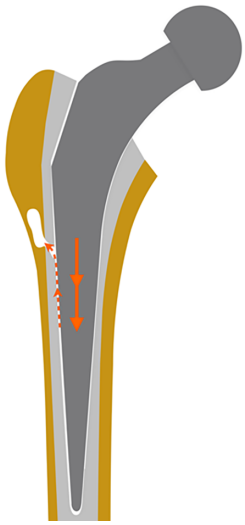

Figure 3 Graph shows how prosthetic micromovements cause a focal osteolysis. The prosthetic micromovements (orange arrows) pump joint fluid under high pressure (orange dashed arrows) from the gap between the stem and the cement through a defect in the cement mantle. The pressure waves may devitalize the adjacent bone tissue, which is resorbed, thus causing a focal osteolysis. From Mjöberg[53] with permission.

THE COOLFIX CEMENT

The specific heat production is directly proportional to the amount of monomer in the cement dough: 556 J/g monomer[55]. A low-monomer bone cement, Coolfix, was developed in the mid-1980s that produced less heat and less evaporating toxic monomer during the polymerization. The basic idea was to minimize the interspaces between the powder beads (which are filled with the liquid monomer) by a *bimodal particle size distribution*: 20 mL of liquid monomer was mixed with 70 g of Coolfix powder (instead of just about 40 g of a conventional bone cement powder). The temperature rise of Coolfix was (as expected) two-thirds of that of a conventional bone cement. The compressive strength was about 85% compared to Palacos R, probably due to the fact that the cement was made too dry (*i.e.* unsaturated) in the ambition to reduce the amount of liquid monomer. Therefore, this prototype Coolfix cement had a high viscosity and was more difficult to handle, especially in the acetabulum. The initial migration of the components in 24 hip prostheses was studied using RSA following randomized use of Coolfix and Palacos R[56]. After 1 year, five of the 12 acetabular components with Palacos R had migrated 0.4–0.7 mm, while all 11 acetabular components with Coolfix (one acetabular component with Coolfix was excluded due to insufficient tantalum bone markers) had migrated less than 0.3 mm (Figure 4). Only one femoral component (with Palacos R) had migrated significantly by then (0.4 mm distally).

An improved composition of Coolfix (the PMMA powders were purchased from Röhm GmbH, Darmstadt, Germany) was developed (Table 1), which had several attractive properties in addition to being less exothermic than a conventional bone cement: The improved cement was easily modeled and non-sticky, had a short mixing time, and smelled less. Unfortunately, the leadership of the Department of Orthopedics, Lund University Hospital, suddenly did not allow further clinical trials unless highly extended preclinical tests after vacuum mixing of the cement were performed; in practice, the project was stopped, and shortly afterwards I left Lund (but after my retirement and after a new department leadership had taken office in Lund, I became affiliated with the Department of Orthopedics, Lund University, once again). The improved Coolfix cement was never clinically tested.

Later, another low-monomer cement (Cemex Rx) was marketed, where, unlike Coolfix, the smallest particles in the powder had been removed. However, compared to Palacos R, no significant difference was achieved in either curing temperature[57] or prosthetic migration[57,58].

CEMENTED TAPER-SLIP STEMS

The continuous migration of taper-slip stems has been reported to be consistent with

Table 1 Coolfix powder composition 70 g

Plexidon M489 (300–500 μm)	32.0 g
Plexidon M527 (30–60 μm)	22.3 g
Plexigum M914	6.3 g
Benzoyl peroxide	0.6 g
Zirconium dioxide	8.8 g

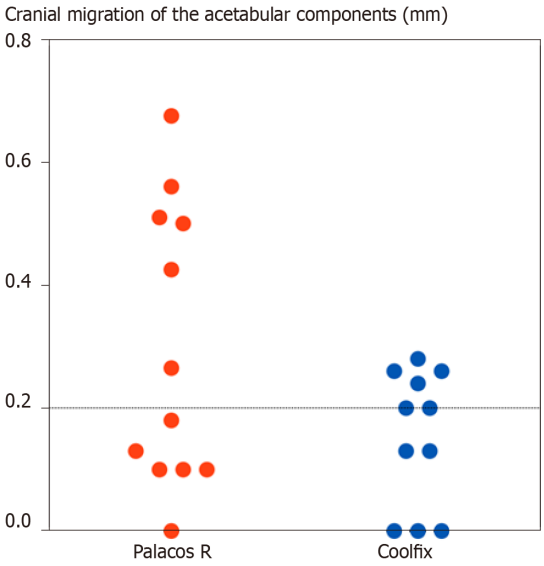

Figure 4 Cranial migration of the acetabular components after 1 year. By then, six of the 12 with Palacos R and four of the 11 with Coolfix had passed the limit (0.2 mm) for significant migration. However, five acetabular components with Palacos R had migrated 0.4–0.7 mm, while all 11 with Coolfix had migrated less than 0.3 mm ($P < 0.04$, Student's *t*-test, one-tailed).

good long-term clinical results[59-62] and has even been considered beneficial by contributing to secure fixation[59,61]. But does continuous migration really contribute to secure fixation? Or otherwise expressed: How much can a stem migrate distally without failing[63]?

The Exeter THA has, according to *the Nordic Arthroplasty Register Association database* (consisting of 100000 s hip arthroplasties)[64], a survivorship fairly on par with the Lubinus THA of up to about 10 years, but afterwards, its failure rate increases faster (Figure 5).

A plausible explanation is as follows: In cases of considerable subsidence, the self-locking effect of a cemented tapered stem declines because the stem and cement mantle no longer fit well together. A play space arises around the stem, and the micromovements of the loosened stem induces periprosthetic osteolysis (due to inflammatory responses to the damage-associated molecular patterns of the necrotic cells and cell fragments generated by devitalizing spikes of high periprosthetic fluid pressure from the unstable stem). When the cement is no longer sufficiently supported by the surrounding bone, the cement mantle will crack and the stem instability will increase, resulting in a rapid subsidence[60] and ultimately a fracture of the stem[65] or a fracture of the proximal femur[66,67].

No significant prosthetic migration is safer in the long run than good 10-year clinical results!

EXCITING NEW TECHNIQUE AND RESEARCH SUGGESTIONS

The recently developed low-dose computed tomography-based implant motion analysis has been shown to have an accuracy and a precision on par with RSA; this measuring method (without the need for bone or implant markers and specialized RSA equipment) "opens up the possibility for simpler implant migration studies"[68-70]. Very exciting technique! Maybe this is a future golden standard for implant

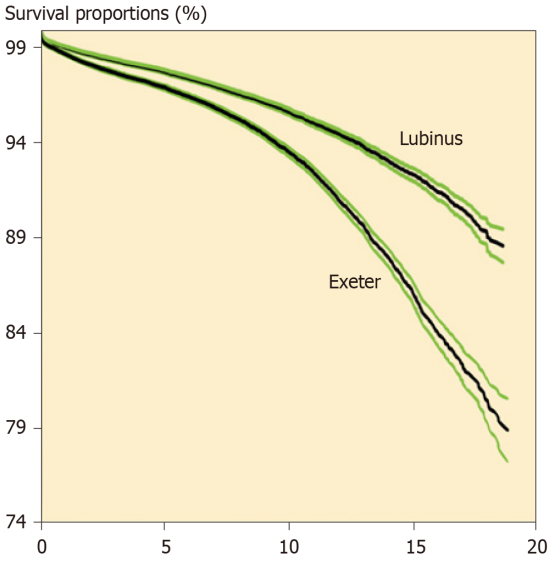

Figure 5 Kaplan-Meier implant survival of cemented total hip devices. Calculated from the Nordic Arthroplasty Register Association database. Green lines are upper and lower 95% confidence limits. Compiled from Junnila *et al*[64] with permission.

motion analysis?

The less heat production and less evaporating toxic monomer during the polymerization, the more the risk of superficial bone necrosis adjacent to the Coolfix cement is reduced. A locally applied bisphosphonate inhibits the resorption of necrotic bone during the healing period[41]. The synergistic effect of this combination (the Coolfix cement and a locally applied bisphosphonate) should increase the probability of permanent prosthetic fixation. Although the improved Coolfix cement, unlike a chemically modified bone cement, after curing is chemically equivalent to conventional bone cements and should have similar mechanical properties, a preclinical characterization is required prior to a clinical trial.

Bone scintigraphy (^{99m}Tc-MDP) is extremely sensitive but generally non-specific for diagnosing loosening[71]. The scan is usually normalized within 6–9 mo after surgery [14], indicating that the healing period is over and that the prosthesis has become osseointegrated. Persistent uptake beyond 1 year represents increased bone turnover and bone perfusion – and probably continuous prosthetic migration. However, no prospective RSA study has been combined with scintigraphy, which would be interesting from both a pathophysiological and diagnostic point of view.

In contrast to the many RSA studies of hip prostheses that have shown that early migration poses a risk of future failure (the larger the early migration, the greater the risk of future failure)[9,20-24], some RSA studies indicate (as mentioned earlier) that certain uncemented femoral components appear to achieve stability during the healing period despite significant early migration[25-27]. However, do these femoral components, as suggested in these studies, really become osseointegrated or do some of them continue to migrate very slowly? Bone scintigraphy could probably tell.

CONCLUSION

Hip prosthetic loosening is often difficult to detect at an early stage. When loosening is eventually detected on standard radiographs it may be interpreted as late loosening but should be interpreted as late detection of loosening, initiated during or shortly after surgery by insufficient initial fixation or by early loss of fixation.

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MINIREVIEWS

Jones type fifth metatarsal fracture fixation in athletes: A review and current concept

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Abstract

Jones type fifth metatarsal fracture is a common occurrence among athletes at all levels. These fractures may occur due to several mechanisms, but inversions and twisting injuries are considered some of the leading causes in sports. However, while Jones fracture incidences are frequent in the sporting world, there is still a lack of consensus on how such fractures should be effectively managed. There are numerous treatment options for patients with fifth metatarsal Jones fractures. The role of nonoperative treatment remains controversial, with concerns about delayed union and nonunion. Surgical stabilization of metatarsal Jones fractures is therefore often recommended for athletes, as it is often associated with a low number of complications and a higher rate of union than nonoperative management. This review will focus on literature regarding the prevalence of Jones type fifth metatarsal fracture, alongside the efficacy of both conservative and surgical treatment within this population.

Key Words: Athletes; Surgery; Fifth Metatarsal; Jones fracture; Rehabilitation; Fracture

Core Tip: Jones type fifth metatarsal fractures are a common injury among athletes. However, there remains a lack of consensus on the effective management of such fractures, especially in a demanding population group where time is often of the essence. Treatment recommendations often depend on the location and understanding of the fracture in addition to the patient's underlying state of health and other factors

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that influence surgical risk and outcome. The role of nonoperative treatment is still controversial, but surgical stabilization of metatarsal Jones fractures is often recommended for athletes and other high-demand population groups.

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INTRODUCTION

Jones type fifth metatarsal fractures are a common occurrence among athletes at all levels. These fractures may occur due to several movement mechanisms, but inversions and twisting injuries are considered some of the leading causes in sports. However, while this fracture type occurs frequently in the sporting world, there is still a lack of consensus on how such fractures should be effectively managed, especially in an industry where time is often of the essence. Treatment recommendations often depend on the location and understanding of the fracture anatomy in addition to the patient's underlying health. Several research studies have demonstrated that nonoperative treatment pathways can be used successfully in these types of fractures, although concern exists about delayed and nonunion fractures. This remains a controversial area. Surgical treatment is often recommended for athletes, as it is often associated with a low number of complications and a higher rate of union than nonoperative treatment. This review focuses on defining this fracture subtype and the efficacy of both operative and nonoperative treatment options. Operative intervention is further evaluated primarily with respect to screw *vs* plate fixation techniques.

OVERVIEW OF THE TYPES OF FIFTH METATARSAL JONES FRACTURES

Jones fracture was first described in 1902 by Sir Robert Jones as a unique type of fracture of the base of the fifth metatarsal; he described this fracture as being 1/3 inch from the base[1]. Statistically, metatarsal fractures account for a significant proportion of foot injuries, comprising 35% of fractures within the foot region and approximately 5%-6% of all skeletal injuries, with an estimated incidence of 6.7 per 10000 individuals [2]. In the normal adult population, females tend to sustain the injury more than males at a ratio of 2:1; however, in sports, which are primarily dominated by males, these injuries are more common among males[3-5]. In their review of foot injuries among athletes, Boutefnouchet *et al*[3] noted that these fractures are 10 times more likely to occur in males, with a mean age of 26 years. In this case, the high prevalence of these injuries in the sporting world was attributed to the strenuous nature of activities, resulting in the application of specific stresses within this region, such as during jumping, running, and tackling.

Anatomically, fifth metatarsal fractures are classified into two groups. According to Sarpong *et al*[2], the two groups to which these fractures belong are proximal and distal fractures. This classification is based on the fractures' healing potential as dictated by the blood supply to the affected zones. The blood supply to the proximal fifth metatarsal was first investigated by Bowes and Buckley[6], using a cadaver model for the study. Their findings discovered that blood supply within this region emanates from three possible sources: the nutrient artery, metaphyseal perforators, and periosteal arteries.

Expansion of the classification system by Torg *et al*[7] resulted in the simplification of how proximal fifth metatarsal fractures are classified. Bowes and Buckley noted that this simplification resulted in the proximal diaphysis distal classification as tuberosity, which made it part of the Jones fracture[6]. Under this system, three categories of Jones fractures emerge: Type I (acute proximal metatarsal fracture), Type II (delayed union proximal metatarsal fracture), and Type III (nonunion proximal metatarsal fracture).

Type I (acute proximal metatarsal fracture)

Type I fractures feature a fracture line and lacks intramedullary sclerosis differentiation. According to many researchers[8-11], the history of injuries in this group should include no history of a previous fracture. However, in some cases, patients may report the existence of previous pain. In other words, at the location of previous pain, the fracture is often presumed to be Type I, and due to the pain being on the lateral cortex, patients often experience limited movement.

Type II (delayed union) proximal metatarsal fracture

As noted by Do *et al*[8], Cheung and Lui[9], Saluta *et al*[12], Type II fractures are different from Type I due to the presence of an earlier injury that is characterized by a widened fracture line and the presence of intramedullary sclerosis.

Type III (non-union proximal metatarsal fracture)

Type III fractures' distinguishing features include a "complete obliteration of the medullary canal by sclerotic bone with a history of repetitive trauma and recurrent symptoms"[6]. In other words, this type of fracture contains a complete disconnection of the adjacent bones, and the treatment of this type of fracture often requires corrective surgery (Table 1).

ANATOMY AND PATHOPHYSIOLOGY OF FIFTH METATARSAL FRACTURES

Understanding foot anatomy is crucial in evaluating an effective treatment plan for athletes with Jones fractures. The fifth metatarsal is distinguished from other lesser metatarsals by the presence of a tendon insertion at the base comprising the peroneus brevis, which inserts dorsally on the proximal tubercle, and the peroneus tertius, which dorsally inserts the diaphyseal junction[2]. In addition, the plantar fascia is attached to the tubercle.

The pathophysiology of fifth metatarsal fractures is mainly represented by acute trauma. According to studies by Do *et al*[8], the mechanism of pain in patients (athletes) with Zone 1 fractures is often experienced during supination with plantar flexion (rolling motion of the outside edge of the foot during a step), such as during pitching in baseball. This type of movement often results in a pull of the plantar fascia lateral band, which results in pain. In Zone 2, injuries often emanate from plantar flexing of the forefoot. In contrast, in Zone 3 injuries, the pain usually originates from repetitive trauma. In the case of athletes, it could be due to continuous pressure when a player jumps, runs, or tackles an opponent. Notably, according to a recent study by Benjamin *et al*[13], athletes with cavovarus feet are prone to repetitive trauma, which results in Zone 3 injuries. This study proposes the theory that the physical structure of an athlete's foot could be one of the significant determinants of Jones-type fracture prevalence.

Similarly, according to other studies, there is a relationship between cavovarus feet and the development of both Jones fractures and stress fractures in the fifth metatarsal. For instance, in their study, "The Cavovarus Foot and Its Association with Fractures of the Fifth Metatarsal," Fuchs *et al*[14] noted that patients with acute Jones fractures presented with radiographic hindfoot varus. Some studies have suggested that since Zone 2 and Zone 3 may exhibit similar characteristics, it is not necessary to differentiate between them. For instance, Sarpong *et al*[2] provides an example of distal diaphyseal fractures, which occur when excessive force is applied within a position of plantar flexion, and an inversion injury occurs. In athletes, such as sprinters or volleyball players, such an injury could occur during jumping, in which toes are used, or an inversion injury is sustained with the ankle in a fully plantar flexed position. In summary, these injuries among athletes are common, as most field actions involve a broad utilization of foot movements, resulting in stress to the fifth metatarsal.

TREATMENT

Treatment options for Jones type fifth metatarsal fracture are based on the zone of the injury, comorbidities of the injured patient, and — if a sub-acute presentation — radiographic signs of healing. Acute Zone 1 injuries are mostly treated conservatively with protected weight-bearing medical boots, such as the air cast variety, hard-soled

Table 1 Summary of fifth metatarsal fractures

Class	Description
Zone 1	(1) Proximal tubercle avulsion; (2) Long plantar ligament leads to a lateral band of the plantar fascia or the peroneus Brevis's contraction; (3) May extend into the Cubo-metatarsal joint; and (4) Nonunion is uncommon
Zone 2 (Jones fracture)	(1) Metaphyseal-diaphyseal junction; (2) Involves the fourth and fifth metatarsal articulation; (3) Vascular watershed area; (4) Acute injury; and (5) Increased risk of nonunion
Zone 3	(1) Proximal diaphyseal fracture; (2) Distal to the fourth and fifth metatarsal articulation; (3) Stress fracture in athletes; (4) Associated with cavovarus foot deformities. or sensory neuropathies; and (5) Increased risk of nonunion

shoes, or casts. These devices are designed primarily for a patient's comfort rather than fracture stability, and can therefore be discontinued when the patient feels the pain has subsided. Operative treatment modalities are not first-line pathways for patients with a Zone 1 injury. In contrast, the level of severity in Zone 2 and Zone 3 fractures tends to be higher than that in Zone 1 fractures and may have better outcomes with surgical management.

Compared with the general population, athletes often require different treatment types due to their specific injury patterns and higher demands. According to a study conducted by Japjec *et al*[15] on how athletes require different treatments of injuries to the fifth metatarsal, it was suggested that on average, nonoperative treatment pathways took as long as 20 wk to heal completely, which was not a feasible amount of time for both the players and their teams[15]. In their analysis, the researchers proposed a new classification of these injuries, which included metaphyseal (Zone 1 and the majority of Zone 2) and metadiaphyseal fractures (remnants of Zone 2 and Zone 3) (see Table 2). However, the exact anatomical boundaries within this classification are not clearly defined and need further research. Nonetheless, the study successfully demonstrated that given the frequency of fractures in athletes, surgical treatment plans are efficient in treating zone 2 and 3 fifth metatarsal Jones fractures.

An analysis of the efficacy of nonsurgical and surgical treatment plants was recently conducted in a virtual study by Mirza *et al*[16]. They aimed to analyze the outcomes within the different treatment pathways of patients with basal fifth metatarsal fractures[16]. Out of the 270 study participants, 73.6% had Zone 1 fractures, 22.2% had Zone 2 fractures, and 4.2% had Zone 3 fractures. The researchers concluded that conventional treatment methods for Zones 1 and 2 took longer to cure patients (12 wk) than surgical procedures (Zone 3), which reduced the healing time by 50%. These findings support following a surgical pathway from the outset in the treatment of athletes with fifth metatarsal Jones fractures.

SURGICAL TECHNIQUES

There are several operative techniques described in the literature for fifth metatarsal Jones fractures. The choice of technique utilized is primarily dependent on the characteristics of the fracture(s). The techniques described include intramedullary screws, closed reduction, and cross-pinning with K-wire (Kirschner-wire) fixation, bone grafting, and internal fixation with a mini fragment plate and screws[6,17,18]. We focus on comparing outcomes between fixation techniques that primarily utilize screws or plates.

Surgical techniques using screws

Surgical techniques are common among athletes due to the short time it takes to heal these fractures and the lower possibility of nonunion. Studies by Watson *et al*[19], Lareau *et al*[20], Willegger *et al*[21], and D'Hooghe *et al*[22] assert that intramedullary screws and aggressive rehabilitation protocols have become popular among professional athletes seeking to return to the field after experiencing Zone 2-3 fifth metatarsal Jones fractures[23,24]. According to these studies, this technique's main advantage is that it is minimally invasive in addition to the short healing time needed and the accelerated mobility. DeLee, Evans, and Julian were the first to demonstrate the efficacy of percutaneous intramedullary screw fixation in a 1983 study titled "Stress Fracture of the Fifth Metatarsal"[6,25,26]. The study focused on utilizing 4.5-mm malleolar screws in diaphyseal stress fracture fixation in 10 athletes in which they reported an average healing time of 7.5 wk. This healing time allowed for adequate time for rehabilitation and return to sporting activities.

Table 2 Stewart classification of Jones fracture[16]

Stewart classification	
Type 1	Extra-articular fracture between the metatarsal base and diaphysis
Type 2	Intra-articular fracture of the metatarsal base
Type 3	Avulsion fracture
Type 4	Comminuted fractures with intra-articular extension
Type 5	Partial avulsion of the metatarsal base with or without a fracture

There are currently various types of intramedullary screws in use by surgeons in the fixation of fifth metatarsal Jones fractures. Among the significant options of this technique include solid and cannulated screws, whose individual performance has been studied. For instance, Bowes and Buckey noted that cannulated screws offer better precision and ease of use when placed over a guidewire[6]. However, some studies have argued that cannulated screws present an increased risk of refracture.

Studies have also evaluated the subsequent failure of cannulated screws in delayed unions, nonunion, and acute Jones fractures. For instance, Bowes and Buckley noted that intramedullary screw fixation using 4.5-mm malleolar screws resulted in re-fracture and may cause delayed union or non-union in Jones fractures[6]. However, in a round table discussion by Carpenter *et al*[27] and recent studies by Bryant *et al*[28], O'Malley *et al*[29] and Tan *et al*[30], this method offers a higher rate of healing among athletes, with lower re-occurrence of fractures. Thus, based on this argument, it could be concluded that the utilization of larger diameters during surgery may help to prevent future fracture.

Surgical techniques using plates (plantar plate fixation)

An alternative to intramedullary screws in fixing Jones fractures is the plantar plate fixation surgical technique. Plantar plate fixation, as reported by Duplantier *et al*[31], Mitchell *et al*[32], Young *et al*[33], and Miller *et al*[34], describes the procedure of plantar plate fixation. Researchers note that the process involves the positioning of a contoured plate[19] across the fracture site, such that the locking holes are aligned on the proximal side (the oblong). In contrast, the remaining locking holes are aligned with the distal side of the injury. One of the noted advantages of the plantar plate fixation method in treating Jones fractures is that it offers stability to the broken bones, accelerating healing. In addition, the procedure provides one of the fastest ways of managing this type of fracture among athletes.

However, several studies on the advantages and disadvantages of plantar plate fixation techniques have indicated that the method presents some risks regarding nonunion and the possibility of injuries reoccurring in the same location. According to Bernstein *et al*[35] and Haslan *et al*[36], with tension-side plating, there have been cases of pain and persistent fracture nonunion, especially in the treatment of stress fractures among athletes. Furthermore, studies indicate that the procedure requires the addition of calcaneus autografts to optimize the healing process. According to Mitchell *et al*[32], previously reported risks associated with percutaneous calcaneal autograft harvesting are currently low. This finding has improved the performance of plantar plating fixation in the treatment of fifth metatarsal Jones fractures. In addition to the issues with biomechanical principles, the literature also suggests that plantar plating is associated with hardware prominence. According to Mitchell *et al*[32], hardware prominence typically occurs due to the surgeon's failure to confirm that the plate used is adequately aligned against the cortex of the bone. Failure to position the plate properly could also result in nonunion, irritation, and an increased risk of refracture. These risks for plantar plate fixation can be reduced by using low-profile screws and plates that are accurately contoured to the cortex. This ensures that the tension side of the fracture is stabilized[37]. Adoption of these techniques allows for plantar plating to be used with good outcomes in high-demand patients, such as athletes.

POST-OPERATION MANAGEMENT PROTOCOL

As mentioned above, surgical procedures might offer faster recovery among athletes who have suffered fifth metatarsal Jones fractures. Recovery takes an average of 3-4

wk, depending on the postoperative procedures[38]. To facilitate healing, specific protocols need to be followed. Watson *et al*[38] stated that postoperative rehabilitation can be divided into five phases, as illustrated in Table 3 and Figure 1.

POSTOPERATIVE COMPLICATIONS

Postoperative complications are common, and some are higher within the athlete population. The risk of injury to the sural nerve and its branches during procedures, such as intramedullary screw fixation, is well recognized. However, historically, injury to the sural nerve or any of its branches has not been reported as a significant postoperative complication arising from the fixation of Jones fractures[9]. Nonetheless, despite the lack of reporting, several studies have indicated the occurrence of unexplained postoperative pain and paraesthesia over the lateral aspect of the foot, which fails to subside even after the removal of the screw or the plate. In such cases, researchers have often concluded that the occurrence of such pain is a result of nerve damage from surgical intervention.

Failure to note the natural curvature of the bone during surgery has been considered a major cause of nerve injury after surgical treatment. As noted by Aynardi *et al*[39], despite the success of intramedullary screw fixation of the fifth metatarsal for metaphyseal-diaphyseal and diaphyseal fractures, the size, shape, and quality of the bone cortices are crucial in preventing surgical injuries to the lateral dorsal cutaneous nerve. According to the researchers, failure to consider the natural curvature of the fifth metatarsal bone during surgery could impede the placement of a guidewire, which can lead to intraoperative complications, such as nerve damage. Therefore, to reduce the risk of nerve injury, surgeons should ensure the proper entry point of the guidewire and screw with a correct trajectory within the medullary canal. This is best achieved by a proper understanding of the patients' specific bony anatomy.

Both delayed and nonunion are commonly attributed to the use of smaller screws in surgery. Watson *et al*[38] noted that delayed unions in Zone 2 and 3 fractures are often a result of choosing screws that are smaller than 4.5 mm in diameter. In the case of athletes, according to Wukich *et al*[40], it is advisable to use larger solid screws as a way of countering the higher amount of torsional stress directed towards the fracture site. Similarly, in the case of nonunion and refractures in Zones 2 and 3, Cheung and Lui[9] recommend treatment with medullary curettage and intramedullary screw fixation or inlay grafting. However, in this case, revision of the previous screw fixation that resulted in complications should be performed with larger diameter screws in addition to reaming of the medullary canal.

Other possible postoperative complications include wound infection, impingement by a prominent screw head, rupture of the peroneus brevis tendon, metatarsalgia, iatrogenic fracture of the metatarsal bone, and the screw missing the medullary canal. Cheung and Lui[9] summarized specific methods of avoiding and managing these complications. First, wound infection and tendon nerve injury can be avoided by careful soft tissue handling during surgery using implants with low profiles. Second, impingement by the screw head can be avoided by adequate countersinking of the cortex before the insertion of the screw and be further addressed by athletes using larger and spacious shoes. Third, screws missing the medullary canal can be avoided through the use of proper surgical techniques, choosing the correct implant, and having a proper understanding of the patients' bony anatomy. Last, the major cause of postoperative metatarsalgia is fibrosis of the joints and tendons adjacent to the site of the operation.

NON-SURGICAL TREATMENT

There are several nonsurgical treatment plans used for fifth metatarsal Jones fractures. These modalities vary by anatomical region of the fracture, patient history, and radiological findings[41-43]. Evidence-based medicine has assisted in the tailoring of individual treatment of metatarsal fractures. For example, as highlighted by several studies, some cases of nondisplaced and neck fractures of the fifth metatarsal are often treated nonoperatively. The preference to treat these injuries using nonsurgical options indicates that their level of severity is low. Examples of nonsurgical treatment options include walking casts, elastic dressings, rigid shoes, hard plastic cast shoes with weight-bearing, and posterior splints[44,45]. The effectiveness of these options depends on both the nature of the treatment option and the type of patient.

Table 3 Postoperative rehabilitation protocol for athletes

Phases of postoperative rehabilitation for fifth metatarsal Jones fractures	
Phase I	After surgery, the patient can toe-touch using weight-bearing medical aids, such as walking boots or crutches. Discontinuation of use of these aids depends on how fast an individual heals or when they can tolerate body weight. Patients are required to use bone simulators at least twice a day and perform four-way ankle-resisted exercises two times a day. These exercises include plantar flexion, dorsiflexion, inversion, and eversion[18]
Phase II	In this phase, the patient can tolerate his or her full weight and can now use a walking boot. Bone simulators and ankle exercises are limited to twice a day. Furthermore, the patient participates in training using underwater treadmills with sessions lasting approximately 20 min at a speed of between 2.5 and 3.0 mph. These parameters are adjusted per the ability of the patient to tolerate an increase. "By the end of Phase II rehabilitation, the patient should be able to do interval training for 20 min in waist-deep water. An example of an interval training protocol is as follows: 60 seconds at a 5-6 mph pace followed by a 90-s run at 7-8 mph with jet resistance at approximately 45%-60% weight bearing"[19,38]
Phase III	At this stage, walking boots are replaced with cross-training shoes with rigid or orthotic inserts. Patients are gradually introduced to single-calf exercises in combination with dorsiflexion stretching and single-leg proprioception training. Progression to full weight bearing is continued and managed using limited change of direction and position exercises. For at least two times a day, the patient is involved in bone stimulation and resistance ankle routines
Phase IV	Patients can use professional sporting shoes such as cleats or boots with rigid or orthotic inserts. Full-weight running is combined with drill works that feature a position-specific change of direction. Single-leg plyometric exercises are included. Additionally, the athlete is required to continue using "bone stimulator, resisted ankle exercises, single-leg calf raises, dorsiflexion stretching exercises, and single-leg plyometric exercises"[19,38]. This phase aims to facilitate a limited return to regular training
Phase V	The patient can now participate in full training. The bone simulator is used twice a day combined with a regular training routine until the patient is fully recovered

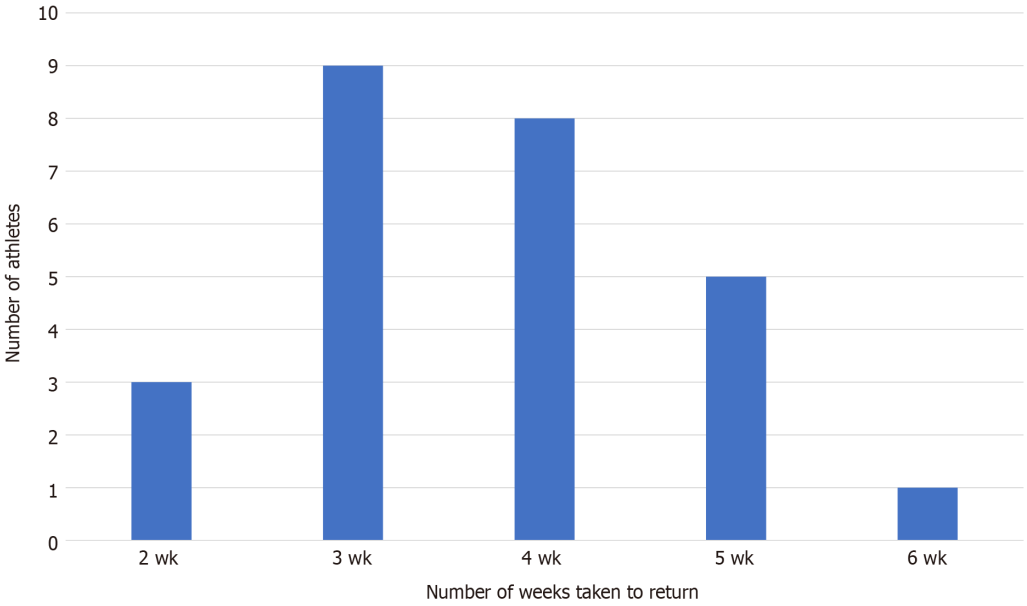

Figure 1 Number of athletes returning to play *vs* weeks in rehabilitation[38].

Recently, various studies have attempted to statistically analyze patients' satisfaction with nonoperative treatment pathways in treating acute Jones fractures. For instance, in studies undertaken by Sesti *et al*[46], it was established that on average, 60% to 70% of patients with acute Jones fracture were very satisfied with nonoperative procedures, 28% were satisfied, 8% reasonably satisfied, and 4% were dissatisfied (see Figure 2). These findings indicate that the choice for nonsurgical treatment is often based on perception, and, in some cases, is at the discretion of the patient.

The literature suggests that there is a significant variation in the effectiveness of conservative treatment within different fracture subtypes. Nondisplaced Zone 1 fractures at the fifth metatarsal base are often treated using protected weight-bearing methods, such as leg casts, that offer low nonunion rates of between 0.5% and 2.1% [47]. In other studies, it has been illustrated that nonoperative procedures for acute Zone 2 and 3 fractures result in longer recuperation times and a higher risk of refracturing. As highlighted in Figure 3, the average times to union for "tuberosity fractures, Jones, stress, segmental shaft, and oblique distal shaft/neck fractures were 3.7, 3.5, 4.8, 3.6 and 3.4 mo, respectively"[6]. Thus, compared with the surgical method, nonoperative techniques are not feasible for professional athletes due to their inability to achieve union in Zone 2 and 3 fractures within acceptable timeframes.

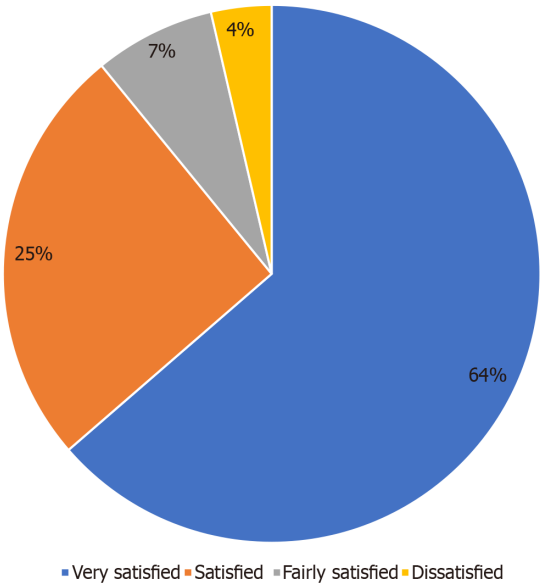

Figure 2 Patient Satisfaction with non-operative treatment of fifth metatarsal Jones fractures.

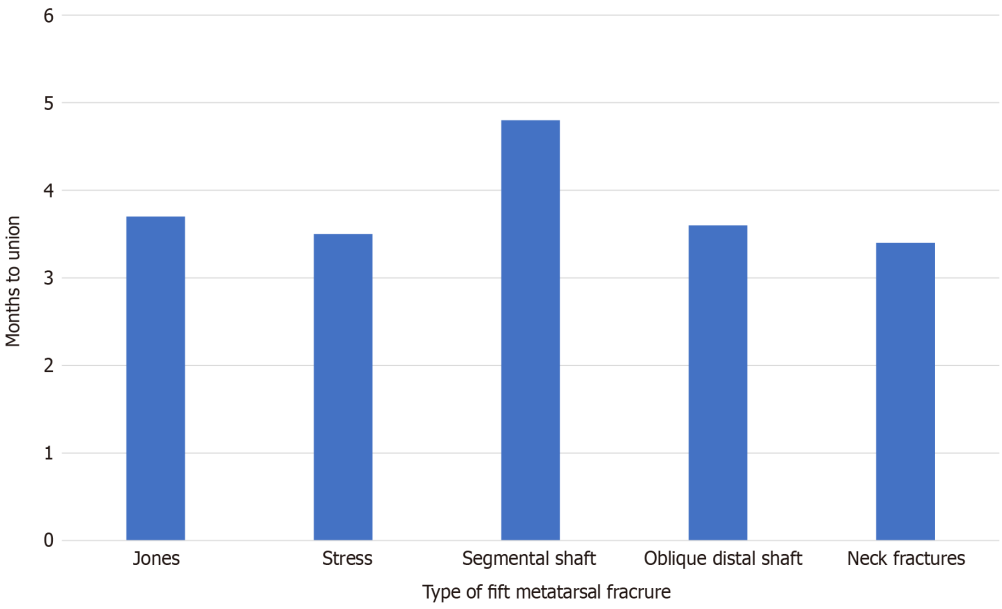

Figure 3 Average number of months to fracture union.

REHABILITATION

Several studies have described and issued recommendations on specific rehabilitation protocols to be followed during the recuperation period. In their research, Marecek *et al*[48] detailed their preferred rehabilitation protocol based on clinical data on patients with acute Jones fractures[48]. The authors note that for patients with Zone 1 fractures, non-weight-bearing options could be used in the first 3 wk after the injury. Similarly, Rhim and Hunt[49], along with Slater *et al*[50] and Qi *et al*[51], suggest the placement of the affected foot in a cast or boot for 2-3 wk. Once a union is observed, the patient can be transitioned to physical therapy, with a focus on regaining strength through eccentric and concentric open-chain exercises or muscle-specific workouts. Non-impact activities, such as elliptical trainers or static bicycles and deep-water running activities, are useful for athletes recovering from acute Jones fractures.

CONCLUSION

As discussed, there are numerous treatment options for patients with fifth metatarsal Jones fractures. For the general population, non-time-sensitive approaches, such as using a short leg cast with immobilization, could be used for treatment. However, for active individuals, such as athletes in competitive sports, the need to quickly return to play often calls for more aggressive treatment plans. Owing to various reports of faster healing and return to play, treatment options among athletes with Jones fractures have significantly shifted from nonoperative procedures to surgical options that include intramedullary screw fixation and plantar plate fixations. These procedures offer predictable union rates in addition to minimum periods of immobilization, which makes them ideal techniques for managing fifth metatarsal Jones fractures in the sporting world.

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MINIREVIEWS

Effects of sclerostin antibody on bone healing

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Abstract

Promoting bone healing after a fracture has been a frequent subject of research. Recently, sclerostin antibody (Scl-Ab) has been introduced as a new anabolic agent for the treatment of osteoporosis. Scl-Ab activates the canonical Wnt (cWnt)-β-catenin pathway, leading to an increase in bone formation and decrease in bone resorption. Because of its rich osteogenic effects, preclinically, Scl-Ab has shown positive effects on bone healing in rodent models; researchers have reported an increase in bone mass, mechanical strength, histological bone formation, total mineralized callus volume, bone mineral density, neovascularization, proliferating cell nuclear antigen score, and bone morphogenic protein expression at the fracture site after Scl-Ab administration. In addition, in a rat critical-size femoral-defect model, the Scl-Ab-treated group demonstrated a higher bone healing rate. On the other hand, two clinical reports have researched Scl-Ab in bone healing and failed to show positive effects in the femur and tibia. This review discusses why Scl-Ab appears to be effective in animal models of fracture healing and not in clinical cases.

Key Words: Canonical Wnt-β-catenin pathway; Fracture healing; Osteoporosis; Romosozumab; Sclerostin antibody

Core Tip: Sclerostin antibody (Scl-Ab) has been recently introduced for the treatment of osteoporosis. Several researchers have reported on the effects of Scl-Ab in bone fracture healing because of its rich osteogenic potential. In this review, we describe the latest reports of preclinical and clinical studies on the bone-healing effects of Scl-Ab.

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INTRODUCTION

Achieving robust bone healing is the ultimate goal in the treatment of bone fractures. The development of methods to promote fracture healing has been a frequent subject of research. Recently, the safety of several osteoporosis drugs has been established in large-scale clinical trials, and it is expected that these drugs could be converted to fracture treatment. In experimental studies, some agents used to treat osteoporosis have had a positive effect on the promotion of bone healing, including parathyroid hormone (PTH), bisphosphonates, and sclerostin antibody (Scl-Ab).

Romosozumab, an Scl-Ab for humans, which recently has been developed for the treatment of osteoporosis, is an anabolic agent that stimulates bone formation. The difference between Scl-Ab and PTH_{1-34} (teriparatide), a former anabolic agent, is that teriparatide increases both bone formation and resorption *via* PTH-PTH receptor signaling, whereas Scl-Ab increases bone formation and simultaneously decreases bone resorption *via* canonical Wnt (cWnt)-β-catenin signaling[1]. This difference shows that the bone formation by PTH_{1-34} is primarily "remodeling-based" and that by Scl-Ab is primarily "modeling-based"[2,3].

In this review, we describe how Scl-Ab effects the cWnt-β-catenin pathway to stimulate bone formation and then discuss the current experimental and clinical evidence in bone healing.

SCLEROSTIN AND THE CANONICAL WNT/BETA-CATENIN PATHWAY IN BONE METABOLISM

The cWnt-β-catenin pathway plays an important role in bone metabolism, including skeletal development and homeostasis and bone remodeling[4]. The pathway is activated by the binding of Wnt proteins to receptor complexes composed of frizzled receptors and co-receptors of the low-density lipoprotein receptor-related protein (LRP) family, LRP5 and LRP6. This event increases the level of β-catenin and induces its translocation to the nucleus and activates the transcription of gene; it further accelerates the differentiation of osteoblast precursors and promotes the maturation of osteoblast and their survival, leading to osteogenesis by the increased and activated osteoblasts. On the other hand, the increased level of β-catenin results in an increased expression of osteoprotegerin, which binds to RANKL as a decoy receptor, preventing the binding of RANKL and RANK. Osteoclast activation and differentiation, which lead to bone resorption, occurs in the presence of RANKL-to-RANK binding. Thus, the activation of this pathway leads to increased bone formation by the increased and activated osteoblasts and to decreased bone resorption due to the disturbed binding of RANKL to RANK[5-7].

In the regulation of the cWnt-β-catenin pathway, osteocytes play an important role as producers and targets of Wnt ligands and as secretors of molecules that regulate Wnt action[8]. One regulation mechanism is the secretion of sclerostin, a potent antagonist of Wnt signaling. Sclerostin is a protein encoded by the *SOST* gene primarily expressed by mature osteocytes, but not by early osteocytes or osteoblasts [9]. Sclerostin binds to the Wnt co-receptors LRP5/LRP6, antagonizing downstream signaling in the cWnt-β-catenin pathway[10]. Thus, when the stoichiometry levels of sclerostin overwhelms the levels of the Wnt ligands, the signals will not be activated, leading to β-catenin degradation, lower bone formation, and higher bone resorption. On the other hand, when the stoichiometry levels favor in Wnt ligands than sclerostin, Wnt-β-catenin signaling will be activated, leading to stabilized β-catenin for translocation to the nucleus and the activation of target genes to increase bone formation and decrease bone resorption[2]. In addition, not only LRP 5 and 6, but also LRP4 was associated with bone homeostasis by interacting with sclerostin; mutation of LRP4, impairing interaction with sclerostin was found in patients suffering from bone overgrowth[11]. Thus, sclerostin is established as a bone formation inhibitor, though the molecular mechanisms are not fully understood.

In humans, the absence of sclerostin expression or secretion causes an abnormally high bone mass. These conditions have been seen in the rare hereditary diseases sclerosteosis and van Buchem disease. Sclerosteosis was first described by Truswell as osteopetrosis with syndactyly and is mostly seen in patients in South Africa; van Buchem disease was described by van Buchem as hyperostosis corticalis generalisata familiaris and is mostly found in patients in the Netherlands[12,13]. In both diseases, the *SOST* gene encoding sclerostin was identified as the gene responsible; a loss-of-function mutation occurs in sclerosteosis, and the downregulation of the expression of the *SOST* gene occurs in van Buchem disease[14]. Bone mineral density (BMD) and bone strength are significantly higher in patients with these diseases than those in the general population[15,16]. In experimental reports using mice, genetic deletion of the *SOST* gene or neutralizing antibodies for sclerostin duplicated the high bone mass found in humans lacking sclerostin[17-19]. Conversely, sclerostin overexpression leads to a decrease in bone mass[20-22].

SCLEROSTIN ANTIBODY THERAPY AND OSTEOPOROSIS

As the mechanisms of sclerostin and the cWnt-β-catenin pathway were elucidated, improvement in bone mass became the expected outcome of inhibiting the action of sclerostin. In a study using a model of ovariectomized rats with postmenopausal osteoporosis treated with Scl-Ab, researchers found a significant increase in bone formation on the trabecular, periosteal, endocortical, and intracortical surfaces. Furthermore, osteoblast and mineralizing surfaces increased, while the osteoclast surface decreased. These results suggest that the use of Scl-Ab increased bone formation and decreased bone resorption for osteoporosis[23]. In another study evaluating the effects of the osteoblast lineage in young rats with Scl-Ab and PTH_{1-34}, the osteoblastic surface and estimated total number of osteoblasts increased to similar levels in both the Scl-Ab and PTH_{1-34} groups at week 4. However, both parameters decreased in the Scl-Ab group while maintaining in the PTH_{1-34} group at week 26. Similarly, the osteoprogenitors increased to similar levels in both groups at week 4, and only those in the Scl-Ab group decreased at week 26. Interestingly, the percentage of labeled perimeter of the periosteal surface of the femur diaphysis was higher in the Scl-Ab group at both weeks 4 and 26, and the percentage of labeled perimeter of the endocortical surface was at the same level at week 4 and was higher in the Scl-Ab group at week 26. These results suggest that Scl-Ab strongly increases the differentiation induction of osteoprogenitors to osteoblasts, while increase of osteoprogenitors are only seen in the early stages of administration. While, PTH_{1-34} increases both the differentiation induction of osteoprogenitors to osteoblasts and the number of osteoprogenitors at similar levels throughout the administration period, although the level of bone formation was similar or even higher in Scl-Ab than in PTH_{1-34}[24].

In cynomolgus monkeys, treatment with Scl-Ab led to increase in BMD and bone strength just like in the rats. No increase in bone resorption markers was noted, while a significant increase in bone formation markers was demonstrated, also suggesting the distinct effects of modeling-based bone formation associated with Scl-Ab, differing from remodeling-based bone formation by PTH_{1-34} in which osteoblast-mediated bone formation follows osteoclast-mediated bone resorption[25]. Summarizing the difference between Scl-Ab and PTH, with Scl-Ab, bone formation is seen with no increase or even some decrease of bone resorption. The effect of bone formation is stronger in the early stages of administration and decreases with longer administration due to lack of osteoprogenitors after the strongly accelerated differentiation to osteoblasts. With PTH, bone formation is also seen with increase of bone resorption (relatively higher formation than resorption). Bone formation is similar in any stage of administration due to increase in both number of osteoprogenitors and differentiation to osteoblasts.

Romosozumab, a Scl-Ab agent for humans, has recently become commercially available for clinical use. A phase III clinical trial has shown that romosozumab strengthened osteoporotic bone by increasing BMD and decreased the incidence of new fractures. The Fracture Study in Postmenopausal Women with Osteoporosis trial evaluated the 12-month efficacy of romosozumab as compared with the placebo. The risk of vertebral fracture was reduced by 73% at 12 mo (incidence, 0.5% in the romosozumab group *vs* 1.8% in the placebo group, $P < 0.001$), and the risk of clinical fracture was reduced by 36% at 12 mo (incidence, 1.6% in the romosozumab group *vs* 2.5% in the placebo group, $P = 0.008$). The percentage of change in BMD from baseline was 13.3% greater in the lumbar spine, 6.9% greater in the total hip, and 5.9% greater

in the femoral neck in the romosozumab group than in the placebo group. An increase in the bone formation marker P1NP was seen in the romosozumab group, and a decrease in the bone resorption marker β-CTX was seen early in treatment, suggesting modeling-based bone formation[26]. Similar results of increased bone formation and strength, decreased fracture risk, and increased levels of bone formation markers with decreased levels of bone resorption markers have been shown in other phase III trials (ARCH trial, romosozumab *vs* alendronate; STRUCTURE trial, romosozumab *vs* teriparatide)[1,27].

SCLEROSTIN ANTIBODY THERAPY AND BONE HEALING

Preclinical evidence

Bone healing is a complex process controlled by numerous cellular signaling pathways regulated by factors expressed in a time and concentration-dependent manner. The cWnt-β-catenin pathway is one of the most critical signaling pathways involved in bone healing[28-30]. The peak of upregulation was from 7 to 14 d in rat models[31,32]. Upregulating and/or controlling the cWnt pathway along with the levels of β-catenin have the potential of accelerating bone healing. Bone healing occurs in two different mechanisms; intramembranous or endochondral bone formation. Marsell *et al*[33] reported Wnt-responsive cells were not observed near the marrow cavity but seen over the periosteal callus, presuming that the cWnt-β-catenin pathway associates with endochondral bone formation rather than intramembranous bone formation. Liedert *et al*[34] suggested that Wnt inhibitors play a role in delayed union and Montjovent *et al* [35] demonstrated non-rigid fixation of femoral defects caused increase levels of inhibitors of Wnt proteins. In non-rigid fixation, endochondral bone formation becomes the main healing process. Inhibiting the inhibitors of Wnt proteins and activating the cWnt-β-catenin pathway may help bone healing in such fractures.

The efficacy of Scl-Ab for bone healing has been demonstrated in several reports with animal models (Table 1). In a mouse tibial-shaft osteotomy model, both the sclerostin knockout and wild-type groups showed an increase in bone mass at the osteotomy site when Scl-Ab was administered[36]. Ominsky *et al*[37] observed in a rat femur fracture model that an increase in bone mass and mechanical strength at the fracture site occurred after 7 wk in the Scl-Ab group. The other researchers also reported similar positive effects of Scl-Ab for a rat femur fracture or osteotomy model [38,39]. Virdi *et al*[40] also observed that in a rat femoral bone ablation model with intramedullary fixation, there was a 1.9-fold increase in fixation strength at week 4 and a 2.2-fold increase at week 8 in the Scl-Ab group compared to the vehicle group. Furthermore, Yee *et al*[41] reported in a type 1 diabetes mellitus (T1DM) mouse model, administration of Scl-Ab mitigates inhibition of osteoblast differentiation caused by the diabetic state. They found a significant benefit in callus bone volume, increase in callus size and a reverse of lower mineralization seen in T1DM mouse model. Studying the mechanisms for the fracture healing effect of Scl-Ab, Feng *et al* reported an increase in the proliferating cell nuclear antigen score and bone morphogenetic protein (BMP)-2 expression at weeks 1 and 2 in a femur osteotomy model in young rats. Furthermore, cartilage decreased and BMD and the mechanical strength of the callus associated with accelerated fracture healing increased at weeks 4 and 6[42].

As an evaluation outside the long tubular bone fracture model, Agholme *et al*[43] inserted screws into the proximal tibia of young rats and measured the pull-out strength; the Scl-Ab-treated group showed a 50% increase after 2 and 4 wk compared with the saline-treated group. They conducted the same experiment comparing with PTH, and the PTH group showed significant higher pull-out strength in the metaphyseal, while Scl-Ab significantly increased femoral cortical and vertebral strength[44]. In a rat model of distraction osteogenesis, no difference occurred in the rate of bone union between the Scl-Ab and control groups, but mechanical strength and bone mass increased in the Scl-Ab group, suggesting that the optimal effect of Scl-Ab treatment is achieved in the later stages of distraction osteogenesis[45]. In addition, in a rat critical-size femoral-defect model with a 6-mm femoral defect, 24% of the Scl-Ab-treated group had healed after 12 wk compared with no cases of healing in the control group[46]. Furthermore, in the treated group, systemic Scl-Ab administration plus local BMP-2 administration resulted in significantly more robust healing of critical-size femoral defects than did BMP-2 alone[47].

On the other hand, Kruck *et al*[48] negatively reported on the effects of Scl-Ab on bone healing. The author created rigid and semirigid fixation models for femoral osteotomy in rats. All groups showed an increase in bone mass, but no difference in

Table 1 The efficacy of sclerostin antibody for bone healing has been demonstrated in several reports with animal models

Animal model	Bone	Bone injury model	Dosage, frequency	Major findings	Ref.
Mouse	Tibia	Osteotomy	100 mg/kg, 1/wk	BV/TV↑, strength↑	[36]
Rat	Femur	Fracture	25 mg/kg, 2/wk	Callus↑, BMC↑, BV/TV↑, strength↑	[37]
Cynomolgus monkey	Fibula	Osteotomy	30 mg/kg, 1/2 wk	Callus↑, BMC↑, strength↑	[37]
Rat	Femur	Ablation	25 mg/kg, 2/wk	Fixation strength↑, cortical thickness↑, BV/TV↑	[40]
Rat	Femur	Fracture	25 mg/kg, 2/wk	BMD↑, BV/TV↑, strength↑, MS/BS↑, BFR/BS↑	[38]
Rat	Femur	Osteotomy	25 mg/kg, 2/wk	Callus↑, BMD↑, BV/TV↑, strength↑, bone area↑, cartilage↓	[39]
Mouse	Femur	Fracture	25 mg/kg, 2/wk	BV/TV↑, BMC↑	[41]
T1DM mouse	Femur	Fracture	25 mg/kg, 2/wk	BV/TV↑, BMC↑	[41]
Rat	Femur	Osteotomy	25 mg/kg, 2/wk	Mature callus↑, BMC↑, BMD↑, strength↑	[42]
Rat	Tibia	Metaphyseal screw	25 mg/kg, 2/wk	Pull-out strength↑, bone volume surrounding screw↑	[43]
Rat	Femur	Distraction osteogenesis	25 mg/kg, 2/wk	Union rate→, (united bones) strength↑, bone volume↑	[45]
Rat	Femur	Critical defect	25 mg/kg, 2/wk	Union rate↑, bone formation markers↑	[46]
Mouse	Femur	Osteotomy rigid fix	25 mg/kg, 2/wk	Periosteal and/or intracortical bridging→, endosteal bridging↑	[48]
Mouse	Femur	Osteotomy semi-rigid fix	25 mg/kg, 2/wk	Periosteal and/or intracortical bridging→, endosteal bridging↑	[48]

T1DM: Type 1 diabetes mellitus; BV/TV: Bone volume to total bone volume ratio; BMC: Bone mineral content; BMD: Bone mineral density; MS/BS: Mineralizing surface rate; BFR/BS: Bone formation rate.

delayed healing occurred with semirigid fixation between the Scl-Ab and control groups. In rigid fixation, Scl-Ab had more bridging of the endosteum, which adversely affected late healing, suggesting delayed callus remodeling and marrow reconstitution at the time of fracture. These results suggest that Scl-Ab promotes bone formation in the early stages of healing, but not in the advanced stages of fracture callus remodeling [48].

Clinical evidence

Two phase II clinical trials have reported the efficacy of romosozumab in adult fresh fractures. Bhandari *et al*[49] reported the efficacy of romosozumab in 402 patients with fresh unilateral tibial diaphyseal fractures (median age, 40 years; range, 18−82 years) who underwent fracture fixation with intramedullary nails. Patients were randomized to a placebo (n = 103) or one of nine different romosozumab groups (n = 299), with three different doses and frequencies of administration (doses: 70 mg, 140 mg, and 210 mg; administration: twice, postoperative day 1 and week 2; three times, postoperative days 1 and 2 and week 6; and four times, postoperative days 1 and 2 and weeks 6 and 12). The percentage of patients with a radiological cure, defined as the bridging of three of the four cortices as shown on the radiographs, which ranged from 63.2% to 84.7% at week 24 and from 83.4% to 96.7% at week 52 in the romosozumab group and from 76.1% at week 24 and 87.1% at week 52 in the placebo group. The estimated median time to radiological cure ranged from 14.4 to 18.6 wk in the romosozumab group and 16.4 wk in the placebo group. Thus, no significant difference occurred between both groups. In addition, no significant difference occurred in the time to clinical healing (defined as the ability to bear weight without pain at the fracture site) between the groups. Furthermore, the authors found no treatment effects of romosozumab on the incidence of unplanned revision surgery, physical function scores, or adverse events. The study concluded that romosozumab did not promote the healing of tibial fractures in this patient population.

Schemitsch *et al*[50] reported on a trial of romosozumab for the treatment of hip fractures in 332 patients (median age, 78 years; range 55−94 years). Patients were randomized to groups receiving a placebo (n = 89) or romosozumab at three different doses (70 mg, 140 mg, and 210 mg). Patients received subcutaneous romosozumab

injections on postoperative days 1, 2, 6, and 12, and the percentage of patients with radiographic evidence of healing ranged from 66.2% to 78.6% at week 24 and from 89.1% to 93.2% at week 52, with no significant difference between the treatment groups. In addition, no significant difference occurred in the estimated median time to radiographic evidence of healing neither between the groups nor in functional mobility assessment, radiographic fracture healing assessment, and hip pain scores. Similar to the results with patients with tibial fractures, romosozumab did not improve fracture healing in patients with hip fractures.

It is unclear why bone healing was not accelerated in humans. In both studies, romosozumab was administered starting on postoperative day 1. Since romosozumab promotes the differentiation of osteoblasts from osteoprogenitors with little increase in osteoprogenitors[24], it is possible that administering romosozumab early in the fracture healing process period is not ideally timed. Yukata *et al*[51] reported that *SOST* gene expression were more abundant in the hard callus in the later stages of bone repair than in the soft callus in the early stages in a mouse tibia fracture model, and PTH administration upregulated *SOST* expression as the hard callus increased. These suggest the need to change the starting point of administration and to consider the combination of romosozumab and PTH, which has the effect of increasing immature cells. Additionally, in both studies the patients were treated at sites for high surgical standards of care and they received rigid fixation. The quality of the surgery and care may out-weighed the effects of romosozumab on fracture healing[49,50]. Future studies may focus on healing of serious fractures, which could only accomplish relatively un-rigid fixation.

CONCLUSION

Despite the preclinical success of Scl-Ab in promoting fracture healing in animals, currently, no clinical evidence exists for the positive effects of Scl-Ab for bone healing in humans. As an osteogenic agent in osteoporosis, Scl-Ab offers promising effects supported by reliable evidence. Although the drug targets the same bone tissue, further research is needed on the differences in the pathogenesis of osteoporosis and fracture, spatio-temporal expression pattern of *SOST* according to bone healing process, and corresponding timing and interval of drug administration.

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MINIREVIEWS

Current concepts in the management of bisphosphonate associated atypical femoral fractures

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Abstract

Bisphosphonates are a class of drugs used as the mainstay of treatment for osteoporosis. Bisphosphonates function by binding to hydroxyapatite, and subsequently targeting osteoclasts by altering their ability to resorb and remodel bone. Whilst aiming to reduce the risk of fragility fractures, bisphosphonates have been associated with atypical insufficiency fractures, specifically in the femur. Atypical femoral fractures occur distal to the lesser trochanter, until the supracondylar flare. There are a number of the differing clinical and radiological features between atypical femoral fractures and osteoporotic femoral fractures, indicating that there is a distinct difference in the respective underlying pathophysiology. At the point of presentation of an atypical femoral fracture, bisphosphonate should be discontinued. This is due to the proposed inhibition of osteoclasts and apoptosis, resulting in impaired callus healing. Conservative management consists primarily of cessation of bisphosphonate therapy and partial weightbearing activity. Nutritional deficiencies should be investigated and appro-priately corrected, most notably dietary calcium and vitamin D. Currently there is no established treatment guidelines for either complete or incomplete fractures. There is agreement in the literature that nonoperative management of bisphosphonate-associated femoral fractures conveys poor outcomes. Currently, the favoured methods of surgical fixation are cephalomedullary nailing and plate fixation. Newer techniques advocate the use of both modalities as it gives the plate advantage of best reducing the fracture and compressing the lateral cortex, with the support of the intramedullary nail to stabilise an atypical fracture with

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increased ability to load-share, and a reduced bending moment across the fracture site. The evidence suggests that cephalomedullary nailing of the fracture has lower revision rates. However, it is important to appreciate that the anatomical location and patient factors may not always allow for this. Although causation between bisphosphonates and atypical fractures is yet to be demonstrated, there is a growing evidence base to suggest a higher incidence to atypical femoral fractures in patients who take bisphosphonates. As we encounter a growing co-morbid elderly population, the prevalence of this fracture-type will likely increase. Therefore, it is imperative clinicians continue to be attentive of atypical femoral fractures and treat them effectively.

Key Words: Bisphosphonates; Atypical fracture; Surgical fixation; Atypical femoral fracture; Osteoporosis

Core Tip: Bisphosphates are a class of drugs used as the mainstay of treatment for osteoporosis. A number of the clinical and radiological features of atypical femoral fractures and osteoporotic femoral fractures are different, indicating that there is a distinct difference in the respective underlying pathophysiology. At the point of presentation of an atypical femoral fracture, bisphosphonate should be discontinued. Currently there is no established treatment guidelines for either complete or incomplete fractures. The evidence suggests that cephalomedullary nailing of the fracture has lower revision rates.

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INTRODUCTION

Bisphosphonates are a class of drugs used as the mainstay of treatment for osteoporosis, as well as other metabolic bone diseases worldwide. Osteoporosis is a systemic disease resulting primarily in a low bone mineral density. It is defined by the World Health Organisation as a T score < -2.5 SD below the mean[1]. It is characterised by a deterioration in bone micro-architecture, and subsequent increased susceptibility to fracture[2]. This results in a significant health, social and economic burden to society [3].

Whilst aiming to reduce the risk of fragility fractures, bisphosphonates have been associated with atypical insufficiency fractures, specifically in the femur. These atypical fractures account for 1.1% of all femoral fractures[4]. This paper aims to review the mechanism of action of these drugs, their risks, benefits and in particular how associated fractures should be managed. It should aid clinicians in their understanding of this counterintuitive sequela of bisphosphonate use and ensure patients are counselled appropriately when considering commencement of bisphosphonate treatment.

BISPHOSPHONATES

Bisphosphonates function by binding to the inorganic components of bone, namely hydroxyapatite, and subsequently targeting osteoclasts by altering their ability to resorb and remodel bone. All drugs in this class have a chemical structure consisting of two phosphonic acids attached to a carbon atom with two side chains (R1 and R2), which are short and long respectively[5,6]. The chemical structure of the side chains influences the properties of the drug with the short side primarily influencing the

pharmokinetics while the long influencing the mode of action and potency. Bisphosphonates with higher binding affinity spread through bone slower than their lower affinity counterparts, however, if treatment is stopped, they remain in the bone for longer. The drug is absorbed in its active form with no systemic metabolism required. 50% of the absorbed drug binds to bone surfaces, most avidly at sites of remodelling, whilst the rest is rapidly excreted by the kidneys.

First generation or more commonly "non-nitrogen-containing bisphosphonates" such as etidronate had a very close structural similarity to inorganic pyrophosphate and were incorporated into newly formed adenosine triphosphate (ATP) molecules and absorbed by the osteoclasts. These toxic ATP molecules accumulated inside the cell and resulted in apoptosis. Second and 3rd generation or more commonly "nitrogenous" bisphosphonates such as alendronate, risedronate, ibandronate, pamidronate and zoledronic acid, have nitrogen containing R2 side chains which when absorbed by the osteoclast bind to and inhibit the activity of farnesyl pyrophosphate synthase, a key regulatory enzyme in the mevalonic acid pathway ultimately resulting in impaired formation of the ruffled border and bone resorption [5].

Currently the National Institute of Clinical Excellence[7] recommends bisphosphonates for any adult who has been identified as being high risk for osteoporotic fragility fracture as per standard risk assessment tools. This is achieved through the use of the fracture risk assessment tool[8]. It must be noted that consideration of individual circumstances and risks/benefit profiles should be considered within the assessment. This ensures a patient led approach to prevention of osteoporosis. The first line option is oral Alendronic acid, which in a 2008 Cochrane systematic review demonstrated a significant reduction in osteoporotic fractures in post menopausal women. Similarly a significant reduction in osteoporotic vertebral fractures was noted when used in primary prevention[9].

Recognised side effects of bisphosphonate use include gastrointestinal irritation, musculoskeletal pain, osteonecrosis of the jaw, and more recently recognised, atypical femoral fractures[6]. Oral preparations are now able to be given once weekly making the gastrointestinal (GI) side effects much more tolerable. Unfortunately they are still poorly absorbed, even under ideal condition such as being taken sitting up, after a prolonged fast. IV preparations such as pamidronate and zolendronic acid require even less frequent dosing and do not cause the same GI side effects however are subject to acute phase reactions characterised by flu like symptoms[10].

ATYPICAL FEMORAL FRACTURES

Atypical femoral fractures are insufficiency fractures that can be related to bisphosphonate use and are identified by major and minor criteria[11] (Table 1). Atypical femoral fractures occur distal to the lesser trochanter, until the supracondylar flare. In general, subtrochanteric and diaphyseal femoral fractures account for 5%-10% of all hip and femoral fractures. A small subset of these fractures (17-29[11,12]) are classified as atypical. Currently, evidence of association between atypical femoral fractures and bisphosphonate use is based upon observational studies. There is growing concern that the long-term effects of bisphosphonates on bone remodelling could cause a shift in the classical pattern of hip and femoral fractures towards this atypical configuration [13]. A Swedish study based upon their national registry (1521131 women over 55 years old with a 5% bisphosphonate use) found 46 atypical fractures in the 83311 bisphosphonate users over the 3 year period examined, and estimated a crude incidence of 5.5 atypical fractures per 10000 patient years[14]. This compared to 13 atypical fractures seen in the 1437820 non-bisphosphonate users in the same 3-year period. This equates to an estimated incidence of 0.09. Although this study demonstrated a high prevalence of bisphosphonate use in patients with atypical fractures, the absolute risk of this was very small. The authors concluded that with an appropriate indication, the benefits of fracture prevention with bisphosphonate use greatly outweigh the risk of atypical femoral fracture. A similar conclusion was drawn from a study reviewing 10 years of data, indicating risk of atypical femoral fracture increased with longer duration of bisphosphonate use, but that the absolute risk remained low compared with the reduction in risk of other osteoporotic fractures[15].

Table 1 Atypical femoral fractures are insufficiency fractures that can be related to bisphosphonate use and are identified by major and minor criteria

Major criteria (all must be met)	Minor criteria (none required)
Fracture line located anywhere between the distal border of the lesser trochanter of the femur to the proximal edge of the supracondylar flare	Localised periosteal reaction at lateral cortex – beaking, flaring
Lateral cortex must be involved (incomplete or complete – normally with medial cortical spike)	Generalised, diaphyseal cortical thickening
Transverse or short oblique fracture line No comminution	Prodromal groin/thigh pain
No or minimal precipitating trauma	Bilateral fracture and symptoms
	Delayed healing
	Co-morbidities (rheumatoid arthritis, vitamin and mineral deficiencies)
	Concomitant use of pharmacological agents (BP, corticosteroids, proton pump inhibitors)
Exclusions	
Neck of femur fractures, fractures relating to primary or secondary bone tumours and peri-prosthetic fractures[11].	

RISK FACTORS OF ATYPICAL FEMORAL FRACTURES

Despite the common use of bisphosphonates for the treatment of osteoporosis, atypical femoral fractures remain rare. The majority of patients who are treated with bisphosphonates will not sustain a clinical change in their femur. However, the consequence of an atypical femoral fracture can have significant impact of mortality and morbidity. Therefore, it is imperative that risk factors are identified and screened accordingly.

A number of the clinical and radiological features of atypical femoral fractures and osteoporotic femoral fractures are different, indicating that there is a distinct difference in the respective underlying pathophysiology. These features are similar to those found in stress fractures, with radiological evidence of a transverse fracture, lack of comminution, and localised cortical thickening at the fracture site (Figure 1)[11,16]. Clinically, patients may experience prodromal pain, as well as bilateral pathology[17].

Biological and biochemical

Bisphosphonate therapy has been shown in randomised controlled trials to increase bone density and reduce the risk of fracture in patients diagnosed with osteoporosis [18,19]. However, there is an association with atypical femoral fractures. Although causation between bisphosphonates and atypical femoral fractures is yet to be demonstrated, several properties of bisphosphonates and their effect on bone physiology are considered to play a role in the development of these fractures[11]. The first is the profound effect that bisphosphonates have on bone turnover[20]. This is achieved through suppression of osteoclast activity[21]. Histologically, this results in reduced resorption depth and a decreased activation frequency of new remodelling units[22], the consequence of which is a reduction in the rate of bone formation. This in turn impairs the ability to repair accumulated microdamage that occurs secondary to usual physiological stresses, leading to a two to seven-fold increase after management with bisphosphonates[23,24]. As well as microdamage accumulation, long-term over suppression of bone turnover results in secondary mineralisation of bone[25]. This hyper-mineralised bone may be more susceptible to fracture due to its brittle properties[26]. This remodelling and hyper-mineralisation results in a 20% decrease in bone toughness without a simultaneous reduction in bone mass[27]. The net effect could be explained by an increase in the young's modulus of the bone, with reduced ultimate tensile strength resulting in a smaller area under the stress-strain curve.

Genetics

While the aforementioned properties and resultant effects of bisphosphonates on normal physiology are associated with atypical femoral fractures, it remains unclear as to why these effects are not universal. More recently, genetic mutations have been found to influence susceptibility to atypical femoral fractures following bisphosphonate therapy, most notably GGPS1[28]. Other variants have been identified to predispose individuals to atypical fractures, irrespective of pharmacological therapy

Figure 1 Plain radiographs before and after atypical bisphosphonate associated femoral fracture fixation. A: Before atypical bisphosphonate associated femoral fracture fixation; B: After atypical bisphosphonate associated femoral fracture fixation.

[29]. A study has highlighted four uncommon polymorphisms associated with atypical femoral fractures, but no common genetic mutations[30]. The presence of a genetic metabolic bone disorder may be another important risk factor in the development of atypical femoral fractures.

Due to the increase in prevalence of bisphosphonate therapy and incidence of atypical femoral fractures, further research will determine the role of molecular genetics in relation to atypical fractures.

Biomechanical

Extrinsic bone strength depends on a combination of structural and material properties of the bone itself. The previously mentioned pathological fracture site is the lateral cortex of the femur; the location of maximal tensile stress[31]. The biomechanical alignment of the hip and femur determines the stresses placed upon the lateral cortex[32]. It has been shown that the lateral femoral bowing angle is the main determinant for location of atypical femoral fracture, with a higher lateral femoral bowing angle predisposing to diaphyseal fracture[31]. For this reason, an argument has been made that individuals of Asian descent are at a higher risk of atypical femoral fracture due to a greater natural bowing to the femoral shaft[33]. There is conflicting evidence regarding the effect of bisphosphonates on the extrinsic bone strength[34], warranting further investigation in this field.

SCREENING

A transverse line on plain radiographs has become pathognomonic of atypical femoral fractures[35]. Whilst this makes a diagnosis of a complete fracture more obvious, it is essential that incomplete or impending fractures are not missed. When patients present with the aforementioned clinical features of an atypical femoral fracture, in particular those who are recipients of bisphosphonate therapy, a high index of suspicion and close attention to detail with regards to any imaging should be maintained. Close examination for fracture lines in the lateral cortex and localised periosteal thickening is warranted, as the sensitivity and specificity of these signs has been shown to be high[36].

More recently, the role of computed tomography (CT) in the diagnosis and evaluation of atypical femoral fractures has been inspected. It has been shown that patients with atypical femoral fractures have had pre-fracture imaging showing a thicker lateral cortex at the site of the injury compared with that of bisphosphonate users who did not go on to develop a fracture[37]. Another study revealed that 34% of asymptomatic individuals with atypical femoral fractures displayed evidence of radiologic progression, with a mean time to progression of 25.6 mo[38]. Therefore, in the detection of future atypical femoral fractures, computed tomography and magnetic resonance imaging may provide valuable diagnostic information regarding the water and mineral content of bone[39-42]. Dual-energy X-ray absorptiometry (DEXA) combined with further image analysis techniques may further permit the discovery of abnormalities associated with atypical femoral fractures, providing a window of

opportunity for early intervention[41]. Bone scintigraphy provides clinicians with another imaging adjunct to ensure early detection[43]. At present, there are no high quality studies which consider bone scintigraphy compared to magnetic resonance imaging (MRI) for identification of occult fractures in bisphosphonate related atypical femoral fractures. However, a recent meta-analysis on the use of advanced imaging in occult hip fractures of the elderly suggests that CT and bone scan (sensitivity, 79% and 87% respectively) are less sensitive for occult hip fractures compared with MRI[44].

Serum markers provide a clinical value for initiation and monitoring bisphosphonate use. The present definition for osteoporosis is based on the value of bone mineral density (BMD) measured by DEXA or occurrence of fragility fracture. BMD response to bisphosphonate use is slow, which makes monitoring bone turnover difficult. Bone turnover markers (BTM) provide a more real time reflection of bone formation and bone resorption through the monitoring of serum and urine. A comprehensive review by Vasikaran *et al*[45] demonstrated that high level of BTMs may predict fracture risk independently to BMD for post-menopausal women. Despite the ability of BTM to monitor the pharmacologic effects of osteoporosis, the inconsistency in metrics of measurement and unsuitable trials on the BTM levels with treatment compared to controls limits its use.

MANAGEMENT OF ATYPICAL FEMORAL FRACTURES

Medical management and considerations

At the point of presentation of an atypical femoral fracture, bisphosphonate or any antiresorptive agent should be discontinued. This is due to the proposed inhibition of osteoclasts and apoptosis, resulting in impaired callus healing. Animal studies suggest that there is larger formation of fracture callus, with resultant increase in bone volume and mineral content, but has delayed hard callus remodeling during endochondral fracture repair[46,47]. In contrast, *in vivo* human studies of human trabecular bone demonstrated bisphosphonates induced osteoclastic proliferation and maturation, with upregulation of type 1 collagen and osteocalcin[48]. It is still unclear whether these medications should be withheld indefinitely or resumed after a certain time period thereby giving the patient a "bisphosphonate holiday"[49,50]. It is important to appreciate that bisphosphonates have different binding and anti-resporptive properties, thus providing a "holiday" from bisphsphonates may have an impact on femoral fractures[51]. Discontinuing bisphosphonates will possibly reverse bone modelling suppression and promote fracture healing. Data from the Kaiser data base suggests that if bisphosphonates are stopped soon after an atypical fracture, then 20% will fracture the contralateral leg, compared to 50% if continued for 3 years after the primary atypical femoral fracture[52]. It must be noted that alternative therapies should be considered if bisphosphonates are discontinued.

Conservative management consists primarily of cessation of bisphosphonate therapy and partial weightbearing activity, and has been proven to be effective in some cohorts[53]. Any nutritional deficiencies should be investigated and appropriately corrected, most notably dietary calcium and vitamin D[11]. More recently, there has been some conflicting evidence surrounding the use of teriparatide in patients with bisphosphonate-associated atypical femoral fractures[54]. It is a recombinant form of parathyroid hormone, and is thought to selectively target bone turnover suppression that occurs as a result of prolonged bisphosphonate use. Whilst some of the evidence is promising, there are also case reports suggesting an absence of this desired effect[55]. Therefore, further investigation is warranted prior to the routine prescription of teriparatide.

Operative fixation

Due to the paucity of evidence for the management of atypical femoral fractures, currently there is no established treatment guidelines for either complete or incomplete fractures. There is agreement in the literature that nonoperative management of bisphosphonate-associated femoral fractures conveys poor outcomes [56,57]. Therefore, it is generally accepted that the current preferred method for first-line management of complete atypical femoral fractures is surgical fixation with a device(s) that can withstand full body loading for a prolonged period to allow bony union. Cephalomedullary nailing, biomechanically gives the most favourable loading properties with on-axis fixation and co-linear strain (Figure 2)[58,59]. Other methods such as plate fixation have been used, usually due to the anatomical location of the fracture but suffer from off–axis fixation and differing strains patterns which can lead

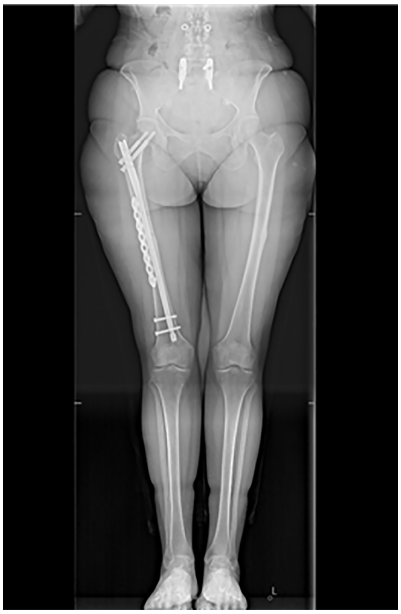

Figure 2 Plain radiograph illustrating fixation of an atypical bisphosphonate associated fracture and beaking on the contralateral limb at the same level.

to failure. There is evidence that fractures managed with plate fixation are at greater risk of requiring revision compared with cephalomedullary nailing (31.3% *vs* 12.9% respectively)[57]. Newer techniques advocate the use of both modalities as it gives the plate advantage of best reducing the fracture and compressing the lateral cortex which has failed in tension with the support of the intramedullary nail to stabilise an atypical fracture with increased ability to load-share, and a reduced bending moment across the fracture site[58,60] (Figure 3). With either fixation technique, however, it is important to avoid fixing the fracture in varus and the operating surgeon should consider creating a small osteotomy along the lateral cortex to remove the pathological bone and best restore the anatomical alignment[50,61].

The evidence base for the management of incomplete atypical femoral fractures is unclear. It has been shown that up to 28.3% of these develop into complete fractures within six months of their detection[62]. Concerning signs include functional pain and a visible transverse fracture line on plain radiographs extending > 50% of the lateral cortex. The rationale behind performing a prophylactic operation on an incomplete atypical femoral fracture is two-fold: progression to complete fracture is prevented and hospital stay is reduced[63]. In addition, the success rate of operative management of complete atypical femoral fractures is reduced by almost 50% when compared with that of incomplete fractures[64]. However, the authors of this study advocate that surgical management for patients presenting with incomplete bisphosphonate-related atypical femoral fractures should be reserved for patients with persistent pain, refractory to nonoperative management or progressive radiographic lesions. There is also recent evidence that prophylactic repair of the contralateral limb may be cost-effective in the treatment of patients presenting with atypical femoral fractures[65].

The literature suggests that operative management of atypical fractures is more challenging than that of typical femoral fractures, necessitating a greater level of surgical expertise and technique[61]. Atypical femoral fracture repair has also been found to have an increased incidence of iatrogenic intraoperative fractures, as well as a higher implant failure rate[66]. The general consensus in the literature is that further large-scale prospective studies are required to evaluate both the outcomes of surgical and conservative management of bisphosphonate-related atypical femoral fractures, as well as trials comparing outcomes from cephalomedullary nailing and other methods of fracture repair in this cohort.

Fracture healing using bone graft in this complex group of patients is an area of consideration to the surgeon. Pathologic by nature, bisphosphonate related atypical femoral fractures are due to chronic osteoclast inhibition, resulting in a site on the femur of reduced remodelling and sclerosis. Autologous bone grafting or bone marrow aspirate may restore the normal bone homeostasis. Currently, the literature is limited in regards to the theoretical benefits. A report by the American Society for Bone and Mineral research found limited evidence to suggest the chronic suppression

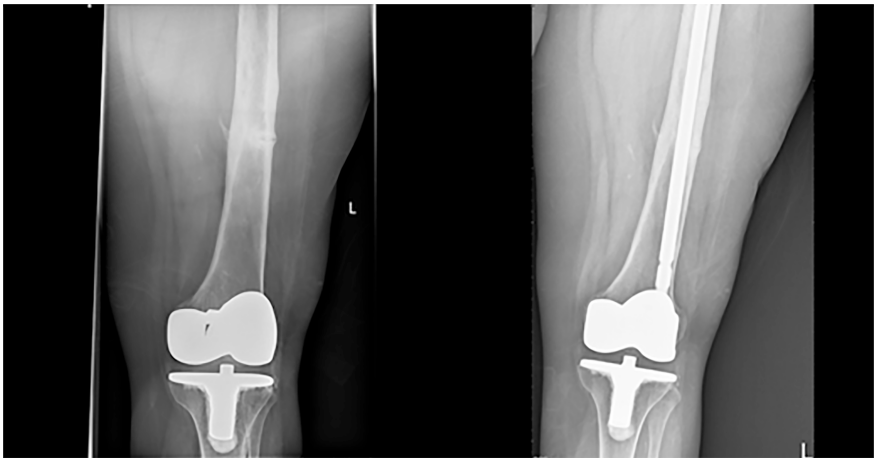

Figure 3 Plain radiographs of the "dreaded lucent line" and distal unlocked intramedullary stabilisation to minimise the stress riser around a knee replacement.

of osteoclasts may affect the efficacy of bone grafting at the fracture site[11]. Conversely, a study showed no decrease in bone formation after transiliac crest grafting in a similar patient population[67]. This shows that further research is required regarding femoral fractures improving time to fracture union.

Complications and considerations specific to atypical femoral fractures

Some of the literature reveals favourable outcomes following surgical repair of the atypical femoral fractures, with a reported 95.7% successfully healing without the need of a further operation[37]. However, a multicentre review with a greater study population found that 12.6% of atypical femoral fracture repair required revision surgery[57]. This is higher than the revision rate for typical femoral fracture repair, which is reported in the literature as 4.7%[68]. However, it must be noted that the median ages in these two patient populations vary widely, as patients receiving bisphosphonate therapy skew the median age in this cohort upwards. There are numerous proposed mechanisms for the difference in rates of revision surgery between atypical and typical femoral fracture repair. The primary explanation is that of delayed healing following operative management of an atypical femoral fracture. The mean time to heal following primary repair of atypical fracture by means of cephalomedullary nailing was 10.7 mo[69]. This may be related to impaired bone remodelling as a result of bisphosphonate use[11]. Although, interestingly, in a review where data regarding preoperative bisphosphonate use was readily available, there was no difference in time to healing when comparing those who had prior treatment with bisphosphonate use for greater than five years and those who had not ($P > 0.05$)[57].

A consideration unique to atypical femoral fractures is the incidence of contralateral pathology in those who present after bisphosphonate therapy. There is variation in the reported incidence of contralateral pathology in this population, ranging from approximately 22%[70] to 62.9%[71]. Regardless, there is evidence enough to suggest routine imaging of the contralateral side in the presence of prodromal pain.

CONCLUSION

Bisphosphonates are integral to the treatment of osteoporosis, although there is a particular association with atypical femoral fractures. Although causation between bisphosphonates and atypical fractures is yet to be demonstrated, there is a growing evidence base to suggest a higher predilection of atypical femoral fractures in patients who take bisphosphonates[14]. As we encounter a growing co-morbid elderly population, the prevalence of this fracture type will likely increase. Therefore, it is imperative clinicians continue to be attentive of atypical femoral fractures. This can, in part, be done by screening and requesting plain film radiographs, CT scans and DEXA imaging modalities for identification of incomplete or impending fractures. The evidence for the management of complete atypical femoral fractures suggests cephalomedullary nailing to be a favourable compared to plate fixation, in regards to

likelihood for revision[58,60]. However, it is important to appreciate that the anatomical location and patient factors may not always allow for this. A common subset of atypical femoral fractures are incomplete. Within this population, there is evidence to suggest a significant proportion go on to suffer complete fractures[62]. Therefore, prophylactic cephalomedullary nailing has been suggested in clinically symptomatic patients and visible transverse fracture lines on plain radiographs extending > 50% of the lateral cortex. This has been shown to be a cost effective means of reducing the burden of complete fractures on hospitals. However, surgical fixation in this population does not come without risk and meaningful dialogue with the patients is suggested to individualise treatment decisions in each case.

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MINIREVIEWS

Virtual orthopedic assessment: Main principles and specific regions

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Abstract

Telemedicine was originally created as a way to treat patients who were located in remote places far away from local health facilities or in areas with shortages of medical professionals. Telemedicine is still used today to address those problems, and is increasingly becoming a tool for convenient medical care. With the emergence of pandemics, telemedicine became almost a mandatory and valuable option for continuing to provide medical care in various specialties. As the threat of pandemic progress has continued for months and may continue for years, it is essential to validate existing tools to maintain clinical assessment and patient treatment to avoid negative consequences of the lack of medical follow-up. Therefore, the establishment of a virtual assessment technique that can be conducted effectively is of outmost importance as a way of adapting to the current situation. This study evaluated the role of telemedicine in the assessment of various orthopedic pathologies by means of a systematic virtual evaluation.

Key Words: Telemedicine; Virtual assessment; Orthopedics; Epidemic diseases

Core Tip: Telemedicine can be used to diagnose many orthopedic disorders and can be used for follow-up care after medical and surgical treatment. Its importance has

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increased dramatically with the emergence of epidemic diseases. However, an initial face-to-face assessment is recommended, especially in complicated cases where the diagnosis is uncertain. In this article, describe the role of telemedicine in the assessment of various orthopedic pathologies by systematic virtual evaluation.

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INTRODUCTION

Telemedicine uses technology for distant communication for health care purposes. With the emergence of epidemic diseases and need for social distance, telemedicine has become a valuable, almost a mandatory option for maintaining medical care provided in various medical specialties. Orthopedic surgery is one of the medical fields to which telemedicine can provide a good channel for continuous follow-up of patients, diagnosing, and managing many diseases during the awful worldwide situation[1].

Virtual assessment and management of orthopedic patients can bypass geographical and time boundaries, improve patient comfort, increase data transmission security, reduce costs, digitize healthcare systems, and facilitate the establishment of medical databases with potential research and audit benefits. On the other hand, its implementation is impeded by the fact that certain steps in the clinical examination cannot be performed without face-to-face interactions are vital for making the diagnosis[2].

Virtual orthopedic assessment depends on three items. The first is history taking, which has a very high impact in telemedicine to guide the physician throughout the entire assessment session. Examination is the next step of the assessment, and it must be adjusted to match the virtual setting of examining the patient without touch. After obtaining the data, physician orders the required laboratory or radiological investigations needed to reach the final diagnosis[3]. In this study, we evaluated the role of telemedicine in the assessment of various orthopedic pathologies through a systematic virtual assessment. Noted that in case of emergencies and inability to reach a definite diagnosis a consultation with an actual visit to a physician cannot be replaced.

INFRASTRUCTURE AND TECHNICAL REQUIREMENTS

The infrastructure and technical requirements needed for telemedicine assessment of orthopedic patients are easily available. Hardware devices include computers, cell phones, or tablets. Cameras and microphones are needed, and a wireless network connection, cable internet connection, or cellular network should be available. Many video platforms can be used during video conference consultations, such as Skype, Zoom, and Google Duo, *etc.*[4]. Specialized orthopedic software such as goniometer applications are useful for both initial consultations and in follow-up assessments of treatment efficacy. They can be also used for X-ray measurements (*e.g.*, to determine the degree of scoliosis). Gait analysis software can be used as it is an important clinical tool to assess gait deviations[5,6].

HISTORY

For reaching an appropriate diagnosis of a patient problem by telemedicine, the surgeon should take a full patient history, with more time for history taking and patient inspection as he cannot assess the patient by touch, but only by visual inspection and by listening to the patient history to gather information that he can interpret before ordering specific investigations needed to confirm his suspected

diagnosis. A full, accurate personal history, patient complaints, history of trauma if it occurred, medical, surgical, and family history, can raise the surgeon's suspicion of a specific cause of the patient problem that can be confirmed by examination and investigation. The personal history, including age, sex, occupation, residence, special habits like smoking, sports, and marital status, is important, as many diseases or fracture types are more likely in specific age groups have a sex difference. For example Freiber's disease is common in female patients 13-18 years of age[7].

Pain is the commonest patient complaint. Surgeon should fully analyze the pain to determine if it is localized or generalized, and the type of pain, what increases the pain, and to what extent it affects the activity of patient. For example how many kilometers can the patient walk or if the pain awakes the patient from sleep. During sleep, muscle spasms, which are a protective mechanism, do not occur, and movement can cause severe pain. Generalized pain usually associated with degenerative changes, complex regional pain syndrome or nerve injury. Localized pain that can be pointed to with a finger may be caused by a fracture, ligament injury, or tendinitis[7,8].

Early morning stiffness or stiffness after rest complain is usually an indicator of arthritis, as rheumatoid arthritis or osteoarthritis. Another cause of stiffness is post traumatic fracture malunion. It should be determined whether swelling is generalized or localized. Generalized swelling has many causes such as rheumatoid, septic, or osteoarthritis, severe soft tissue injury, or systemic diseases affecting the heart, like heart failure. Localized swelling has many causes, like bone fracture or ligament injury. If there is history of trauma, the mode should be determined, as the specific mode of trauma causes specific problems[7,9].

SHOULDER VIRTUAL ASSESSMENT

Shoulder pain is a common reason for seeking medical advice. Localized anterolateral shoulder pain in the "Codman zone" associated with night pain is a clue of some degenerative shoulder pathology, either impingement or rotator cuff tear. Posterior shoulder pain usually occurs with scapular dyskinesia as well as cervical muscle spasm. Shoulder stiffness is a complaint usually associated with pain that may occur because of impingement, rotator cuff tear, arthritis, or frozen shoulder "adhesive capsulitis". Instability and recurrent shoulder dislocation complains are often seen in athletes and in young age groups[10,11].

Inspection should be done for swelling, muscle wasting, or scars of previous operations. Inspection from the front is done to see whether there is a prominent sternoclavicular joint (subluxation) or clavicle deformity (old fracture), prominent acromioclavicular joint (subluxation or osteoarthritis), or deltoid wasting (disuse or axillary nerve palsy). Assessment done from side and behind is done to see whether the scapulae is normally shaped and situated, or small and high, as in Sprengel's shoulder or Klippel–Feil syndrome, or if there is winging of the scapula owing to paralysis of the serratus anterior[11].

An active range of motion (ROM) evaluation is done by instructing the patient to perform movements shown by physician, with assessment of obvious limitation if present and asking the patient which movement is painful, which most often is shoulder abduction. Ask the patient to perform external rotation with adduction and with abduction, if limited in comparison to other side it may indicate a frozen shoulder [10,11].

Special shoulder examination tests include an impingement assessment done by asking the patient to perform forward flexion of the shoulder with 90 degrees of elbow flexion and then shoulder internal rotation. Ask the patient whether it is painful or not and where exactly he feels the pain. If it is "mostly in the lateral and anterolateral shoulder region", then it indicates the presence of impingement. The resisted abduction test requires equipment, any item that weighs 2 kg, and is done by asking the patient to do a shoulder abduction while lifting the 2 kg object with internal rotation of the shoulder. The test simulates the empty can test for rotator cuff tear (Figure 1). Testing for slap lesion is done by resisted shoulder flexion with the forearm pronated and asking the patient resist the movement with his other hand over the forearm. The test is positive with a slap lesion and it simulates the speed test. An abduction external rotation test is performed by asking the patient to perform external rotation with abduction of the shoulder and ask if he/she feels afraid of dislocation. The test simulates the apprehension test for anterior shoulder instability. Scapular dyskinesia is tested by asking the patient to perform forward flexion of the shoulder while inspecting his back to follow scapular motion and monitor the symmetry of

Figure 1 Modified empty can test.

scapular motion during the movement. Scapular winging is tested by instructing the patient to lean with both hands against a wall. Watch the inferior angle of the scapula. Any tendency of winging of the scapula immediately becomes apparent[12].

ELBOW VIRUAL ASSESSMENT

A patient complaint of localized pain related to the lateral epicondyle is specific for tennis elbow, radial tunnel syndrome, or osteochondritis of the capitellum. Localized pain over the medial epicondyle is specific for golfer's elbow, cubital tunnel syndrome, and ulnar collateral ligament injury. Aching pain usually caused by arthritic changes. Pain with activity is usually caused by tendinosis or instability[13]. Virtual elbow assessment should include inspection of the elbow from all sides in flexion and extension, looking for any swelling, muscle wasting, scars of previous operations, and any deformity. The elbow should be inspected in extension with the arm by the side and the forearm supinated for determining carrying angle. It is increased (cubitus valgus) in cases of lateral condyle fracture nonunion and premature lateral epiphysis closure, and decreased (cubitus varus) in supracondylar humerus fracture[13].

Active ROM is tested by a flexion and extension test done with the patient's shoulder abducted 90 degrees. Normal flexion is to 140 degrees and extension to −10 degrees. Pronation and supination ROM are tested after instructing the patient to place the elbow flexed 90 degrees by his side. Normal pronation is from 0 to 70 degrees and supination is from 0 to 85 degrees (Figure 2). Limited range is usually found in patients with old fractures and arthritis. Both sides should be compared[14,15].

Special tests, such as Thomsen's test, specific for tennis elbow is done by asking the patient to clench his fist, extend his elbow and dorsiflex his wrist against resistance. Patients with tennis elbow will experience pain over lateral epicondyle[7]. For Tinel's test, which is specific for ulnar nerve entrapment and neuropathy, the patient should be asked to flex his elbow to 20 degrees and a healthcare giver is asked to tap gently between the olecranon and medial epicondyle over the ulnar groove. The test is positive for ulnar neuropathy if the patient has a tingling sensation down the forearm until the ulnar part of hand. For a specific test of golfer's elbow, the patient is asked to flex his elbow and then supinate the forearm. A healthcare giver is asked to extend the elbow against resistance. If positive, the patient will have pain over the medial epicondyle. The chair pushup test is for assessment of posterolateral rotator instability in cases of injury to the lateral collateral ligament complex. It is done with the patient in a seated position with the hands grasping the arms of the chair. The elbows, in about 90° of flexion, are supinated and the arms abducted. The patient attempts to rise from the chair by pushing down. A positive result is pain as the elbow slowly extends while the patient rises[14,15].

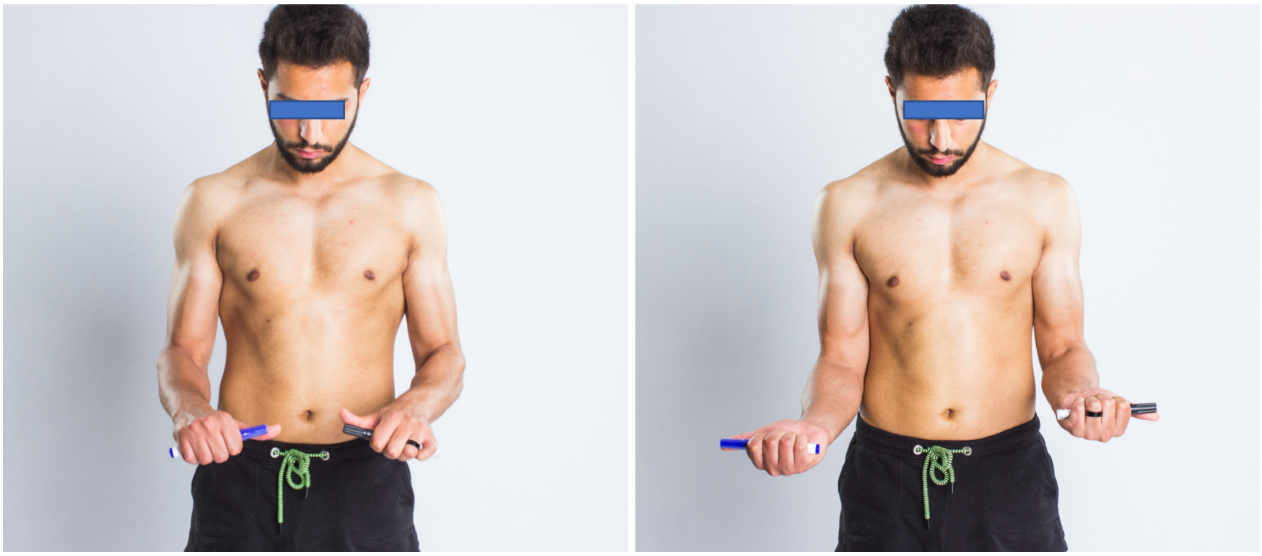

Figure 2 Assessing the active pronation and supination range of the elbow.

HAND VIRTUAL ASSESSMENT

Specific patients complaints are very important for making a specific diagnosis. Localized ulnar-side wrist pain may indicate conditions including a triangular fibrocartilage complex tear, or distal radioulnar joint instability/arthritis. Radial-side wrist pain suggests De Quervain's tendinitis, scaphoid fractures, *etc.*[16]. Wrist drop suggests radial nerve injury, while partial claw hand suggests ulnar nerve involvement[16,17]. A painless, slowly growing swelling at the dorsum of the hand just distal to the lister tubercle is suggestive of ganglion. Complaints of clicking and locking suggest Trigger finger, especially in the presence of a nodule on the corresponding metacarpophalangeal (MP) joint[18].

Hand inspection should be from the shoulders to the hands from all sides, with comparison between both sides. We inspect the hand to detect any deformity of alignment, scars, swelling, color changes, callosities, and ulcerations. Deformities such as short stumpy fingers seen in achondroplasia, as swan neck deformity, mallet finger, Boutonniere deformity, Z deformity of the thumb, and Dupuytren's contracture deformities should be inspected. Muscle wasting should also be noted as it suggests a root, plexus, or nerve lesion. A wasted Theaner eminence is associated with median nerve injury, wasted hypotheanar and interossei with ulnar nerve injury, and wasted anatomical snuff box with radial nerve injury[19].

Active movement of the finger joints is tested individually. Each finger is flexed maximally, while other fingers are extended and clearly seen, and then extended maximally. The normal active ROM is 0 to 90 degrees for the metacarpophalangeal (MP) joint, 0-100° for the proximal interphalangeal (IP) joint, 0 to 80 degrees for the distal IP joint, −20 to 15 degrees for thumb carpometacarpal joint, −5 to 55 degrees for thumb MP joint, and −20 to 80 degrees for the thumb IP joint. Similar assessments of thumb adduction, abduction, and apposition, wrist flexion and extension, ulnar and radial deviation can be made. The patient abducts and adducts the fingers as possible, with thumb adduction, radial abduction, and apposition[17].

Neurological sensory assessment can be assessed by asking a care giver to touch specific sites with cotton while comparing both sides with the patient's eyes closed. The sites are the tip of index finger (for median nerve injury), tip of little finger (for ulnar nerve injury), and the snuff box region (for radial nerve injury)[20,21]. Neurological motor assessments are done by asking the patient to make an "OK" sign by touching tip of thumb and the index finger to assess injury of the anterior interosseous nerve. With injury of the posterior interosseous nerve, the patient will have weak wrist extension with radial deviation. Loss of wrist extension is seen with radial nerve injury[20]. The ulnar nerve is assessed with Froment's test by asking the patient to grasp a piece of paper in the first web space on both sides while a caregiver holds the other side. Failure to adduct the thumb, and flexing it instead, indicates a positive test, with ulnar nerve injury[22]. For assessment of carpel tunnel syndrome Phalen's test (Figure 3) can be done by asking the patient to place the wrists in a maximal flexion position, which will reproduce the symptoms, if positive[23].

Figure 3 Phalen test.

HIP VIRTUAL ASSESSMENT

Hip pain is a common complaint of those seeking medical advice. Patients with hip problems also complain of limping, mechanical symptoms such as, clicking, snapping, catching, popping, and locking. The patient should be asked about a history of constitutional symptoms as fever, sweating, and nocturnal pain. The medical history should also address avascular necrosis of hip, usually seen in patients with systemic lupus and immune system disorders. Hip function can be objectively assessed with validated hip scores that can be assessed in the initial and in follow-up visits, especially after treatment. The Harris Scoring System and Western Ontario and McMaster Universities Arthritis Index hip scores are commonly used[3,10].

For inspection of the hip, undressing to underwear, if possible, is required to inspect the whole lower limb. Inspect from the front, sides, and back for skin scars, sinuses, discoloration, swellings, and muscle weakness or wasting (*e.g.*, Trendelenburg test). Inspect for any deformities in the sagittal plane and in the coronal view. Observe the gait, positive or negative limb length discrepancy from the front, sides and behind. Try to assess stride length, its components, and possible associated stiffness, shortening, pain and gluteal insufficiency[10].

Active ROM can be performed *via* telemedicine. For flexion, ask the patient to lie supine then flex each hip one time as possible. For extension, ask the patient to lie supine at the edge of a couch, then ask him/her to lie down one limb a time. For abduction and adduction, the camera should be at a level high enough to have a top view. Ask the patient to lie supine and then move the thighs away from each other far as possible and then back to the other side, crossing over as far as possible. For internal and external rotation, ask the patient to sit on the edge of the couch, and then move the legs away from each other as far as possible and then back toward the other side, crossing over as far as possible[10].

Fixed flexion deformities also can be assessed. An alternative to the Thomas test that can be conducted *via* telemedicine is to ask the patient to lie supine. Then starting in the knee-to-chest position and ask to actively extend each limb. Limb length assessment for discrepancy is done with the Geleazzi test (Figure 4), which can be effectively conducted *via* telemedicine. Ask the patient to lie supine and then flex both knees and hips 45 degrees. A static shot is taken from the top and the side views. Another way to determine limb length discrepancy is that in a normal patient the heels should be level with each other and the plane of the anterior superior iliac spines at right angles to the edge of the couch. If there is significant, true shortening the heels will not be level and the discrepancy is a guide to the amount of shortening. The pelvis will not be tilted[10].

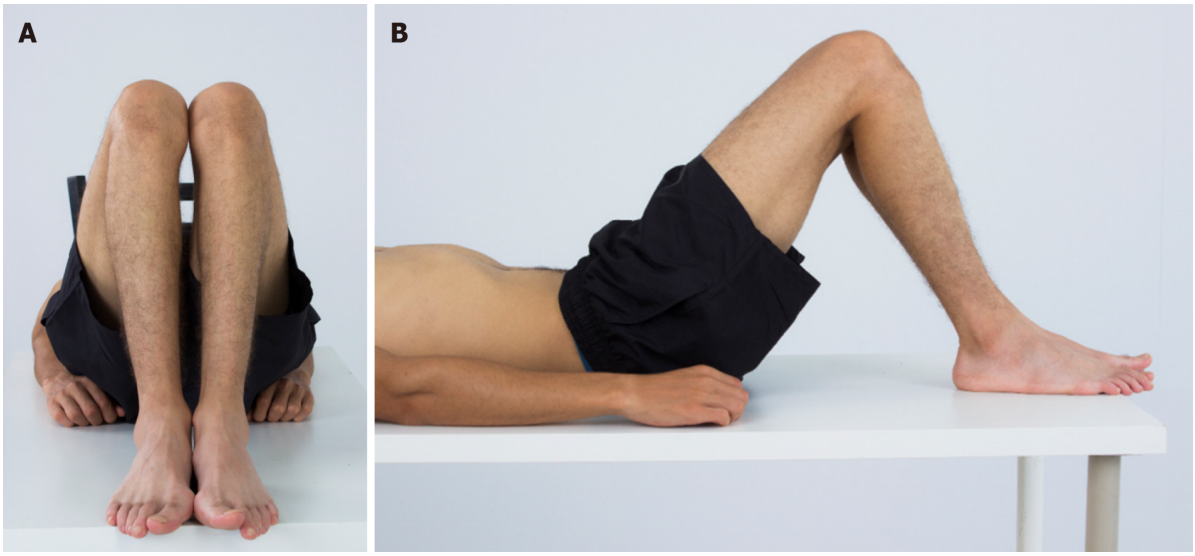

Figure 4 Geleazzi test to assess limb length discrepancy. A: Top view; B: Side view.

KNEE EXAMINATION

Specific complaints reveal the most common symptoms of patients with knee instability. Accurate assessment of the symptoms tells the physician a lot about the exact diagnosis[10,24]. Inspection should be done with bilateral knee exposure after instructing the patient to wear short swimwear. Look for genu recurvatum, genuvalgum, and genuvarum while patient is standing and for the position of the patella relative to the femoral condyles. The position of the patella should also be examined with knee flexion to assess the lateral position in case of lateral patellar dislocation. Then ask the patient to extend the knees, and look for any gross disturbance of patellar tracking. It should move smoothly in the patellar groove. Quadriceps wasting is assessed by asking the patient to put a towel underneath the popliteal fossa and push against it[24].

Active ROM done by instructing the patient to flex and extend the knees, assess if there is any limitation of movement, and ask the patient if the movement is painful or not. If the patient cannot fully extend the knee actively, extension lag and knee flexion deformity are differentiated by asking the patient to put his other leg beside the examined leg and try to complete the range of extension. If the examined leg is extended more, the reason is extension lag, and if it is not extended more, then it is knee flexion deformity[10,24].

Rupture of the posterior cruciate ligament may permit the tibia to sublux backwards. The knee should be flexed to 20°, with a sandbag under the thigh. The patient should be asked to lift the heel from the couch while observing the knee from the lateral aspect. Any posterior subluxation should normally correct during extension of the knee, confirming the diagnosis[10,24].

The Thessaly test (Figure 5) is done to examine for meniscal injury. It is performed at 5° and 10° of flexion. The patient can use a front wall as a support during a single leg squat to maintain balance the knee is flexed to the required amount. With the other lifted clear, the patient twists slowly from side to side. The result is positive if the patient experiences joint-line pain or sensations of locking or catching within the knee [10,24]. Common peroneal nerve testing is done easily by assessing the patient's ability to do ankle and big toe dorsiflexion[24].

ANKLE AND FOOT VIRTUAL EXAMINATION

Ankle joint assessment should be done with ipsilateral foot and knee assessment. For full inspection of ankle and foot, the patient should be asked to remove the shoes and socks with exposure to at least above the knee. Inspection should be from all sides, the anterior, posterior, lateral, medial, dorsal, and plantar surfaces of foot, and while standing and sitting. The surgeon should inspect the gait of the patient and also inspect the other side. We inspect the ankle and foot to detect any alignment

Figure 5 Thessaly test. Patient stands on one leg at a time, then rotates slowly from side to side. The maneuver should be performed three times, and the test is considered positive if the patient experiences pain, locking, or catching.

deformity, scars, swelling, color change, callosities, and ulcerations[25]. While the patient is standing in an anterior view, the surgeon should note whether the external rotation of the foot in the sagittal plane is within the normal range of 5-18 degrees. Causes of toe-out or toe-in signs should be investigated if noticed[25,26]. The big toe should be evaluated for abnormalities such as hallux valgus or hallux varus. Alignment of the lesser toes should be inspected to detect any abnormal alignment, such as hammertoe[25]. From the medial aspect with the patient standing, the surgeon should note whether the medial longitudinal arch of foot if normal or shows a deformity such as pescavus or pesplanus[7,25]. From the posterior with the patient standing, hindfoot alignment is evaluated by the angle between an imaginary line bisecting heel and another line bisecting the calf, which is normally in valgus about 5-10 degrees[25]. The importance of palpation of the foot is to determine the point of maximum tenderness, which is easily done in the ankle and foot by asking the patient to use the index finger to palpate all over the sides and surfaces of ankle and foot and asking which is the point of maximum tenderness.

Active ROM done by instructing the patient to do the same movements as the surgeon or as shown in a figure, with assessment of any obvious limitations. The patient should be asked which movement is painful and to compare both ankles. Active ROM is tested by asking the patient to stand on tiptoes to assess active plantar-flexion and to stand over the heels to assess active dorsiflexion. Active inversion and eversion are tested by asking the patient to stand over the inner and outer borders of the foot. Ankle passive dorsiflexion and planter flexion are done with the help of caregiver by holding the patient's heel neutral with one hand, inverting the midfoot with the other hand, and dorsiflex the ankle with the knee extended and then with the knee flexed at 90 degrees. Flexion is limited in case of stiffness, ankle fracture, or posterior structure. If the angle of dorsiflexion is same with knee flexion or extension, then the cause is the soleus muscle. If dorsiflexion is greater with the flexed knee, then the cause is gastrocnemius contracture[26].

Thompson's test is used to test the integrity of the tendon Achilles. The patient is asked to take the prone position with the feet off the end of table. A caregiver is asked to squeeze the calf on the normal and on the affected side. If the planter flexion movement is lost on the affected side, then a tear in the Achilles tendon is indicated [25]. The Coleman Block Test (Figure 6) is performed by placing the patient's foot on wooden block, 2.5-4 cm thick, with the heel and lateral border of foot on the block and bearing full weight while the first, second, and third metatarsals are allowed to hang freely. The test is used to assess the flexibility of hindfoot deformity in cases of cavovarus foot[27]. The tiptoe test is used to differentiate between flexible and rigid pesplanus deformity. In flexible flatfoot, the foot arch forms again when standing tiptoe[27,28].

Figure 6 Block test for assessment of hindfoot flexibility in cavovarus foot deformity.

SPINE VIRTUAL ASSESSMENT

Deformity with a progressive course in adolescence suggests scoliosis, while in old age and obesity back pain radiating to the extremity can suggest spondylosis. Ambulation or inadequate upper or lower limb function may indicate myelopathy or signify the degree of compression and possible need of surgical intervention. Bowel/bladder and sexual symptoms must to be evaluated to exclude the possible development of cauda equina syndrome[29,30]. The proper inspection of the entire spine is done by asking the patient to undress to underwear as possible. Normal sagittal curvature has cervical lordosis, thoracic kyphosis, and lumbar lordosis. Lost lumbar lordosis may indicate a protective spasm or posterior pelvic tilt, while exaggerated lumbar lordosis may suggest spondylolisthesis. Coronal alignment assessment should be done in a systematic descending manner, looking from head to heels. Gait should be inspected. Abnormal gaits related to spine disorders include a short step gait for back muscle spasm, an unsteady gait for myelopathy, and a sciatica gait for nerve root tension and lumbar disc prolapse. Heel to toe walking helps to approximately assess the motor power of the L4 and S1 nerve roots[31,32].

Start with cervical ROM assessment by asking the patient to point the camera sagittal to the of neck. Then ask the patient to move the chin to the chest and measure the distance between them (flexion) using a virtual ruler. Extension is determined with the patient looking at the ceiling and measuring the angle between the face and a horizontal line using goniometer-based software if available. Lateral bending is determined with the camera pointed at the front of the neck. Ask the patient to touch the ear to the shoulder and measure the distance between them using a virtual ruler. Rotation can then be determined by asking the patient to turn the chin to the shoulder. The same concepts are followed in thoracolumbar ROM assessment. Ask the patient to lean forward with extended knees and measure the degrees of flexion, Extension is the determined by extending the back as much as possible and measuring the degrees of extension as the angle between the back and a vertical line. Coronally, lateral bending is determined by asking the patient to lean laterally and advance the fingers down the legs with extended knees and measuring the degree of bending by finger to floor distance. Then, for thoracic rotation, with the patient sitting on a chair and the camera at a higher level, ask him/her to rotate the trunk, and measure the angle between shoulder and the coronal planes.

Sensory assessment can be done with a chart of the upper and lower limbs that shows the dermatomes at clear, easily located points. A caregiver can help by using cotton and the chart to compare both sides, with the patient's eyes closed. Motor assessment can be performed using simple measures to exclude weakness. If the patient can perform the movement against resistance, then the muscle grading is three or more. If any degree of resistance is offered, the grade is four or five. For cervical nerve root motor assessment, ask the patient to flex the elbow (C5), to extend the

elbow (C7), to extend the wrist (C6), to flex the fingers (C8), and to abduct them (T1). Similarly, lumbar nerve root assessment can be conducted by asking the patient to sit and then elevate the hip maximally (L1, 2), to lie supine with knees flexed 30 degrees into a triangle. Ask the patient to extend completely (L3), then to lie on the side and ask him/her to elevate the limb with the knee extended (L5). In all the previous motions, a caregiver is asked to provide resistance. We can rely on slump test to diagnose lumbar nerve root stretch *via* telemedicine instead of the straight leg test. Ask the patient to sit on the edge of the couch, lean the trunk forward while the neck extended to maintain a forward gaze, and then extend the knee as actively as possible. Ask for presence of pain and its location to confirm the diagnosis (Figure 7). The Valsalva maneuver with the knee is extended can confirm nerve stretch by pain accentuation[31,33].

PEDIATRIC ASSESSMENT

The age of the child is crucial for developing a differential diagnosis, for example, hip symptoms in a 7-year-old boy with delayed bone age can suggest Perthes disease[34,35]. Birth history is an important consideration especially when neuromuscular conditions such as cerebral palsy are suspected. Birth history can be divided into prenatal, natal, and postnatal periods. In the prenatal period, any history of maternal infection in the first trimester or vaginal bleeding may provide a clue for possible brain injury that could lead to cerebral palsy. Important factors to consider in the natal period include birth weight, type of presentation, mode of delivery, home or hospital delivery, any birth injuries, and whether the child was delivered full-term or preterm. Postnatally, any neonatal jaundice necessitating UV light intervention, need for neonatal intensive care unit, incidence of hypoxia or cyanosis, and Apgar score should be noted[36,37]. A family history can be important for detecting diseases such as neurofibromatosis. A nutritional history is important to consider as well, especially in the pediatric patient, and may help identify nutritional rickets as the underlying etiology for deformities in toddlers. Finally, a developmental history with both physical and mental milestones can be useful, particularly in suspected cases of neurodevelopmental disorders[38].

General examination should include facial abnormalities that may occur in Down syndrome, blue sclera that can suggest osteogenesis imperfecta, and abnormalities in height and proportions that suggest dysplasia, and café au lait spots that are characteristic of neurofibromatosis[39]. The evaluation should include observation of joint alignment to determine whether the patient has a symmetrical shoulder level, symmetrical scapulae, and a level pelvis. Search for any possible coronal knee deformities, and document intermalleolar and intercondylar distance. Observe for other potential knee deformities, including squinting patellae caused by excessive femoral anteversion, ankle deformities, and deformities of the forefoot, midfoot, and hindfoot. A similar systematic sequence can be applied to the upper limb[39].

Gait assessment should be done from coronal and sagittal views while observing the appearance of the hip, knee, and foot. Inspect for any possible anterior or posterior pelvic tilt, scissoring of the thighs, any coronal knee deformities, squinting patellae, any flexed knee gait, pes planovalgus or pes cavovarus, forefoot abduction, big toe deformities, and coronal ankle deformities. Observe for general patterns of gait deformities such as jumping, crouch, equine, ataxic, and circumduction gaits. Trendelenburg gait may occur in the setting of hip diseases like developmental dysplasia of the hip or coxa vara, short limb gait in a limb length discrepancy, out-toeing gait which may be seen in slipped capital femoral epiphysis (SCFE), and high stepping gait that often occurs in knee flexion deformities[34,35,39]. The Geleazzi test for limb length measurement can be effectively translated to telemedicine. Ask the patient to lie supine and then flex both knees and hips to 45 degrees from the top and the side views, which can then be used to interpret the cause of limb length discrepancy[39].

INVESTIGATION

Plain X-rays are usually needed for evaluation of fractures, loose bodies, and the presence of arthritis. Anteroposterior and lateral views are standard and are usually required. Special views such as foot obliques or mortise view of the ankle are useful for assessment of syndesmosis, scaphoid view for scaphoid fracture diagnosis, stress

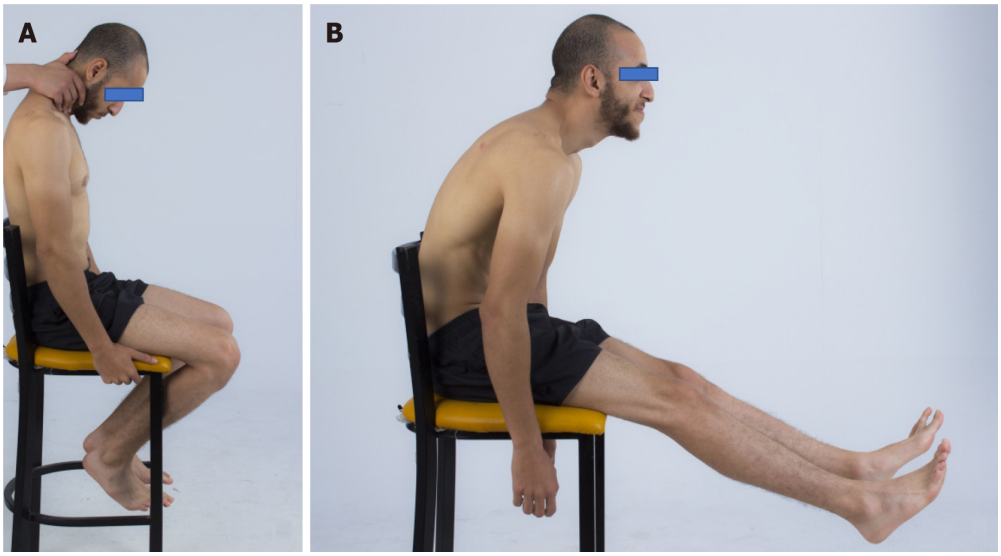

Figure 7 Special tests. A: Lhermitte test; B: Slump test.

views, such as clenched fist, for carpal instability, Other plain X-ray views are useful. The Zanca view may help visualize acromioclavicular joint pathologies, The Stryker notch view can show a Hill-Sachs lesion[40-42]. Computed tomography is used to show details, configuration of fractures as evaluation of intra-articular extension as in pilon fracture, or evaluation of osteochondral lesions and arthritis. Magnetic resonance imaging is used to assess the integrity of soft tissues, ligaments, tendons, occult fracture, vascular status of bone, and is also useful to detect disc herniation and nerve root compression. Nerve conduction tests are used for evaluation of nerve entrapments. Scanograms can be used to measure limb length discrepancy and the site and degree of discrepancy[41,43,44].

Laboratory studies like complete blood count, erythrocyte sedimentation rate, and C-reactive protein can be useful for detecting the presence of infection. A metabolic profile and vitamin D assay can be useful for the evaluation of nutritional rickets and SCFE. Renal function tests should be ordered if renal osteodystrophy is suspected. Finally, a serum creatin kinase-MB test should be ordered if muscle dystrophy is suspected.

CONCLUSION

Virtual assessment and management of orthopedic patients can cross geographical and temporal boundaries, improve patient comfort, increase data transmission security, reduce cost, digitize healthcare system data, and facilitate the establishment of medical databases, with potential research and audit benefits, which confirm its efficacy during health crises and epidemic diseases.

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MINIREVIEWS

Machine learning in orthopaedic surgery

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Abstract

Artificial intelligence and machine learning in orthopaedic surgery has gained mass interest over the last decade or so. In prior studies, researchers have demonstrated that machine learning in orthopaedics can be used for different applications such as fracture detection, bone tumor diagnosis, detecting hip implant mechanical loosening, and grading osteoarthritis. As time goes on, the utility of artificial intelligence and machine learning algorithms, such as deep learning, continues to grow and expand in orthopaedic surgery. The purpose of this review is to provide an understanding of the concepts of machine learning and a background of current and future orthopaedic applications of machine learning in risk assessment, outcomes assessment, imaging, and basic science fields. In most cases, machine learning has proven to be just as effective, if not more effective, than prior methods such as logistic regression in assessment and prediction. With the help of deep learning algorithms, such as artificial neural networks and convolutional neural networks, artificial intelligence in orthopaedics has been able to improve diagnostic accuracy and speed, flag the most critical and urgent patients for immediate attention, reduce the amount of human error, reduce the strain on medical professionals, and improve care. Because machine learning has shown diagnostic and prognostic uses in orthopaedic surgery, physicians should continue to research these techniques and be trained to use these methods effectively in order to improve orthopaedic treatment.

Key Words: Artificial intelligence; Machine learning; Supervised learning; Unsupervised learning; Deep learning; Orthopaedic surgery

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Core Tip: With the mass interest artificial intelligence and machine learning have garnered in orthopaedic surgery, a literature review of recent studies is necessary. By demonstrating the utility of various machine learning algorithms across various subspecialties of orthopaedic surgery, researchers should encourage physicians to understand the benefits of machine learning techniques and learn how to effectively incorporate these elements into their own practice to improve patient care. This clinical review outlines the concepts of machine learning and summarizes current and future orthopaedic applications of machine learning in risk assessment, outcomes assessment, imaging, and basic science fields.

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INTRODUCTION

The application of artificial intelligence (AI) has taken our world by storm. AI has been used in many aspects of modern life such as recommendation systems used by Netflix, YouTube, and Spotify, search engines like Google, and social-media feeds like Facebook and Twitter[1]. Additionally, AI has entered the realm of medicine. For example, there is substantial evidence that AI performs on par or better than humans in various tasks such as analyzing medical images as well as correlating symptoms and biomarkers from electronic medical records with the characterization and prognosis of disease[2]. Specifically in orthopaedic surgery, certain subfields of AI have been successfully implemented to improve clinical decision making and patient care[3].

To better understand the utility of AI in orthopaedic surgery, some terms must first be defined. AI started as a theory that computers could eventually learn to perform tasks through pattern recognition with minimal to no human involvement[1,4]. Today, the definition has been adapted to include the application of algorithms that provide machines the ability to solve problems that traditionally required human intelligence [1,5]. AI, which is often used as an umbrella term, encompasses subfields such as machine learning (ML), which is defined as a series of mathematical algorithms that enable the machine to "learn" the relationship between the input and output data without being explicitly told how to do so[3]. Furthermore, machine learning contains the subfield of deep learning (DL) which can be used to find correlations without labelling, that are too complex to render using previous machine learning algorithms, by processing input data through artificial neural networks[6,7].

In the field of orthopaedic surgery, ML has been used for different applications such as fracture detection, bone tumor diagnosis, detecting hip implant mechanical loosening, and grading osteoarthritis (OA)[3]. As time goes on, the utility of AI and ML in orthopaedic surgery continues to grow and expand. The purpose of this review is to provide an understanding of the concepts of ML and a background of current and future orthopaedic applications of ML in risk assessment, outcomes assessment, imaging, and basic science fields.

WHAT IS ML?

ML focuses on developing automated computer systems that predict outputs through algorithms and mathematics[8,9]. Classic or conventional ML algorithms that are meant to extract knowledge from more tabulated data sets include decision trees, random forests, nearest neighbors, linear regression, support vector machine (SVM), and k-means clustering[3,10]. On the other hand, more recently developed DL algorithms and artificial neural networks (ANN) are used to extract knowledge from imaging data sets. Regardless of which algorithms are used, ML requires software to "learn" patterns or relationships from sets of empirical data. This "learning" can be achieved through three different means: supervised learning, unsupervised learning,

and reinforcement learning[11-13].

Types of ML

Supervised learning, also termed inductive learning, is the most prevalent type of ML and occurs when data is labeled to tell the machine exactly what patterns it should look for[14]. For example, if an ML algorithm is used to detect arthritis on a knee radiograph, the arthritic features must be manually identified and labeled by a human along with the label of whether the radiograph is an example of an arthritic or normal knee[1]. On the other hand, unsupervised learning, also termed deductive or analytic learning, occurs when the data is not labeled and the machine looks for patterns[14] (Figure 1). In continuing with the last example, the arthritic features in unsupervised learning would not be labeled and therefore the algorithm relies on self-organization [1]. Lastly, reinforcement learning acts more like a reward or punishment system. Unlike supervised learning which makes data available at the beginning of the task, reinforcement learning uses feedback about the correctness after the task has been completed[15]. Usually, supervised learning is used because it requires the least amount of data and thus the least amount of time to learn.

DL and ANN

DL is modeled after the human brain's neural connections *via* complex and layered algorithms termed ANN[1,14]. The complex layering allows the algorithm to learn more complex and subtle patterns compared to more simple one or two layer networks[5,16,17]. Two known models of deep learning within the ANN include convolutional neural network (CNN) and recurrent neural network. The main type, CNN, has two main functions: (1) to extract features from imaging; and (2) classification[3]. The CNN extraction feature relies on the idea that filters learned on a small subset of a larger image to detect certain features can also be applied to other parts of the larger image in order to detect the same feature at different locations[3]. The CNN starts by searching for simple features in an image and then pools these simple features together to extract more complicated high-level features[3,18] (Figure 2). For the classification feature, the CNN acts as a classic neural network that combines all the high-level feature maps (generated from the aforementioned filters) from the deepest convolution layer and uses them to output a classification score[3]. During training, the CNN is presented with a series of images that have known classifications; the CNN must make a classification decision for each image and then calculate the classification error by comparing its classification decision with the known classification of the image. Through this training process, the CNN is able to update its learnable parameters and make classification decisions on images never before seen[3].

DL algorithms have been successfully applied to complex problems to improve diagnostic accuracy and speed, flag the most critical and urgent patients for immediate attention, reduce the amount of human error, reduce the strain on medical professionals, and improve orthopaedic care[3]. Specifically in orthopaedic surgery, the greatest application of DL is in image classification.

RISK ASSESSMENT

While ML has traditionally been used in medicine for rule-based approaches such as safe drug prescription, recent use of ML and DL in orthopaedic surgery has focused on clinical decision support such as risk assessment[14,19]. Currently, logistic regression is one of the most commonly used methods for identifying risk factors predictive of developing complications; however, in comparison, ANN allows for the identification of nonlinear patterns that make predictions more accurate[20-22].

Throughout orthopaedic literature, the application of ML and DL in risk assessment for various complications has been studied extensively (Table 1). For example, in Kim *et al*[23], ML models were used to predict mortality, venous thromboembolism, cardiac complications, and wound complications following posterior lumbar fusion. The ML models outperformed the American Society of Anesthesiologists (ASA) scores proving that ML can be more effective at predicting complications. Similarly, in Harris *et al* [24], ML was used to predict 30 day mortality and morbidity after total joint arthroplasty. While the ML model was found to be more accurate than standard models for cardiac complications and mortality, it was less effective for rarer complications such as re-operation and deep infection. More recently, Gowd *et al*[25] used supervised ML models to predict postoperative outcomes following total shoulder arthroplasty. ML algorithms outperformed the standard model for predicting adverse events,

Table 1 Summary of machine learning for orthopaedic surgery risk assessment

Ref.	Conclusion
Bevevino *et al* [26]	ANN capable of accurately estimating the likelihood of amputation
Gowd *et al*[25]	Supervised ML outperformed ASA classification models in predicting adverse events, transfusion, extended length of stay, surgical site infection, return to operating room, and readmission
Harris *et al*[24]	ML was moderately accurate in predicting 30-d mortality and cardiac complications after elective primary TJA
Kim *et al*[23]	ANN more accurate than ASA in predicting mortality, VTE, cardiac and wound complications following posterior lumbar spine fusion

ML: Machine learning; ANN: Artificial neural network; ASA: American Society of Anesthesiologists; TJA: Total joint arthroplasty; VTE: Venous thromboembolism.

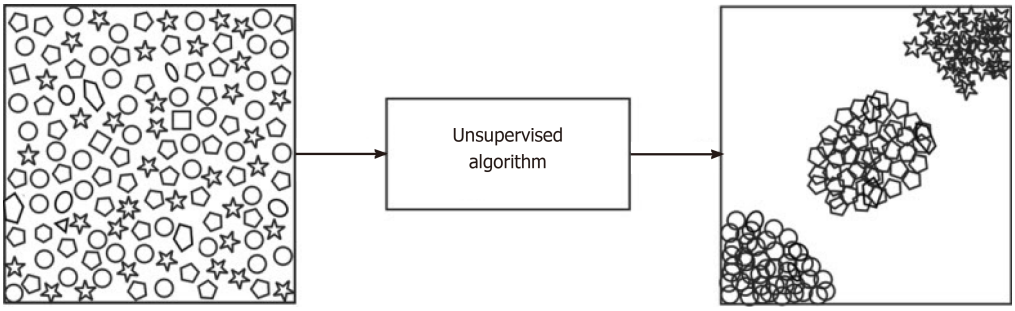

Figure 1 A visual illustration of an unsupervised algorithm[11]. Reused with permission. Citation: Sidey-Gibbons JAM, Sidey-Gibbons CJ. Machine learning in medicine: a practical introduction. *BMC Med Res Methodol* 2019; **19**: 64.

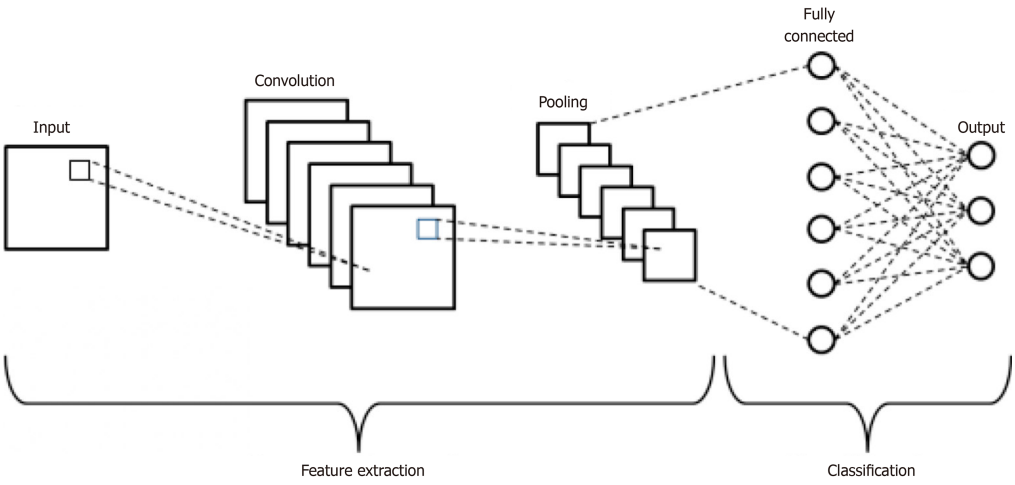

Figure 2 Schematic diagram of a basic convolutional neural network architecture[18]. Reused with permission. Citation: Phung VH, Rhee EJ. A High-Accuracy Model Average Ensemble of Convolutional Neural Networks for Classification of Cloud Image Patches on Small Datasets. *App Sci* 2019; 9: 4500.

transfusion, extended length of stay, surgical site infection, return to the operating room, and readmission. Furthermore, in risk assessment related to orthopaedic trauma, Bevevino *et al*[26] used a DL model to predict the likelihood of amputation based on 155 combat-related open calcaneal fractures and compared it to a standard logistical regression model. Twenty-six features with a proven or theoretical association with successful or unsuccessful limb salvage were analyzed; some of the features included were various patient demographics, mechanism of injury, wound size and location, and fracture type. Once again, the DL method was 30% more accurate and better suited to clinical use than the standard logistical regression model.

The orthopaedic literature shows that ML continuously outperforms more traditional legacy risk-stratification measures such as ASA classification, Charlson Comorbidity Index, and modified 5-item frailty index, in predicting complications

following a variety of orthopaedic procedures as well as identifying safe candidates for specific orthopaedic procedures like anterior cervical fusion and discectomy[25,27-29]. In all of the studies outlined above, the ML and DL algorithms outperformed the standard models indicating a higher level of accuracy for risk assessment[23-26]. Furthermore, comorbidity indices have previously been used to gauge perioperative risk, evaluate the need for postoperative admission, and determine prophylactic treatments[30-32]. With continued validation, ML algorithms may replace this paradigm. Whereas logistical regression models have typically been used for many years to predict risk, survival, mortality, and morbidity, the application of ML and DL, particularly in predicting the risk of complications following spine surgeries, joint surgeries, and orthopaedic trauma, shows much promise[14].

OUTCOMES ASSESSMENT

Over the last twenty years or so, the ability to predict outcomes has positively impacted medicine and patient care. From risk scores that guide anticoagulation (CHADS2) to the use of cholesterol medications (ASCVD), data-driven clinical predictions have become routine in medical practice[33]. Because ML has the ability to analyze large data sets, the accuracy of prediction significantly improves[33]. Specifically in orthopaedic surgery, recent literature has shown the utility of ML algorithms in outcomes assessment for orthopaedic oncology survival, patient-reported outcome measures (PROMs), hospital length of stay, and cost (Table 2).

When compared to ML algorithms, current prognostication models for survival following metastatic spinal disease are not built for estimation of short-term survival (30 to 90 d) and some studies even suggest a lack of accuracy in classic models[34-37]. In Janssen *et al*[38], authors compared a boosting ML algorithm to a classic scoring system and nomogram at 30 d, 90 d, and 1 year to study survival estimates in patients with long bone metastases. In all training data sets, the boosting ML algorithm was found to be far superior at each time point[38]. Paulino Pereira *et al*[37] conducted a similar study where they compared the boosting ML algorithm, nomogram, and the classic scoring system to predict survival in metastatic spine disease. In this study, the boosting ML algorithm was comparable to nomogram in its predictive ability for testing data sets. Thio *et al*[39] and Bongers *et al*[40] used ML methods on patient demographics, tumor characteristics, treatment, and outcome data to create an ML algorithm that could predict 5 year survival rate in patients with chondrosarcoma[39,40]. In the latter study, the authors found that the ML algorithm overestimated the survival rate in their data set, but when applied to a smaller data set, it overestimated survival to a lesser extent.

Within the last ten years, the concept of PROMs has gained rapid support in orthopaedic surgery as a way to measure healthcare quality and value[41]. The minimally clinically important difference (MCID) or the minimum change in PROM scores that patients perceive as clinically meaningful offers a threshold of score that portends clinical relevance[41-43]. Using predictive models to identify patients at risk of not achieving MCID is important for resource allocation as well as better monitoring especially for presurgical decision support[41]. Fontana *et al*[41] used three ML models to predict which patients would not achieve a MCID in four PROMs two years following total joint arthroplasty (TJA). When applied to presurgical registry data, the three ML models predicted 2-year postsurgical MCIDs with fair-to-good ability showing that ML has good predictive power in MCID following TJA. In another study, Menendez *et al*[44] used ML to understand sentiment by exploring the content of negative patient-experience comments after total shoulder arthroplasty (TSA). Through a ML based approach, they found that patient satisfaction was highly correlated to hospital environment, nontechnical skills, and delays. Menendez *et al*[44] showed the potential utility of AI and ML models to analyze post-surgical PROM surveys to determine quality and satisfaction after TSA.

A newer trend in orthopaedic surgery is using ML concepts to predict hospital length of stay as well as cost[45-47]. Today, ML models can be used to predict how long or how much a patient's surgery will cost prior to the elective procedure[48,49]. Ramkumar *et al*[45,47] and Navarro *et al*[46] used ML techniques on preoperative big data to predict length of stay and patient-specific payments following total hip arthroplasty (THA) and total knee arthroplasty (TKA), respectively[45-47]. In both studies, the ML techniques showed excellent predictability in length of stay. As complexity of the case increased, accuracy for predicting payment decreased proportionately in THA. On the other hand, as complexity of the case increased in TKA, accuracy for

Table 2 Summary of machine learning for orthopaedic surgery outcomes assessment

Ref.	Conclusion
Bongers *et al*[40]	ML algorithm overestimated ability to predict 5-year survival in patients with chondrosarcoma
Fontana *et al*[41]	Used ML to demonstrate fair-to-good ability in predicting 2-year postsurgical MCID following TJA
Greenstein *et al*[51]	Used EMR-integrated ANN to predict discharge disposition after TJA on small data set
Janssen *et al*[38]	Boosting ML algorithm far superior in training data sets to classic scoring system and nomogram in predicting survival in patients with long bone metastases at 30 days, 90 days, and 1 year
Karnuta *et al*[50]	Bayes ML algorithm demonstrated excellent accuracy in prediction of length of stay and cost of an episode of care for hip fracture
Menendez *et al*[44]	Used ML on patient-narrative analysis to show patient satisfaction after TSA is linked to hospital environment, nontechnical skills, and delays
Navarro *et al*[46]	Created a valid ML algorithm that predicted length of stay and costs before primary TKA
Pereira *et al*[55]	Boosting ML algorithm comparable to nomogram in its ability to predict survival in metastatic spine disease with testing data sets
Ramkumar *et al*[45]	Created a valid and reliable ML algorithm that predicted length of stay and payment prior to primary THA
Ramkumar *et al*[47]	Developed several ML based models for primary LEA that preoperatively predict cost, length of stay, and discharge disposition
Thio *et al*[39]	Created a high performing ML algorithm that could predict 5-year survival in patients with chondrosarcoma

ML: Machine learning; MCID: Minimally clinically important difference; TJA: Total joint arthroplasty; EMR: Electronic medical record; ANN: Artificial neural network; TSA: Total shoulder arthroplasty; TKA: Total knee arthroplasty; THA: Total hip arthroplasty; LEA: Lower extremity arthroplasty.

predicting costs increased by 3%, 10%, and 15% for moderate, severe, and extreme risk populations[46]. Similarly, Karnuta *et al*[50] used an ML algorithm on preoperative patient data to predict length of stay and cost after hip fracture; they found their ML algorithm to be 76.5% accurate for predicting length of stay and 79% accurate for predicting cost. Furthermore, Greenstein *et al*[51] used ML to preoperatively predict the likelihood a patient will be discharged to a skilled nursing facility after TJA. This study served as proof of concept that ML could be used as a prediction tool not only for big data sets, but also for small data sets. Using ML techniques to predict length of stay and cost has led to monumental improvements in establishing value-based care in orthopaedic surgery.

In orthopaedic surgery, AI and ML based techniques have demonstrated utility in predicting outcomes related to orthopaedic oncology, PROMs, length of stay, and cost. While ML techniques for survival in orthopaedic oncology have not yet been perfected, ML has proven to be effective with PROMs as well as predicting length of stay and cost. By using ML methods to make better outcome predictions, orthopaedic surgeons can improve their decision-making ability, which not only leads to better patient care, but also more efficient utilization of healthcare resources[52].

IMAGING

Since orthopaedic surgery diagnosis and treatment heavily rely on radiologic modalities [*e.g.*, computed tomography (CT), magnetic resonance imaging (MRI), and conventional radiographs], the vast majority of AI and ML based research has been applied to imaging. Recent advances in AI and ML have shown remarkable results with a few studies showing computers surpassing human test subjects at certain image interpretation tasks[53,54]. Within musculoskeletal medicine, DL has been shown to be useful for both text and image analysis[55-57]. ML and DL based techniques have the potential to assess earlier disease status and are currently the focus of significant orthopaedic research, particularly in the following subspecialties: Spine, joints/arthritis, trauma, and oncology (Table 3).

Spine

In spine surgery, technology has risen with the use of computer assisted navigation, robotic surgery, and augmented reality, all of which require reconstructions of the spinal column from CT or MRI scans[58-61]. This can only be achieved *via* ANNs and

Table 3 Summary of machine learning for orthopaedic surgery imaging applications

Ref.	Subspecialty	Conclusion
Al-Helo *et al*[66]	Spine	Neural network (93.2% accurate) and k-means approach (98% accurate) used on CT scans for segmentation and prediction of lumbar wedge fractures
Forsberg *et al*[62]	Spine	Annotated MRIs with information labels for each spine vertebrae used to accurately detect (99.8%) and label (97%) cervical and lumbar vertebrae
Hetherington *et al*[64]	Spine	CNN successfully identified lumbar vertebral levels on ultrasound images of the sacrum
Jamaludin *et al*[65]	Spine	CNN model achieved 95.6% accuracy comparable to experienced radiologists in disc detection and labeling of T2 weighted sagittal lumbar MRIs
Pesteie *et al*[63]	Spine	Used ML system to detect laminae and facet joints in ultrasound images to assist in epidural steroid injection and facet joint injection administration
Ashinsky *et al*[71]	Joints/arthritis	ML algorithm predicted clinically symptomatic OA on T2 weighted maps of central medial femoral condyle with 75% accuracy
Liu *et al*[72]	Joints/arthritis	CNN performed rapid and accurate cartilage and bone segmentation within the knee joint
Shah *et al*[73]	Joints/arthritis	CNN used to automate the segmentation and measurement of cartilage thickness based on MRIs of healthy knees
Xue *et al*[70]	Joints/arthritis	CNN model trained to diagnose hip OA comparable to an attending physician with 10 years of experience in diagnosing hip OA
Kruse *et al*[75]	Trauma	ML improved hip fracture detection beyond logistic regression using dual x-ray absorptiometry
Olczak *et al*[74]	Trauma	DL networks identified fracture, laterality, body part, and exam view on orthopaedic trauma radiographs of the hand, wrist, and ankle
Oh *et al*[78]	Oncology	ML showed superior predictive accuracy in predicting pathological femoral fractures in metastatic lung cancer

ML: Machine learning; CNN: Convolutional neural network; OA: Osteoarthritis.

DL through automated segmentation and detection of vertebrae. Numerous studies in the orthopaedic spine literature have analyzed the accuracy of DL techniques, especially for labeling and detection. For example, in Forsberg *et al*[62], annotated MRIs with information labels for each spine vertebrae were used to detect and label cervical and lumbar vertebrae. The highest performance showed an accuracy of 99.8% for detection and 97% for labeling. Furthermore, Pesteie *et al*[63] and Hetherington *et al*[64] used ANNs trained with ultrasound images to automatically detect optimal vertebra level and injection plane for percutaneous spinal needle injections; Pesteie *et al*[63] showed highest accuracy to be 95% and maximum precision to be 97%. ML and DL techniques have been shown to be useful in diagnosis as well. Jamaludin *et al*[65] used DL techniques to read T2 weighted sagittal lumbar MRI images, automate the identification of disc spaces, grade the degenerative changes such as spondylolisthesis and central canal stenosis, and compare them to what experienced radiologists would do (Figure 3). The DL model performed almost as well as experienced radiologists on test data with a best accuracy rate of 95% for the prediction of spondylolisthesis. Because this model did not require labeling and feature description, authors believe the model will gain more accuracy and reliability with the addition of coronal and axial views. Al-Helo *et al*[66] used ML techniques, specifically neural network and k-means approach, to learn lumbar wedge fracture diagnoses from CT image labeling for segmentation and prediction. The neural network showed an accuracy of 93.2% for lumbar fracture detection, while the k-means clustering approach attained an accuracy of 98%. These studies prove that the automation of radiologic grading is now on par with human performance; this can be incredibly beneficial in aiding clinical diagnoses in terms of grading and speed of analysis.

Joints/arthritis

OA, a highly prevalent disease associated with articular cartilage degeneration, can be effectively diagnosed in a cost-effective manner with X-ray imaging and in a more sensitive manner with MRI which can detect subtle morphologic changes in articular cartilage[67-69]. Throughout orthopaedic literature, DL has been used for hip and knee diagnostic purposes based on medical images. For the hip, Xue *et al*[70] trained a CNN with 420 hip X-ray images to highlight saliency regions. These saliency regions allow the deep learning model to extract the necessary information in order to diagnose hip OA (Figure 4). The CNN model was able to achieve an accuracy of 92.8%, comparable

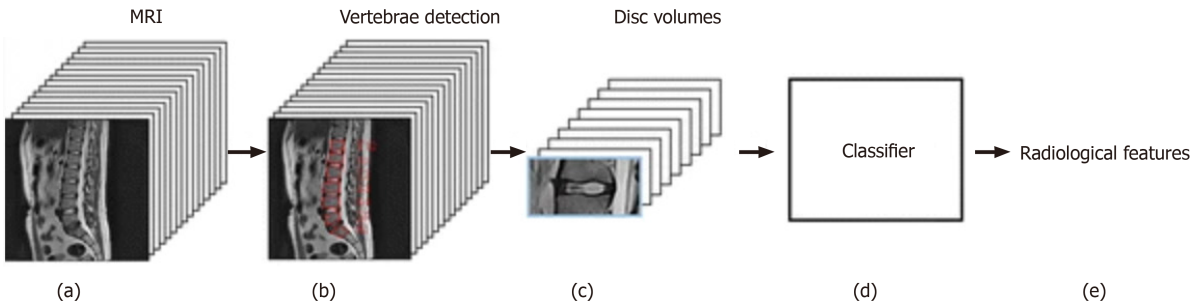

Figure 3 Input processing pipeline of T2 sagittal magnetic resonance imaging and output predictions of radiological features[65]. Reused with permission. Citation: Jamaludin A, Lootus M, Kadir T, Zisserman A, Urban J, Battié MC, Fairbank J, McCall I; Genodisc Consortium. ISSLS PRIZE IN BIOENGINEERING SCIENCE 2017: Automation of reading of radiological features from magnetic resonance images (MRIs) of the lumbar spine without human intervention is comparable with an expert radiologist. *Eur Spine J* 2017; 26: 1374-1383.

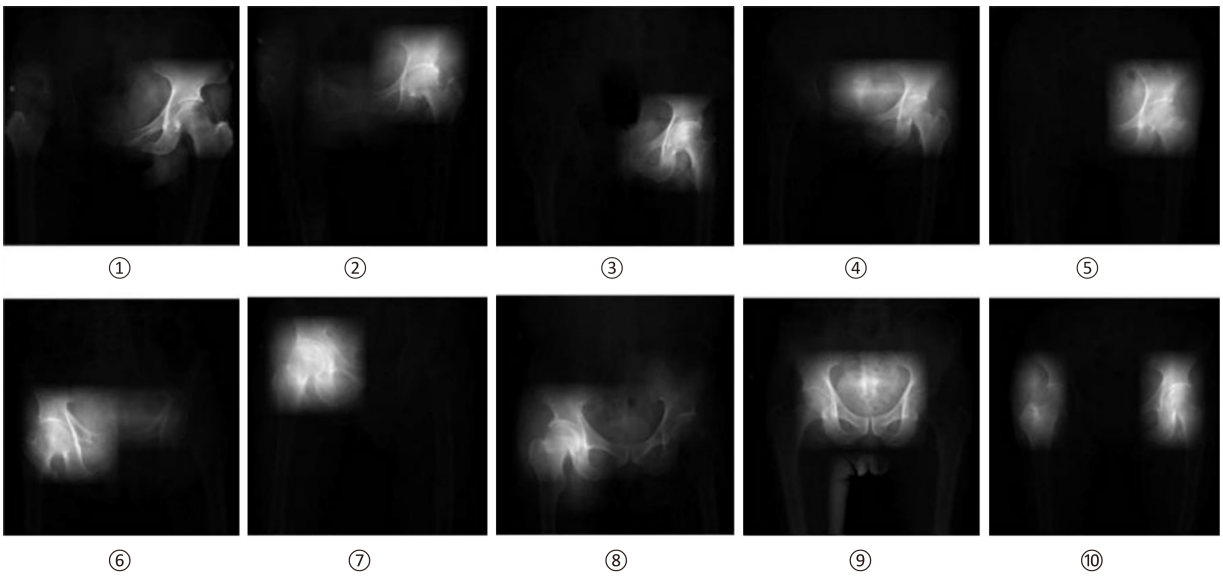

Figure 4 Saliency images from left hip joint (1-5), right hip joint (6-8), and both hip joints (9,10)[70]. Reused with permission. Citation: Xue Y, Zhang R, Deng Y, Chen K, Jiang T. A preliminary examination of the diagnostic value of deep learning in hip osteoarthritis. *PLoS One* 2017; 12: e0178992.

to an attending physician with ten years of experience in diagnosing hip OA. For the knee, Ashinsky *et al*[71] used a ML algorithm on T2 weighted maps of the central medial femoral condyle in order to predict progression to clinically symptomatic OA; the ML algorithm was able to predict the onset of OA with 75% accuracy. Liu *et al*[72] applied a CNN to a knee image data set for bone and cartilage segmentation and labeling (Figure 5). Authors reported a performance accuracy of 75.3% for femoral cartilage labeling and 78.1% for patellar cartilage labeling. Similar to Liu *et al*[72], Shah *et al*[73] used a CNN to successfully automate cartilage segmentation methods and measurement of articular cartilage thickness. This study showed that ML can be used to analyze cartilage thickness in an automated and efficient manner. The results of the studies summarized above indicate that DL has promising potential in the field of intelligent medical image diagnosis practice, especially for hip and knee OA.

Trauma

For orthopaedic trauma, ML derived tools can be used on imaging techniques to assist in diagnostic ability, particularly for detection of fractures. Olczak *et al*[74] applied ML to 256000 orthopaedic trauma radiographs with good results compared to radiologists. In this study, a database of hand, wrist, and ankle radiographs were used and four outcomes - laterality, exam view, fracture, and body part - were identified (Figure 6). Five DL networks were used and reached 99% accuracy when identifying body part, 90% on laterality, 95% on exam view, and 83% on detecting fractures[74]. Furthermore, Kruse *et al*[75] used ML to predict hip fractures from dual x-ray absorptiometry; they found that ML could improve hip fracture prediction beyond logistic regression. In

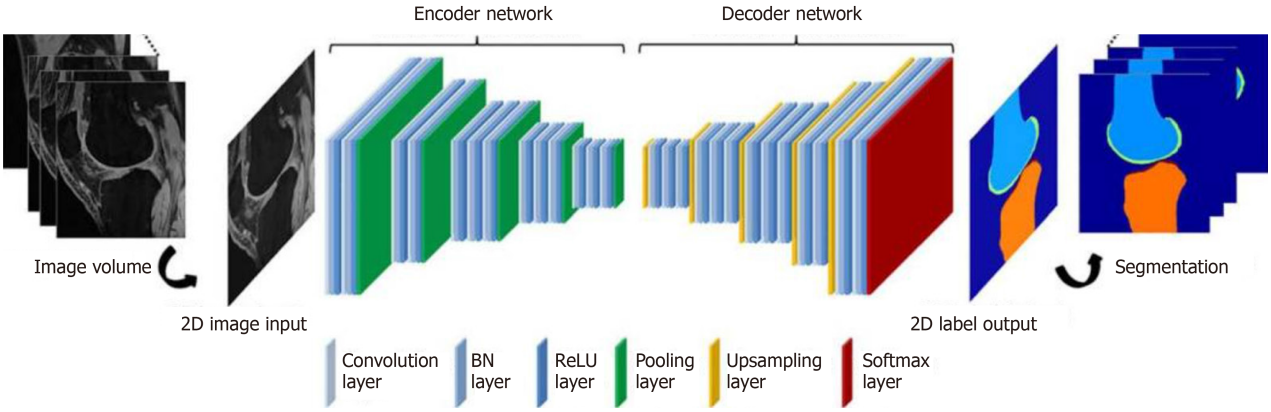

Figure 5 Convolutional neural network depiction of a knee image data set for bone and cartilage segmentation and labeling[72]. Reused with permission. Citation: Liu F, Zhou Z, Jang H, Samsonov A, Zhao G, Kijowski R. Deep convolutional neural network and 3D deformable approach for tissue segmentation in musculoskeletal magnetic resonance imaging. *Magn Reson Med* 2018; 79: 2379-2391.

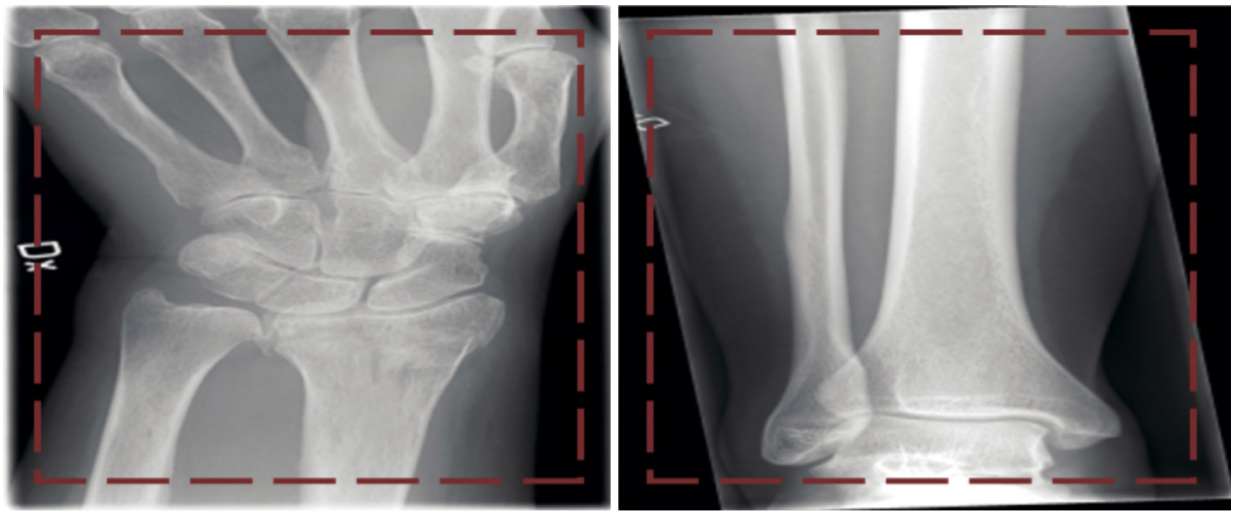

Figure 6 Two images (left, wrist fracture; right, no fracture) from the dataset presented to the network[74]. Reused with permission. Citation: Olczak J, Fahlberg N, Maki A, Razavian AS, Jilert A, Stark A, Sköldenberg O, Gordon M. Artificial intelligence for analyzing orthopedic trauma radiographs. *Acta Orthop* 2017; 88: 581-586.

orthopaedic trauma, ML based techniques have immense utility in predicting fractures. AI and ML based methods could be beneficial in the future of orthopaedic trauma as they may enhance workflow in the emergency department[76].

Oncology

In orthopaedic oncology, management of metastatic bone disease is a major focus, especially with respect to fracture and impending fracture care[77]. Oh *et al*[78] used ML on CT imaging and clinical features to extract radiologic features and derive predictions for pathological femoral fractures in metastatic lung cancer and compared the ML model with one that used CT features alone. The ML model, which included clinical features, showed superior predictive accuracy compared to the model that used CT features alone. By using AI and ML to accurately predict impending skeletal-related events, such as pathologic fracture, orthopaedic surgeons can prophylactically treat patients and thus improve patient outcomes[77].

BASIC SCIENCE APPLICATIONS

In the past, ML has been applied to basic science topics in medicine to predict chemical properties of drugs and proteins, predict vaccine immunogenicity, and identify promising drug targets[79-82]. In orthopaedic surgery, AI and ML has been applied to

Table 4 Summary of machine learning for orthopaedic surgery basic science applications

Ref.	Application	Conclusion
Begg *et al*[83]	Gait analysis	Used SVM to automate recognition of gait changes due to aging
Joyseeree *et al*[84]	Gait analysis	Used random forest, boosting, and SVM to identify disease on gait analysis data
Sikka *et al*[85]	Wearable technology	Utilized ML analytics *via* wearable technology to improve sports performance and identify risk factors for injury in sports
Cilla *et al*[86]	Implant design	ML techniques used to optimize short stem hip prosthesis to reduce stress shielding effects and achieve better short-stemmed implant performance

ML: Machine learning; SVM: Support vector machine.

more translational basic science concepts such as kinetics and gait analysis, wearable technology, and implant design[83-86] (Table 4).

It is well established in orthopaedic literature that aging influences various gait measures, such as gait velocity, stride length, and stance and swing phase times[87]. By applying ML to automate recognition of gait pattern changes, researchers can identify key variables of gait degeneration that might be predictors of falling behavior. Begg *et al*[83] used SVM, a specific ML approach, to automate recognition of gait changes due to aging using three types of gait measures: basic temporal/spatial, kinetic, and kinematic. When comparing gaits of twelve young participants to twelve elderly participants, the ML technique showed an overall accuracy of 91.7%. Furthermore, gait recognition improved when features were selected from different gait data types with an effective potential of 100% accuracy. Similarly, Joyseeree *et al*[84] applied ML algorithms, specifically random forest, boosting, and SVM, to gait analysis data for disease identification. Following a training and testing period, random forest and SVM had an accuracy of 100%, while boosting had an accuracy of 96.4%.

Another basic science application where ML has shown great promise is wearable technology. With the increase in wearable and portable technology, the general public as well as professional athletes have the power to monitor basic human physical and physiologic function that can combine with health records for analysis. *Sikka et al* used ML analytics *via* wearable technology such as camera-based monitoring systems, heart rate monitoring devices, radio-frequency identification tracking systems, and accelerometers, to improve sports performance[85]. Additionally, the data collected can be used to identify risk factors for injury in sports and therefore can proactively prevent injuries and direct injury prevention programs[85]. In the future, healthcare providers could utilize this information not only to develop optimal training programs for elite athletes while minimizing risk of injury and loss of play time, but also to create more cost-efficient care that is individually tailored for the average patient.

While shape optimization algorithms, which are different from ML, have previously been used to assess stem performance, the potential to further optimize short stem implants using ML has only recently been addressed[88-91]. For example, Cilla *et al*[86] used ANNs and SVMs to analyze four parameters with the end goal being to optimize short stem implant design, specifically for THA, to produce optimal performance, lack of bone resorption, and reduced stress shielding (Figure 7). They found that implants should be designed with a small stem length and a reduced length of the surface in contact with the bone to reduce stress shielding. The optimization approach using ML techniques can offer new and innovative possibilities in the design of hip implants and more. These analyses can be used to design new prostheses as well as aid orthopaedic surgeons in decision-making when choosing the most adequate implant.

CONCLUSION

In recent years, ML has garnered interest across various medical specialties and has proven its utility in orthopaedic surgery. Some studies even show that developed and validated ML models are capable of outperforming human specialists. Similarly, in orthopaedic surgery, ML has been incredibly useful in spine pathology detection, prosthesis control, gait classification, OA detection, and fracture detection. These

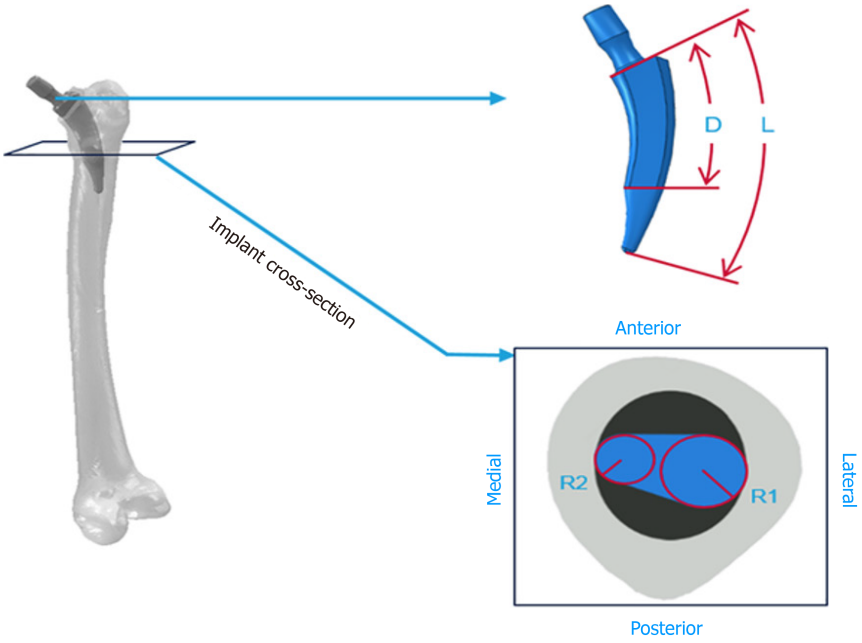

Figure 7 Graphic representation of the four parameters (*L*, total stem length; *R1*, radial circumference in the lateral side; *R2*, radial circumference in the medial; *D*, distance between the implant neck and the central stem surface)[86]. Reused with permission. Citation: Cilla M, Borgiani E, Martínez J, Duda GN, Checa S. Machine learning techniques for the optimization of joint replacements: Application to a short-stem hip implant. *PLoS One* 2017; 12: e0183755.

results corroborate the information that computers can outperform physicians in numerous tasks, even in orthopaedics. By and large, ML has diagnostic and prognostic uses that with continued research can offer more implications regarding orthopaedic treatment. With its surging trend of interest, AI and ML is expected to see an increase in use with risk assessment, outcomes assessment, imaging, and basic science applications in orthopaedics. Furthermore, because ML provides physicians the unique opportunity to understand their patients better, physicians should be trained to use these methods effectively in order to improve orthopaedic patient care.

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ORIGINAL ARTICLE

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Trends and risk factors for opioid administration for non-emergent lower back pain

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Informed consent statement: The present study utilized a publicly available database. Therefore,

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Abstract

BACKGROUND

Non-emergent low-back pain (LBP) is one of the most prevalent presenting complaints to the emergency department (ED) and has been shown to contribute to overcrowding in the ED as well as diverting attention away from more serious complaints. There has been an increasing focus in current literature regarding ED admission and opioid prescriptions for general complaints of pain, however, there is limited data concerning the trends over the last decade in ED admissions for non-emergent LBP as well as any subsequent opioid prescriptions by the ED for this complaint.

AIM

To determine trends in non-emergent ED visits for back pain; annual trends in opioid administration for patients presenting to the ED for back pain; and factors associated with receiving an opioid-based medication for non-emergent LBP in the ED

METHODS

Patients presenting to the ED for non-emergent LBP from 2010 to 2017 were retrospectively identified from the National Hospital Ambulatory Medical Care Survey database. The "year" variable was transformed to two-year intervals, and a weighted survey analysis was conducted utilizing the weighted variables to generate incidence estimates. Bivariate statistics were used to assess differences in count data, and logistic regression was performed to identify factors associated

with patients being discharged from the ED with narcotics. Statistical significance was set to a *P* value of 0.05.

RESULTS

Out of a total of 41658475 total ED visits, 3.8% (7726) met our inclusion and exclusion criteria. There was a decrease in the rates of non-emergent back pain to the ED from 4.05% of all cases during 2010 and 2011 to 3.56% during 2016 and 2017. The most common opioids prescribed over the period included hydrocodone-based medications (49.1%) and tramadol-based medications (16.9), with the combination of all other opioid types contributing to 35.7% of total opioids prescribed. Factors significantly associated with being prescribed narcotics included age over 43.84-years-old, higher income, private insurance, the obtainment of radiographic imaging in the ED, and region of the United States (all, $P < 0.05$). Emergency departments located in the Midwest [odds ratio (OR): 2.42, $P < 0.001$], South (OR: 2.35, < 0.001), and West (OR: 2.57, $P < 0.001$) were more likely to prescribe opioid-based medications for non-emergent LBP compared to EDs in the Northeast.

CONCLUSION

From 2010 to 2017, there was a significant decrease in the number of non-emergent LBP ED visits, as well as a decrease in opioids prescribed at these visits. These findings may be attributed to the increased focus and regulatory guidelines on opioid prescription practices at both the federal and state levels. Since non-emergent LBP is still a highly common ED presentation, conclusions drawn from opioid prescription practices within this cohort is necessary for limiting unnecessary ED opioid prescriptions.

Key Words: Opioids; Low back pain; Emergency Department; Spine; Complications; Trends

Core Tip: A trend of diminishing opioid prescription for low back pain in the emergency department can be appreciated over a span of eight years. Such a trend may be a reflection of policies and guidelines aiming at opioid regulation. Factors that may increase the likelihood of opioid prescription for low back pain include age over 43.84-years-old, higher income, private insurance, the obtainment of radiographic imaging in the emergency department, and presenting within the Midwest/South/West regions of the United States. Providers should be cognizant of such risk factors given the burden imposed by opioid prescriptions on the healthcare system.

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INTRODUCTION

Low back pain (LBP) is one of the most common healthcare complaints and musculoskeletal disorders seen in the emergency department (ED)[1,2]. The prevalence of LBP ranges from 49% to greater than 80% in the United States[3]. While non-emergent LBP can be treated by primary care physicians, studies suggest that patients will visit the ED for evaluation of symptoms, potentially leading to overcrowding and distracting from other serious health complaints[4,5]. Patients presenting to the ED for non-emergent LBP have been found to receive unnecessary imaging with excess radiation, be admitted to the hospital for pain control, or be given prescriptions of opioid pain medication[6-8].

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Studies have shown inconclusive results in the efficacy using opioids to treating patients for LBP, with worse outcomes at 6-month follow-up. Furthermore, studies have shown similar efficacy of opioids compared to non-opioid medications in the treatment of both acute and chronic LBP[9-12]. Within the past decade, opioid prescribing for non-cancer pain has increased dramatically, along with an increase in opioid abuse and resulting deaths[13-16]. Davies *et al*[16] analyzed opioid prescribing rates from January 2005 to December 2015, stratifying patients by age. Their findings revealed that opioid prescriptions in patients older than the age of 85 increased nearly 2-fold. The American College of Emergency Physicians recommends utilizing opioids in the ED only when pain is severe, debilitating, or refractory to other treatments[17]. Further guidelines were mandated by the American Academy of Emergency Medicine, recommending opioids as a second-line treatment[18]. Despite the calls for regulation, evidence of deviation from guideline recommendations persists. Indeed, Hayden *et al*[19] reported 5% of previously opioid-naïve patients who present to the emergency department for low back pain become prolonged opioid users.

Temporal trends of ED visits for LBP, opioid prescription patterns for non-emergent LBP, and patient factors associated with receiving an opioid prescription have not been well documented but are necessary to combat the continuing opioid epidemic in the United States. Therefore, the purpose of this study was to determine trends in non-emergent ED visits for back pain; annual trends in opioid prescriptions for patients presenting to the ED for back pain; and factors associated with receiving an opioid based prescription for non-emergent LBP in the ED

MATERIALS AND METHODS

Database and Patient Selection

This was a retrospective study. The National Hospital Ambulatory Medical Care Survey (NHAMCS) was reviewed between the years 2010 and 2017. The NHAMCS is publicly available and is designed to collect data on the utilization and provision of ambulatory care services in hospital, emergency, and ambulatory care departments. Data is obtained from a sample of visits to non-federally employed office physicians. Prior to 2012, NHAMCS relied on paper instruments; the survey switched to computerized data collection in 2012. Each physician is randomly assigned to a one-week reporting period. During this period, data for a systematic random sample of visits are recorded by United States Census interviewers using a computerized Patient Record form. The survey uses a four-stage probability design with samples of primary sampling units (PSUs), hospitals within PSUs, clinics and emergency service areas within hospitals, and patient visits within clinics and emergency service areas. More details on NHAMCS can be found at cdc.gov.

Patients were included if they presented to one of the aforementioned ambulatory care settings captured by the NHAMCS with a complain of back pain. Patients with back pain were identified using the following string codes as a chief complaint: (1) "Back symptoms"; (2) "Back pain, ache, soreness, discomfort"; (3) "Back cramps, contractures, spasms"; (4) "Low back pain, ache, soreness, discomfort"; and (5) "Low back cramps, contractures, spasms". Patients were excluded if they were under the age of 18 or were admitted for inpatient hospital stay.

Statistical analysis

A weighted survey analysis was conducted utilizing the weighted variables to generate incidence estimates. A chi-square analysis was performed to assess differences in count data. The "year" variable was transformed to two-year intervals as per the recommendations by the Center for Disease Prevention and Control[20]. Logistic regression analysis was conducted to identify factors associated with patients being discharged from the ED with narcotics. Group variables entered into our logistic regression model were removed if all group level's *P*-value exceeded 0.1. Presenting pain was discretized to the following categories: "Low" = 0 to 3; "moderate" = 4 to 6; and "severe" = 7 or more. A *P* value of 0.05 was set as the threshold for statistical significance. All statistical analysis was conducted using R statistical software (Vienna, Austria). The 'survey' package was utilized to analyze survey data.

RESULTS

Trends in presentation to the ED for non-emergent back pain

After implementation of inclusion and exclusion criteria, the study group included 7726 cases, which was 3.8% of the 41658475 total ED visits [95% confidence interval (CI): 34317928 to 48999021] (95%CI: 3.65% to 3.99%). There was a decrease in the rates of non-emergent back pain to the ED from 4.05% of all cases (95%CI: 3.81 to 4.31) during 2010 and 2011 to 3.56% (95%CI: 3.21 to 3.91) during 2016 and 2017 (Figure 1).

Incidence of opioid prescription at discharge for non-emergent LBP

Fifty-two percent of all cases that presented to the ED for non-emergent LBP were prescribed an opioid-based medication between 2010 and 2017 (95%CI: 49.9% to 54.0%). However, the rates of opioid-based prescriptions decreased between the period of 2010 and 2011 (55.9%; 95%CI: 52.9% to 58.9%) and the period of 2016 and 2017 (45.0%; 95%CI: 39.86% to 50.22%) (Figure 2). The most common opioids prescribed included hydrocodone-based medications (49.1% of all opioids prescribed; 95%CI: 46.3% to 52.0%) and tramadol-based medications (16.9% of all opioids prescribed; 95%CI: 14.8% to 19.0%), with the combination of all other opioid types contributing to 35.7% (95%CI: 32.6% to 39.0%) of total opioids prescribed.

Trend analysis revealed a decrease in the prescriptions of hydrocodone-based medications for non-emergent LBP patients presenting to the ED between the period of 2010 and 2011 (28.0%; 95%CI: 25.3% to 30.7%) to the period of 2016 and 2017 (19.3%; 95%CI: 15.6% to 23.1%). However, there was no notable change in the rates of non-emergent LBP patients that received tramadol or other opioid types (Figure 3).

Factors associated with opioid prescriptions

Estimated household income was associated with receiving an opioid base narcotic. When compared to patients coming from the lowest income quartile (below 32793 dollars annually), patients belonging to the third income quartile (40627 dollars to 52387 dollars annually) had higher odds of receiving an opioid based medication [odds ratio (OR): 1.35; 95%CI: 1.13 to 1.61; $P \leq 0.001$] (Table 1). Patients who were privately insured (OR: 1.29; 95%CI: 1.04 to 1.58; $P = 0.018$) or were self-payers (OR: 1.25; 95%CI: 1.00 to 1.56; $P = 0.048$) had higher odds of receiving an opioid based medication when compared to Medicaid patients. Other factors associated with being discharged with opioid based medications included if radiographic images were obtained (OR: 1.47; 95%CI: 1.30 to 1.66; $P < 0.001$), age greater than 43.94-years (OR: 1.01; 95%CI: 1.00 to 1.01; $P = 0.001$), and if patients reported having severe back pain (OR: 2.14; 95%CI: 1.63 to 2.81; $P < 0.001$). ED location was also significantly associated with opioid prescription for back pain. Emergency departments located in the Midwest (OR: 2.42; 95%CI: 1.94 to 3.01; $P < 0.001$), South (OR: 2.35; 95%CI: 1.91 to 2.88; $P < 0.001$), and West (OR: 2.57; 95%CI: 1.94 to 3.42; $P < 0.001$) all yielded greater odds of prescribing opioid-based medications for non-emergent LBP when compared to EDs in the Northeast region.

DISCUSSION

While it has been shown that the overall prescription rates of opioids within the United States are gradually decreasing over the past five years, there is a paucity of literature evaluating trends in opioid prescriptions specifically in patients presenting to the ED with non-emergent LBP[21]. Overall, our study reports a significant decrease in the number of non-emergent LBP ED visits from 2010 to 2017, as well as a decrease in opioids prescribed at these visits. Furthermore, we noted several independent risk factors for increased opioid prescription following non-emergent LBP, including age over 43.84-years-old, higher income, private insurance, the obtainment of radiographic imaging in the ED, and region of the United States.

Our findings are consistent with previous literature demonstrating an overall decrease in ED opioid prescriptions[22-25]. Marra *et al*[22] analyzed NHAMCS information from 2005 to 2015 for patients presenting to the ED with pain of all causes, finding that prescribing rates at discharge decreased significantly by 32% during the study duration[22]. Since pain is one of the most common reasons for ED visits, a major limitation of Marra *et al*[22] study was grouping pain causes into a single cohort. The decrease in opioid prescriptions for non-emergent LBP found in our study was representative of the overall decrease in ED opioid prescriptions for general pain over a similar time interval as established by Marra *et al*[22]. As such, our findings provide

Table 1 Risk factors associated with emergency department opioid-based medication prescription for non-emergent low back pain

	Odds ratio	Lower 95%CI	Upper 95%CI	*P* value
Home income [quartile 1 (below 32793 dollars)]	Reference			
Home income [quartile 2 (32794-40626 dollars)]	1.17	0.98	1.40	0.078
Home income [quartile 3 (40627-52387 dollars)]	1.35	1.13	1.61	0.001
Home income [quartile 4 (52388 dollars or more)]	1.11	0.91	1.34	0.318
Insurance				
Medicaid	Reference			
Medicare	1.03	0.84	1.28	0.753
Other	1.38	0.71	2.67	0.337
Private insurance	1.29	1.04	1.58	0.018
Self-pay	1.25	1.00	1.56	0.048
Workers compensation	1.10	0.72	1.70	0.660
Images obtained	1.47	1.30	1.66	< 0.001
Mean centered age	1.01	1.00	1.01	0.001
Pain-low	Reference			
Pain-moderate	1.28	0.96	1.71	0.093
Pain-severe	2.14	1.63	2.81	< 0.001
Seen in ED within the last 72 hr	0.77	0.56	1.06	0.106
United States Census Region				
Northeast	Reference			
Midwest	2.42	1.94	3.01	< 0.001
South	2.35	1.91	2.88	< 0.001
West	2.57	1.94	3.42	< 0.001

ED: Emergency department; CI: Confidence interval.

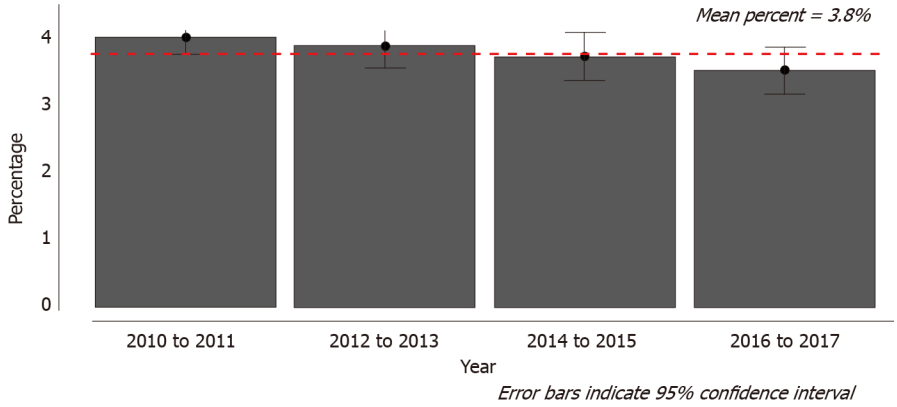

Figure 1 Incidences of non-emergent lower back pain that present to the emergency department between 2010 and 2017.

needed granularity in terms of specifically the non-emergent LBP population presenting to the ED

In elderly individuals, non-emergent LBP has been shown to have a prevalence ranging from 21.7% to 75%, with a direct correlation between age and LBP[26]. Our findings suggest that older age is an independent risk factor for increasing opioid prescriptions following ED admission for LBP, which may perhaps be due to older individuals presenting with increased severity of back pain. Severity of non-emergent

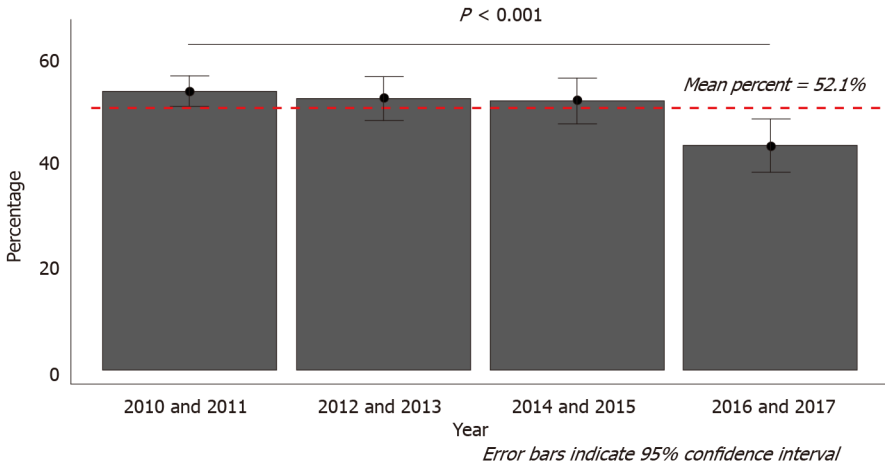

Figure 2 Percent of cases who presented to the emergency department with non-emergent back pain, that were prescribed opioid based medications upon discharge between 2010 and 2017.

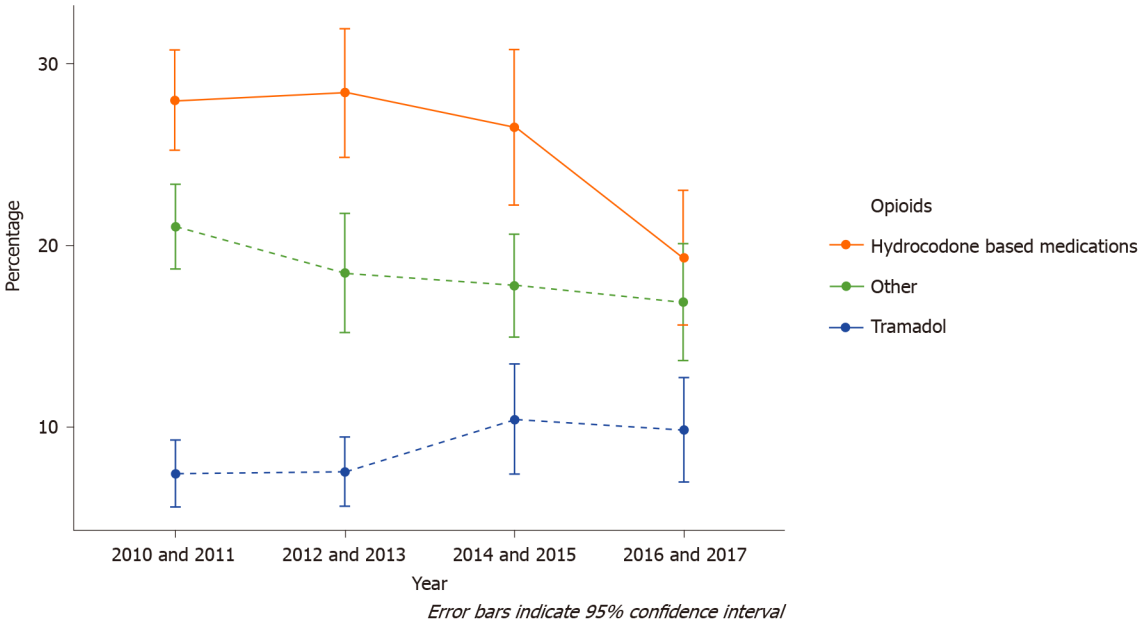

Figure 3 Types of opioids prescribed for non-emergent back pain that presented to the emergency department.

LBP is known to be highly correlated with increasing age, particularly relative to other common causes of opioid prescriptions following ED admission such as pain secondary to trauma[27,28]. This increased LBP severity in older patients likely contributed to the increased opioid prescriptions in older patients shown in our analysis.

In particular, our study found age over 43.84-years to be an independent risk factor for opioid pres-criptions in non-emergent LBP patients. However, the direct relationship between age and ED opioid prescriptions found in our study has not been demonstrated for all chief complaints presenting to the ED For instance, Ward *et al*[24] utilized the Data to Intelligence database aggregating electronic health record data from EDs within the United States from January 1, 2014 to May 31, 2014, and found no direct relationship between increasing age and opioid prescription. In their study, patients between the ages of 18 to 27 had the highest adjusted odds ratio (OR: 1.09) of being discharged with an opioid prescription, followed by patients between the ages of 40 to 54 (OR: 1.08), and lastly between the ages of 28 to 39 (OR: 1.02)[24]. Ward *et al* [24] studied all ED admissions, not limited to back pain, and attempted to account for variations in chief complaints utilization a categorization approach, however, the authors acknowledged remaining heterogeneity in terms of the chief complaints in their dataset. In comparison, our study only included patients presenting with non-

emergent LBP, such that the chief complaints were entirely homogenous, which contributed to the direct correlation we found between age and ED opioid prescriptions in non-emergent LBP patients.

With respect to insurance status, Ali *et al*[29] reported that 8% of patients with private insurance had potentially problematic opioid prescriptions, compared to 14% of patients with Medicaid. Problematic opioid prescription was defined in their study as opioid prescriptions which did not match the indication severity based on protocol established in previous literature[29]. Although our study did not address problematic opioid prescriptions, we did find that patients with private insurance or who were self-payers were more likely to be prescribed an opioid for non-emergent LBP compared to Medicaid patients.

In terms, of the Medicaid population specifically, Janakiram *et al*[25] performed a multistate analysis utilizing the Truven Marketscan Database from 2013 to 2015 and found Medicaid patients were more likely to receive prescriptions from an ED provider compared to a general practitioner, with back pain (14%) being the third leading cause for receiving an opioid prescription. Implementation of prior authorization plans within Medicaid plans has shown to not only minimize opioid-related morbidity within this cohort, but also discourage the initiation of long-acting opioid therapy[30,31]. Interestingly, studies have shown patients who present to the ED could be more appropriately managed by their primary care physician, which would potentially driving down ED visits. These studies demonstrate that adequate care reduces annual ED visits and decreases healthcare expenditure[32-34], therefore, lack of access to primary care may be the driving force of increasing patient visits to the ED especially for non-emergent indications such as LBP[35-37]. In other words, limited access to various primary care is likely associated with increased ED visits in patients with underlying mental and physical comorbid conditions.

Extended access primary care services have also been shown to decreased the amount of ED visits as well as pain prescriptions for non-emergent presentations[33]. Extended access primary care services offer patients the ability to book appointments outside of core contractual hours, either in the early morning, evening or at weekends. Whittaker *et al*[33] measured the impact of extended access in 56 primary care practices by offering seven-day extended access through providing care during the evenings and weekends, compared to 469 primary care practices with routine working hours. Implementing this extended access of care demonstrated a reduction in both the frequency and cost of patient-initiated ED visits for "minor" problems[33]. The majority of non-emergent LBP fits within this categorization of "minor" problems, so it is possible that more widespread extended access primary care services have the potential to reduce ED admissions and opioid prescriptions.

LBP has also been shown to be more prevalent and severe in older men compared to older women. Interestingly, our study found no difference in opioid prescriptions between men and women presenting to the ED with non-emergent LBP[38].

Finally, numeric pain scores have been implicated in contributing to the prescribed opioid epidemic, with opioids being administered to those who report higher pain scores[39]. In a recent cross-sectional study, Monitto *et al*[40] explored the association of patient factors with opioid dispensing, consumption, and medication remaining on completion of therapy after hospital discharge. Their findings suggest higher discharge pain scores can predict higher opioid dispensing and consumption. This is consistent with our findings as increasing pain scales was significantly associated with discharge from the ED with an opioid prescription. With further validation, these pain scales can be potentially utilized to predict and ultimately standardize the number of opioids patients presenting to the ED with non-emergent LBP should be prescribed.

This study has a few limitations which must be considered when interpreting our results, most of which are inherent to the use of an administrative database. First, recent studies have addressed concern regarding the validity of the NHAMCS database due to slight variability in documentation across the years[41]. Our study limited this potential issue by purposely utilizing variables that were collected in a consistent fashion over the years studied. Second, since information from the database is ascertained from individual ED visits, the study did not allow for longitudinal information on these patients or allowing us to determine the appropriateness of therapy[22]. For example, we were unable to identify patients with a history of substance abuse. However, this limitation does not preclude the validity of our findings as our study methodology included only cases of non-emergent back pain that presented to the ED and did not warrant admission. Finally, our study assessed data from 2010 to 2017, as this was the only time interval available from NHAMCS. Despite these limitations, the study provides valuable information regarding annual trends in ED visits for back pain, prescribing patterns, and patient risk factors for

being discharged with an opioid prescription.

CONCLUSION

Despite legislative efforts to improve access to care, ED continue to be burdened by non-emergent maladies such as LBP. Our study demonstrated a significant decrease in number of patients presenting to the ED with non-emergent LBP between 2010 and 2017, as well as a significant decrease in opioids prescribed in the ED for this indication of the same time period. Regression analysis identified age over 43.84-years-old, higher income, private insurance, the obtainment of radiographic imaging in the ED, and region of the United States as independent risk factors for being discharged with prescription narcotics after presenting to the ED for LBP. Emergency departments located in the Northeast region were the least likely to discharge patients with narcotics. Ultimately, physician-directed patient education is necessary to minimize ED burden by non-emergent LBP, and a heightened awareness of previous narcotic prescribing practices is needed to mitigate narcotic prescriptions for patients presenting to the ED with non-emergent LBP. Future prospective studies are necessary to determine the impact of state and federal legislative mandates on the influence of opioid prescriptions given at discharge.

ARTICLE HIGHLIGHTS

Research background

Low back pain a major cause of emergency department (ED) visits and ranges in incidence between 49% and 80% in the United States. Patients presenting to the ED for non-emergent LBP often receive unnecessary prescriptions of opioid pain medication.

Research motivation

Several guidelines have been implemented to mitigate opioid prescription for low-back pain. However, the impact of such guidelines is yet to be ascertained.

Research objectives

This study aimed to outline the trends of annual opioid prescriptions for patients presenting to the ED with non-emergent back pain; and risk factors associated with being prescribed an opioid based prescription for non-emergent LBP in the ED.

Research methods

We reviewed the National Hospital Ambulatory Medical Care Survey for all patients who presented to the ED with low back pain. Patients over 18 years of age who were not subsequently admitted were included. The primary outcome was opioid-based medication prescription. Trends and factors of opioid-based medication prescription were evaluated to identify chronological and patient-specific risk factors.

Research results

We reviewed the National Hospital Ambulatory Medical Care Survey for all patients who presented to the ED with low back pain. Patients over 18 years of age who were not subsequently admitted were included. The primary outcome was opioid-based medication prescription. Trends and factors of opioid-based medication prescription were evaluated to identify chronological and patient-specific risk factors.

Research conclusions

Overall opioid prescription demonstrated a mild decrease over the past decade; however, a pattern of diminished hydrocodone-based medications is associated with a mild increase in tramadol-based medication prescription. This pattern may be due to recent legislative guidelines.

Research perspectives

Further research is required to identify future trends that may be a more veritable reflection of more recent policies regulating opioid prescription for low back pain – particularly tramadol based medications.

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ORIGINAL ARTICLE

Retrospective Study

Correlation of stress radiographs to injuries associated with lateral ankle instability

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Abstract

BACKGROUND

Stress radiographs have demonstrated superior efficacy in the evaluation of ankle instability.

AIM

To determine if there is a degree of instability evidenced by stress radiographs that is associated with pathology concomitant with ankle ligamentous instability.

METHODS

A retrospective review of 87 consecutive patients aged 18-74 who had stress radiographs performed at a single institution between 2014 and 2020 was performed. These manual radiographic stress views were then correlated with magnetic resonance imaging and operative findings.

RESULTS

A statistically significant association was determined for the mean and median stress radiographic values and the presence of peroneal pathology (P = 0.008 for tendonitis and P = 0.020 for peroneal tendon tears). A significant inverse relationship was found between the presence of an osteochondral defect and increasing degrees of instability (P = 0.043).

CONCLUSION

Although valuable in the clinical evaluation of ankle instability, stress radiographs are not an independent predictor of conditions associated with ankle in-stability.

Key Words: Ankle stress radiographs; Lateral ankle instability; Osteochondral defect;

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Core Tip: Ankle Stress Radiographs were predictive of intraoperative findings. Specifically, they may assist the surgeon in clinical decision making regarding osteochondral lesions of the talus and peroneal tendon pathology.

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INTRODUCTION

Ankle instability is one of the most common sports related injuries with an incidence of 7 per 1000 persons per year[1]. Close to 40% of patients who sustain an inversion injury to their ankle report residual symptoms long after they have recovered from the injury to their lateral ligaments. This residual pain may be secondary to associated conditions that occur at the time of the injury or as a result of chronic instability[2]. The differential diagnosis for associated injuries or causes of residual symptoms is large and includes: occult fractures of the ankle, fractures of the metatarsals, peroneal tendon tears, osteochondral lesions of the talus (OLT), tarsal coalitions, neurogenic injuries, radicular pain, autonomic dysreflexia, impingement, syndesmotic injuries, and subtalar instability. Determining which symptoms are related to ligamentous injury and which symptoms are related to associated conditions can be a diagnostic dilemma. Clinicians use multiple resources to determine which patients have symptoms secondary to ligamentous instability at the tibiotalar joint *vs* symptoms related to other causes. Plain radiographs are often the first modality utilized and radiographs of the ankle and foot can rule out fractures. Unless there is frank instability, a superior retinaculum avulsion, or a large osteochondral fracture, static radiographs do not provide much information on the integrity of the lateral ligaments or associated conditions. Stress radiographs can provide information on the dynamic stability of the tibiotalar joint are often obtained in the evaluation of ankle instability. Previous studies have demonstrated that stress radiographs are more specific than magnetic resonance imaging (MRI) in the evaluation of ligamentous instability[3]. Ultrasound and MRI have a role in evaluating for associated injuries such as chondral injuries and tendon pathology. While being a highly sensitive modalities, MRI has also been shown to miss 20%-80% of associated injuries[4,5]. It would be ideal to have one imaging study that could assist the surgeon in making the diagnosis of instability and at the same time rule out or rule in associated pathology. Since stress radiographs have demonstrated superior efficacy in the evaluation of ankle instability, the purpose of this study is to determine if there is a degree of instability evidenced by stress radiographs that is associated with OLTs and peroneal pathology concomitant with ankle ligamentous instability.

MATERIALS AND METHODS

A retrospective review of consecutive patients aged 18-74 who had stress radiographs performed at a single institution between 2014 and 2020 was performed. Once the patients with documented stress radiographs were identified, the electronic medical record was utilized to collect the following information: degree of widening on the talar tilt stress radiograph, millimeters of anterior translation on the anterior drawer stress radiograph, presence of an OLT on MRI or noted in the operation report if an operation was performed, presence of a peroneal tendon tear or tendonitis noted on the MRI or in the operation report, and documentation of operative management of an OLT or peroneal tendon. All patients who had a stress radiograph performed were

included in the study. The presence of operative instability was not an inclusion or exclusion criteria.

Stress radiographs were performed manually. Although various providers performed the radiographs, the technique was standardized. An example of a stress radiograph is seen in Figure 1. An initial mortise film was obtained prior to the talar tilt stress view. Once the mortise was aligned, the tibia was held to maintain the mortise while an inversion force was applied to the ankle. Verification of an appropriate mortise view was obtained. The anterior drawer was obtained by first verifying that a perfect lateral of the talus was visible on digital radiography. The tibia was then held in the same alignment and an anterior force was applied to the calcaneus. Verification of the lateral was obtained. All stress radiographs were routinely measured by a board-certified radiologist unaffiliated with the study. An example of the technique utilized to measure the stress radiographs is demonstrated in Figure 2.

The associated findings to include OLTs and peroneal pathology were determined from the MRI reports and operative reports. All MRI reports were read by board certified radiologists unaffiliated with the study. Operative findings were obtained from the dictated operation reports. Because continuous data were not normally distributed, statistical analysis was performed with a nonparametric Wilcoxon Rank Sum Test to assess differences in median levels of anterior drawer and talar tilt angel between patients with and without selected outcomes. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, United States).

RESULTS

There were 87 patients meeting inclusion criteria including 14 females and 73 males. The mean talar tilt was 8.6° (range 0-25). The mean anterior drawer was 4.6 mm (range 0-9.9 mm). Peroneal tendonitis was documented in 22 patients (25%). Peroneal tendon tears were documented in 6 patients (7%). An OLT of any size was documented in 42 patients (48%). An OLT greater than 1 cm in its largest diameter was documented in 16 patients (18%). Operative management of an OLT to include microfracture or chondroplasty was performed in 35 patients (40%). Cartilage restoration with Biocartilage or DeNovo NT allograft was performed in 7 patients (8%). An operative exploration of the peroneal tendons was performed in 19 patients (22%). A peroneal tendon repair was required in 2 patients (2%). A lateral ligament repair or modified Broström procedure was performed in 64 patients (74%).

In order to evaluate the relationship between associated findings and stress view values, unpaired *t*-tests were utilized to evaluate mean differences in anterior drawer and talar tilt between patients with and without selected outcomes. There were no statistical associations based upon the anterior drawer as depicted in Table 1. By contrast, the talar tilt angle was associated with several outcomes. Patients with the diagnosis of peroneal tendonitis had a larger talar tilt on average than patients without peroneal tendonitis (mean = 11.8° *vs* 7.5°, $P = 0.004$). Similarly, patients with peroneal tears also had larger tilt angles on average than those without tears (mean = 13.8° *vs* 8.2°, $P = 0.026$). The remainder of associations are depicted in Table 2.

Tables 3 and 4 summarize results of nonparametric analyses to assess differences in median levels of anterior drawer and talar tilt, respectively, between patients with and without selected reasons for surgery. For anterior drawer, the evaluation shows an inverse relationship found between the degree of instability as measured on the anterior drawer image and the presence of an OLT. Patients who had an OLT had a median anterior drawer of 4.1°, while patients without an OLT had an anterior drawer measurement of 5.1°, $P = 0.035$.

For talar tilt, several significant findings are noted. Larger degrees of tilt were seen in patients who had peroneal tendonitis or peroneal tendon tears, and an inverse relationship was found between the degree of instability and the presence of an OLT. Patients with an OLT had a median talar tilt of 6° while patients without an OLT had a median talar tilt of 9°, $P = 0.039$. Large OLTs were evaluated separately from all OLTs and patients who had a large OLT of greater than 1 cm in diameter were found to have a talar tilt median of 3° while patients who did not have a large OLT were found to have a talar tilt of 8°, $P = 0.025$. As the senior surgeon utilized 9° of instability as an operative indication for a lateral ligament repair or Broström procedure, the data set confirms that selection criteria when utilizing both the mean and median values.

For each area of pathology that had a significant difference found for the mean or median values on stress radiographs, predictive statistics were performed to include

Table 1 Anterior drawer (mean ± SD)

Outcome	Outcome = No			Outcome = Yes			*P* value
	n	mean	SD	*n*	mean	SD	
Peroneal tendonitis	65	4.5	2.7	22	4.9	3.2	0.533
Peroneal tear	81	4.7	2.7	6	3.4	4.0	0.251
MRI OLT	45	5.0	3.0	42	4.2	2.5	0.206
MRI OLT < 1 cm	61	4.9	2.9	26	3.9	2.4	0.107
MRI > 1 cm	71	4.6	2.9	16	4.8	2.6	0.791
Broström	23	4.7	2.2	64	4.6	3.0	0.805
Operative peroneal exploration	68	4.7	2.8	19	4.4	2.8	0.675
Operative peroneal repair	85	4.6	2.8	2	5.8	1.7	0.548
Operative OLT microfracture/chondroplasty	52	5.1	2.8	35	3.9	2.7	0.066
Operative OLT restoration/repair	80	4.6	2.9	7	4.9	1.8	0.753

MRI: Magnetic resonance imaging; OLT: Osteochondral lesions of the talus.

Table 2 Tilt angle (mean ± SD)

Outcome	Outcome = No			Outcome = Yes			*P* value
	n	mean	SD	*n*	mean	SD	
Peroneal tendonitis	65	7.5	5.4	22	11.8	6.7	0.004
Peroneal tear	81	8.2	6.0	6	13.8	4.4	0.026
MRI OLT	45	9.8	6.0	42	7.3	5.8	0.051
MRI OLT < 1 cm	61	8.8	6.3	26	8.1	5.4	0.610
MRI > 1 cm	71	9.2	5.8	16	6.0	6.4	0.057
Broström	23	3.3	3.3	64	10.5	5.6	< 0.001
Operative peroneal exploration	68	8.3	6.0	19	9.7	6.0	0.372
Operative peroneal repair	85	8.6	6.0	2	10.0	8.5	0.739
Operative OLT microfracture/chondroplasty	52	9.1	6.2	35	7.8	5.8	0.339
Operative OLT restoration/repair	80	9.0	6.0	7	4.4	4.9	0.057

MRI: Magnetic resonance imaging; OLT: Osteochondral lesions of the talus.

sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV). The results of this analysis are listed in Tables 5 and 6. Initial analysis of the talar tilt was performed using 10° as the threshold value as seen in Table 5. Given the significant inverted association demonstrated for OLTs and the anterior drawer stress radiograph, predictive analysis was performed for the anterior drawer test utilizing 5° as the threshold as seen in Table 6. Predictive statistics were not performed for the Broström procedure as the surgical candidates were selected largely based upon the stress radiographic results which resulted in the significant association between the Broström procedure and larger values on stress radiographs. In addition, predictive statistics were not performed for OLTs as a significant inverse relationship was demonstrated.

DISCUSSION

The lateral ligaments of the tibiotalar joint do not provide stability to the joint in isolation. The bony architecture of the tibiotalar joint contributes to its stability with

Table 3 Anterior drawer median and inter quartile range

Outcome	Outcome = No			Outcome = Yes			*P* value
	n	Median	IQR	*n*	Median	IQR	
Peroneal tendonitis	65	4.5	3.0-6.6	22	4.8	4.0-7.0	0.487
Peroneal tear	81	4.6	3.3-7.0	6	2.1	0.0-7.0	0.318
MRI OLT	45	5.2	2.7-7.5	42	4.3	3.0-5.6	0.110
MRI OLT < 1 cm	61	5.1	3.3-7.1	26	4.2	3.0-5.0	0.062
MRI > 1 cm	71	4.6	2.7-7.0	16	4.7	3.7-6.9	0.891
Broström	23	4.7	4.0-6.9	64	4.5	2.4-7.1	0.870
Operative peroneal exploration	68	4.9	3.3-6.9	19	4.3	2.7-7.0	0.550
Operative peroneal repair	85	4.5	3.0-7.0	2	5.8	4.6-7.0	0.514
Operative OLT microfracture/chondroplasty	52	5.1	3.7-7.2	35	4.1	2.7-5.6	0.035
Operative OLT restoration/repair	80	4.5	2.9-7.0	7	4.8	4.0-6.9	0.827

MRI: Magnetic resonance imaging; OLT: Osteochondral lesions of the talus; IQR: Inter quartile range.

Table 4 Tilt angle median and inter quartile range

Outcome	Outcome = No			Outcome = Yes			*P* value
	n	Median	IQR	*n*	Median	IQR	
Peroneal tendonitis	65	7	3-12	22	12	6-18	0.008[1]
Peroneal tear	81	8	3-12	6	15	10-16	0.020[1]
MRI OLT	45	9	5-14	42	6	2-13	0.043[1]
MRI OLT < 1 cm	61	8	3-14	26	8	3-13	0.763
MRI > 1 cm	71	8	4-13	16	3	1-10.5	0.025[1]
Broström	23	3	1-4	64	10	6.5-14	< 0.001[1]
Operative peroneal exploration	68	8	3-12	19	11	4-15	0.318
Operative peroneal repair	85	8	3-13	2	10	4-16	0.670
Operative OLT microfracture/chondroplasty	52	8	4-13	35	7	3-13	0.360
Operative OLT restoration/repair	80	8	3.5-13	7	3	1-6	0.039[1]

[1]Significant difference. MRI: Magnetic resonance imaging; OLT: Osteochondral lesions of the talus; IQR: Inter quartile range.

the talus widest anteriorly making the joint most stable in dorsiflexion[6]. In plantarflexion, the fibula internally rotates and moves inferiorly to maintain the stability of the mortise[7]. In addition to the syndesmotic ligaments, the tibiotalar joint is constrained medially by the deltoid ligamentous complex and laterally through the collateral ligament complex. Dynamic stability of the tibiotalar joint is provided by the surrounding extrinsic musculature. The tibialis anterior, extensor hallucis longus, extensor digitorum longus, and peroneal tertius contribute to dorsiflexion in the anterior compartment. Within the compartment, the tibialis anterior and extensor hallucis longus also contribute to inversion. This is balanced by the peroneal tertius which provides eversion in addition to dorsiflexion. In the lateral compartment, the peroneal longus and brevis both contribute to eversion which helps to mitigate inversion stresses across the ankle. Posteriorly, the tibialis posterior, flexor digitorum longus, and flexor hallucis longus all help to produce ankle inversion in conjunction with plantar flexion due to the oblique rotational axis of the tibiotalar joint[6].

Given that the lateral ligaments do not provide stability to the ankle in isolation, it follows that the lateral ligaments are not injured in isolation. Clinical studies have demonstrated that that ankle instability occurs with associated pathology such as

Table 5 Initial analysis of the talar tilt

	Talar tilt ≥ 10°	Talar tilt < 10°	Sn (%)	Sp (%)	PPV (%)	NPV (%)
Peroneal tendonitis	13/35	9/52	59	66	37	83
Peroneal tear	5/35	1/52	83	63	14	98
Any peroneal pathology	14/35	10/52	58	67	40	81
Any OLT	15/35	27/52	36	56	43	48

The sensitivity, specificity, positive predictive value, and negative predictive value are documented for the presence or absence of peroneal pathology in relationship to the talar tilt stress radiograph. Note that given the significant inverse relationship found between osteochondral lesions of the talus and stress radiographs, the predictive statistics were inverted as well utilizing a positive test as being a talar tilt < 10°. Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; OLT: Osteochondral lesions of the talus.

Table 6 The anterior drawer test

	Anterior drawer < 5 mm	Anterior drawer ≥ 5 mm	Sn (%)	Sp (%)	PPV (%)	NPV (%)
OLT	30	13	70	57	64	68

The sensitivity, specificity, positive predictive value, and negative predictive value are documented for the presence or absence of peroneal pathology in relationship to the anterior drawer stress radiograph. Note that given the significant inverse relationship found between osteochondral lesions of the talus and stress radiographs, the predictive statistics were inverted as well utilizing a positive test as being an anterior drawer < 5 mm. Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; OLT: Osteochondral lesions of the talus.

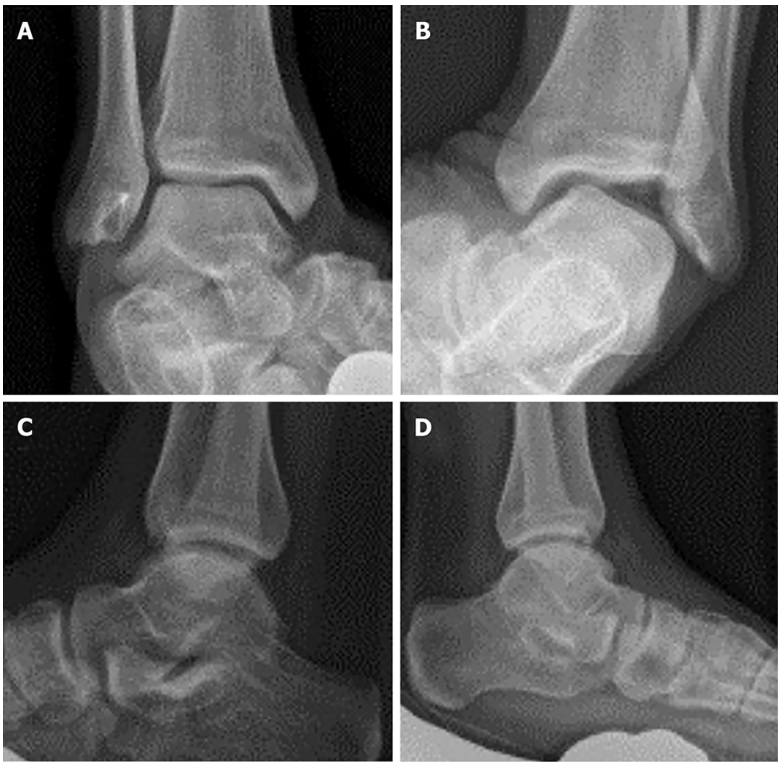

Figure 1 Stress radiographs. A: An example of a stable ankle which has previously undergone a modified Broström procedure is depicted; B: The contralateral ankle demonstrating instability on the talar tilt examination is depicted; C and D: The corresponding anterior drawer stress radiographs.

peroneal tendinopathy in up to 28% of cases[8]. Peroneal tendinopathy is considered to be an overuse injury related to inflammatory and degenerative changes[9]. In theory, chronic lateral ligament insufficiency may lead to overuse of the peroneal tendons as the peroneal longus and brevis provide dynamic support to the ankle. Our findings were consistent with this as we found a significant increase in peroneal

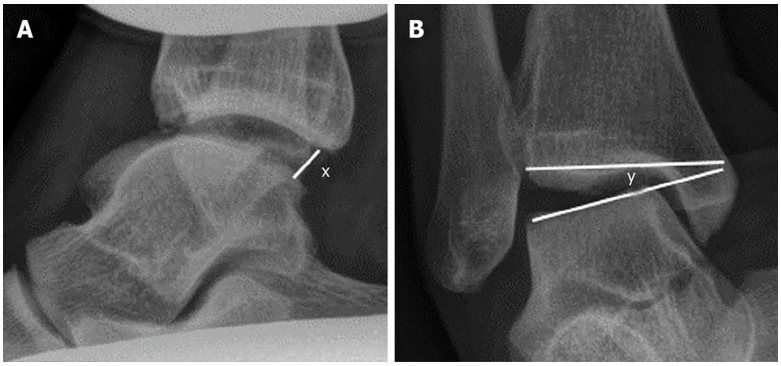

Figure 2 The measurements for stress radiographs are depicted here. A: The anterior drawer distance is obtained by drawing a line from the most posterior aspect of the distal tibial plafond to a point on the talus that is perpendicular to the articular surface of the talus. The distance 'x' is measured in millimeters; B: The anterior drawer is depicted. In order to measure the anterior drawer one line is drawn along the distal articular surface of the tibia and a second line is drawn along the proximal articular surface of the talus. The angle 'y' formed by the intersection of these two lines is the talar tilt angle and is measured in degrees.

tendonitis in patients who had a talar tilt of 11.8° when compared to patients who had a mean talar tilt of 7.5°.

Split tears of the peroneal brevis tendon are relatively common. A cadaveric study without clinical correlation found a prevalence of split tears in 37.5% of the 112 ankles evaluated[10]. Peroneal muscles are the first muscles to respond and contract in response to ankle inversion[11]. In theory, increasing inversion of an ankle secondary to ligamentous instability could place an increasing strain upon the peroneal tendons. In a review of 180 open ankle lateral ligament repair procedures, Strauss *et al*[8] found 51 (28%) ankles with a peroneal tendon injury. The authors did not further break down the type of injuries found or the treatment provided. Our study found that peroneal tendon tears occurred in patients with a mean talar tilt of 13.8° and was not seen in patients with a mean talar tilt of 8.2°. This data would suggest that increasing degrees of instability may be associated with an increasing incidence of peroneal tendon tears.

Classic imaging studies of peroneal pathology can include plain radiographs, ultrasound, computed tomography (CT), and MRI. Data from plain radiographs is limited in regard to peroneal pathology unless a 'fleck' sign is visualized which is pathognomonic for a superior peroneal retinaculum avulsion. Aside from evaluating associated osseous pathology, CT scan has a limited role in the evaluation of peroneal tendons. Ultrasound is provider dependent but has been shown to accurately predict peroneal tendon tears in 90% of cases[12]. MRI is commonly utilized and can document peroneal tendosynovitis or tears. The artifact that occurs as the tendons curve around the lateral malleolus, however, can decreased the sensitivity to 80% and the specificity to 75%[13].

Although we were able to find an association between larger degrees of instability and the presence of peroneal pathology, we were not able to find a degree of instability that was predictive of instability. Threshold values of 10 mm on the anterior drawer test or 10° on the talar tilt test have been found to correlate with clinical instability[14]. We evaluated the statistical performance of stress radiographs in terms of peroneal pathology. Since the mean talar tilt associated with peroneal tendonitis was 11.8°, and the mean talar tilt associated with a peroneal tendon tear was 13.8°, we evaluated the Sn, Sp, PPV, and NPV of the talar tilt utilizing 10° as the threshold for a positive test for peroneal pathology. We considered a value of 85% to be clinically meaningful given the significant association determined between the mean and medians for each pathology studied. A talar tilt test of < 10° had a NPV of 98% when evaluating the presence of a peroneal tendon tear in our analysis. The remainder of the values were not found to be clinically meaningful as demonstrated in Table 5.

We also looked at the relationship between OLTs and instability. The tibiotalar joint has a high level of congruency. In plantarflexion and dorsiflexion, the contact surface area of the ankle is decreased and the contact pressures increased[15,16]. Multiple previous studies have suggested an association between increased instability and OLTs. In a study of 148 patients with ankle instability who underwent operative management, Hintermann *et al*[17] found 26 patients (18%) with full thickness cartilaginous lesions of the talus. In a similar study of 65 patients undergoing operative management for lateral ankle instability by Cha *et al*[18], the authors found OLTs in 33 patients (51%). In this study, 22 of these lesions were classified as softening

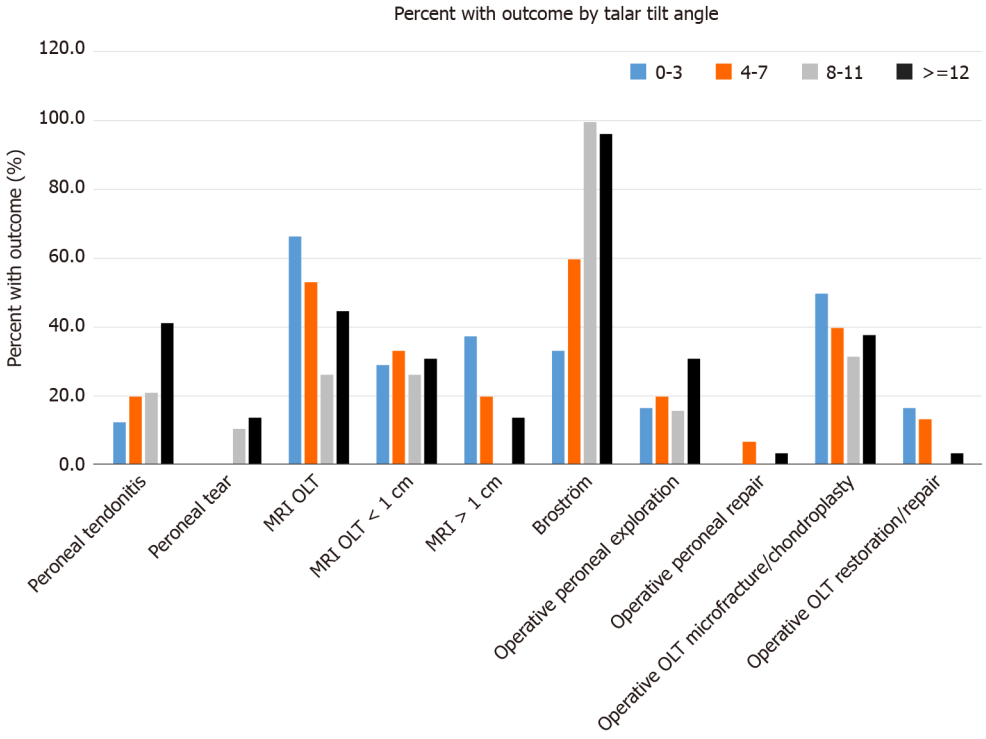

Figure 3 The presence of an associated condition is listed next to the number of ankles that have that condition when organized according to the degree of instability as measured on the talar tilt image. MRI: Magnetic resonance imaging; OLT: Osteochondral lesions of the talus.

or superficial fissuring with 20 (18%) being classified as deep fissures or exposed bone [18]. It is unclear as to how many of these lesions required surgical management. In a study of 283 patients requiring surgery for ankle fractures, OLTs were found in 61 patients (73%) during operative arthroscopy. More severe fracture patterns were associated with an increased incidence of OLTs[19]. The association of ankle instability with OLTs, however, has not been consistent in every study. In a recent study, Park *et al*[20] evaluated 195 patients with a history of an inversion injury who were evaluated with both MRI and stress radiographs. The authors defined radiographic instability as having a talar tilt of greater than or equal to 10°. An increased talar tilt was associated with a lower incidence of OLT and the presence of an OLT was associated with a decreased tibiotalar tilt. We found similar findings in our study group. Ankles that did not have an OLT had a mean talar tilt of 9.8° while patients who did have an OLT had a mean talar tilt of 7.3°. When we evaluated our data utilizing the median values rather than the mean to account for outliers, we found a very similar inverse relationship between the presence of an OLT and the degree of instability. We found that the 42 patients who had an OLT had a median talar tilt of 9° while the median talar tilt for the 45 patients who did have an OLT was 6°. As seen in Table 4, this inverse relationship remained significant for larger OLTs and for OLTs that underwent operative management. The inverse relationship in our data set is best depicted in Figure 3. We were not able to find a clinically meaningful value on the anterior drawer test or the talar tilt test in terms of sensitivity, specificity, the positive predictive value, or the negative predictive value. As seen in Table 5, we utilized 10° as the threshold for the talar tilt test. Given the inverse relationship noted for OLTs and instability, a positive test was described as a test having a value of less than 10°. Although a threshold of 10mm has been described for a positive anterior drawer test when evaluating for instability, we utilized a threshold of 5 mm based upon our evaluation of the medians with those patients with an OLT having a median anterior drawer of 3 mm *vs* 8 mm for patients without an OLT. Similar to the talar tilt results, a value of less than 5 mm on the anterior drawer was not predictive of an OLT in our analysis as demonstrated in Table 6.

This study has strengths and weaknesses. We evaluated not just the presence of associated conditions but also documented which conditions were treated surgically. With that said, the presence of conditions on imaging studies or documented during surgery is objective data, while the decision to perform a repair could be subject to bias. The relationship between stress radiographs and functional instability has not been clearly defined. For this reason, we did not evaluate the prevalence of associated

conditions based upon a defined degree of instability but rather evaluated the mean and median instability measured when associated conditions were present. The data confirms the relationship between instability and peroneal pathology demonstrating that patients with peroneal pathology had a significantly higher mean and median talar tilt measurement. In addition, we documented a significant inverse relationship between radiographic instability and the presence of an OLT. This is the second study to evaluate the inverse relationship seen between instability and OLTs.

CONCLUSION

In evaluating stress radiographs as they relate to associated conditions, we found several areas of significance. Increasing instability was associated with a statistically significant higher prevalence of peroneal tendinopathy and peroneal tendon tears. We also demonstrated an inverse relationship between the presence of OLTs and higher degrees of instability. The broad application of these findings to clinical practice is limited as demonstrated with low sensitivity, specificity, and predictive values for the thresholds measured. Ankle instability remains a complex diagnosis with known associated conditions. While stress radiographs may assist the surgeon in defining mechanical instability, this imaging study alone cannot be utilized to rule out or rule in concomitant pathology that is associated with ankle instability.

ARTICLE HIGHLIGHTS

Research background

Once patients were diagnosed with instability based upon stress radiographs, the surgical procedure was delayed due to the need to obtain a magnetic resonance imaging in order to define which patients had associated conditions. Prior to this study, the surgeons involved felt that higher degrees on instability were associated with the incidence of associated conditions that could result from instability.

Research motivation

In general, we hoped to avoid a delay in treatment due to the need to obtain advanced imaging. We assumed that patients with higher degrees of instability would have osteochondral lesions or peroneal pathology and would require diagnostic arthroscopy or peroneal exploration while patients with a lesser degree of instability could be addressed with a limited surgical procedure focused on the lateral ligaments.

Research objectives

We aimed to determine a degree of instability that could predict the incidence of peroneal pathology or osteochondral defects.

Research methods

A retrospective analysis of patients who had previously been diagnosed with ankle instability was performed. We stratified the patients based upon their degree of instability as defined by stress radiographs and evaluated the incidence of peroneal pathology and osteochondral defects as related to the varying degrees of instability.

Research results

Increasing degrees of instability was associated with a statistically significant increased prevalence of peroneal pathology. An inverse relationship was found between increasing degrees of instability and the presence of osteochondral defects. While we did confirm the association of ligamentous instability to peroneal pathology and the inverse relationship found between osteochondral defects and instability, we did not find a degree of instability that was predictive of peroneal pathology or osteochondral defects.

Research conclusions

Stress radiographs were not found to be predictive of peroneal tendon pathology or osteochondral defects of the talus.

Research perspectives

This is only the second study to demonstrate an inverse relationship between ankle instability and osteochondral defects of the talus. This is a novel discovery, but the injury mechanism that leads to ligamentous instability without chondral injury is unclear. Potentially axial load injuries are more likely to result in chondral injuries as opposed to rotational injuries that may lead to ankle instability. Further work is required to better understand this injury pattern.

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CASE REPORT

Atypical osteochondroma of the lumbar spine associated with suprasellar pineal germinoma: A case report

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Author contributions: Suwak P contributed to the case report design, image formatting, manuscript preparation; Barnett SA, and Song BM contributed to the image formatting, manuscript preparation; Heffernan MJ contributed to the case report design, manuscript preparation.

Informed consent statement: Informed consent was obtained, and the study was approved by the institutional review board.

Conflict-of-interest statement: Heffernan MJ reports personal fees from Zimmer Biomet, Inc. Barnett SA, Suwak P, and Song BM have nothing to disclose.

CARE Checklist (2016) statement: The CARE Checklist guidelines were followed for the production of this case report.

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Abstract

BACKGROUND

Osteochondromas are the most common benign bone tumor, accounting for 36% of benign bone tumors. Often found within the appendicular skeleton, osteochondromas of the spine are rare, comprising 4% to 7% of primary benign spinal tumors.

CASE SUMMARY

We report a case of a solitary lumbar osteochondroma in an 18-year-old male with a history of a suprasellar pineal germinoma treated with combined chemotherapy and radiation. He underwent mass excision and partial laminectomy with the ultrasonic bone scalpel (Misonix, Farmingdale, NY, United States) at the L5 Level without the use of adjuvants. The patient returned to work and full activities without back pain at 3 mo postoperatively.

CONCLUSION

Osteochondromas are common tumors of the appendicular skeleton but rarely occur within the spine. This case discussion supplements current osteochondroma literature by describing an unusual presentation of this tumor.

Key Words: Spine osteochondroma; Lumbar osteochondroma; Laminectomy; Radiation-induced osteochondroma; Spine surgery; Case report

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Core Tip: Osteochondromas of the spine are a rare but treatable condition. For symptomatic lesions, complete resection is largely curative without adjuvant therapy. The patient in this case report was pain free at his post-operative visits without signs or symptoms of recurrence or complication. He returned to work as a manual laborer at 3 mo. Further reports of patients diagnosed with osteochondromas and a history of childhood radiation will enable better understanding of radiation-induced osteochondromas and the rates and locations at which they occur.

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INTRODUCTION

Osteochondromas are the most common benign bone tumor, accounting for 36% of benign bone tumors[1]. Often found within the appendicular skeleton, osteochondromas of the spine are rare, comprising 4% to 7% of primary benign spinal tumors[2,3]. Spine osteochondromas typically originate in the posterior elements as opposed to the vertebral bodies. The cervical spine is most affected (50%), followed by the thoracic and lumbar regions[4]. Characterized as outgrowths of bone covered with a cartilaginous cap, these lesions are considered aberrations of normal growth. Perichondral ring disruption at an active physis leads to cartilage herniation through the periosteal layer. Over time, the cartilaginous fragments undergo ossification and expand[5]. Their expansile nature may cause compression of surrounding structures resulting in pain and neurologic symptoms[4,6,7].

Radiation-induced osteochondroma is a known phenomenon that occurs in patients with a childhood history of radiation therapy[8]. Compared to spontaneous solitary osteochondromas and hereditary multiple exostosis, radiation-induced lesions are radiologically and pathologically identical[8,9]. The presence of a radiation-induced osteochondroma in the lumbar spine is extremely unusual, as in our presented case. A review of literature reveals only two cases of radiation induced osteochondroma occurring in the lumbar spine (one occurring in the L1 body of a 29-year-old female and the L3 spinous process of a 15-year-old female[10-12]. The case of the 15-year-old female appeared in a larger childhood post-radiative tumor study and was not formally presented. Difficulty in diagnosis stems from inconsistent visualization on plain radiographs. Computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standard in the evaluation of spinal osteochondromas, especially in the setting of spinal cord compressive symptoms[13,14].

We present an atypical, symptomatic lumbar spine osteochondroma in an 18-year-old male with a history of chemotherapy and radiation. This case report received institutional review board approval.

CASE PRESENTATION

Chief complaints

An 18-year-old-male presented to the pediatric orthopaedic clinic with the complaint of a posterior midline protuberance at the level of the lumbar spine.

History of present illness

Per the patient, the mass had been present for one year and was gradually enlarging. He noted pain with prolonged sitting and while lying supine.

History of past illness

There was no history of prior trauma or activity-related injury to his low back, however the patient worked as a manual laborer. The patient denied constitutional or neurologic symptoms. His history was significant for a suprasellar pineal germinoma

successfully treated with chemotherapy and radiation at 9-years of age.

Personal and family history

No family history of hereditary multiple exostosis was reported.

Physical examination

On physical examination, there was a palpable osseous protuberance approximately 5 cm in width along the posterior midline at the level of the lumbar spine. The mass was fixed and exquisitely tender to palpation. Further examination of the body and extremities revealed no other masses. Neurologic testing was benign with normal sensorimotor response in all extremities, symmetric reflexes, no upper motor neuron or radicular signs, and no balance or gait abnormalities.

Laboratory examinations

No laboratory examinations were performed.

Imaging examinations

Initial radiographic evaluation demonstrated a large osteochondroma arising from the right spinous process/Lamina junction at the level of the L5 vertebral body (Figure 1). Subsequent CT and MRI imaging confirmed the radiographic findings without evidence of intraspinal abnormality or encroachment on the vertebral canal (Figures 2 and 3). Given the symptomatic nature and location of the mass, the patient was offered surgical treatment in the form of mass excision.

FINAL DIAGNOSIS

A diagnosis of an osteochondroma arising from the right spinous process/Lamina junction at the level of the L5 vertebral body was made, and this was later confirmed with surgical pathology.

TREATMENT

Intraoperatively, mass excision with partial laminectomy was performed through a posterior midline incision. Careful paramedian dissection was performed in order to free the soft tissues surrounding the mass without destabilization of the interspinous ligaments or the right L5-S1 facet joint. Once isolated, the mass was excised *en bloc* with use of a harmonic bone scalpel. A Woodson elevator was utilized under the lamina to gauge depth and ensure that the ventral surface of the lamina remained intact. After excision, a paraspinal muscular flap closure was performed to minimize the potential space created by the mass. Gross surgical pathology revealed a large bony mass measuring 3.8 cm × 3.5 cm × 2.5 cm that included a 1 cm thick sessile cartilaginous cap. Surgical margins were noted to be smooth (Figure 4). Microscopic examination demonstrated mature hyaline cartilage, fibrous perichondrium, and trabecular bone without cellular atypia or malignant features. Enchondral ossification was present within the sample without marrow elements identifiable within the trabecular bone. Pathology was consistent with benign osteochondroma (Figure 5).

OUTCOME AND FOLLOW-UP

Post-operatively, the patient was discharged on postoperative day 1 following removal of his drain. His post-operative course was uncomplicated. He returned to his work as a manual labor without pain or limitation at three months following surgery.

DISCUSSION

Osteochondromas are benign osteocartilaginous proliferations at a growth plate that typically stop increasing in size at skeletal maturity[5,15]. They infrequently occur in the spine (1% to 4% of osteochondromas) with the majority localized to the cervical spine[4]. Cases of lumbar osteochondromas, like the case presented, are scarce.

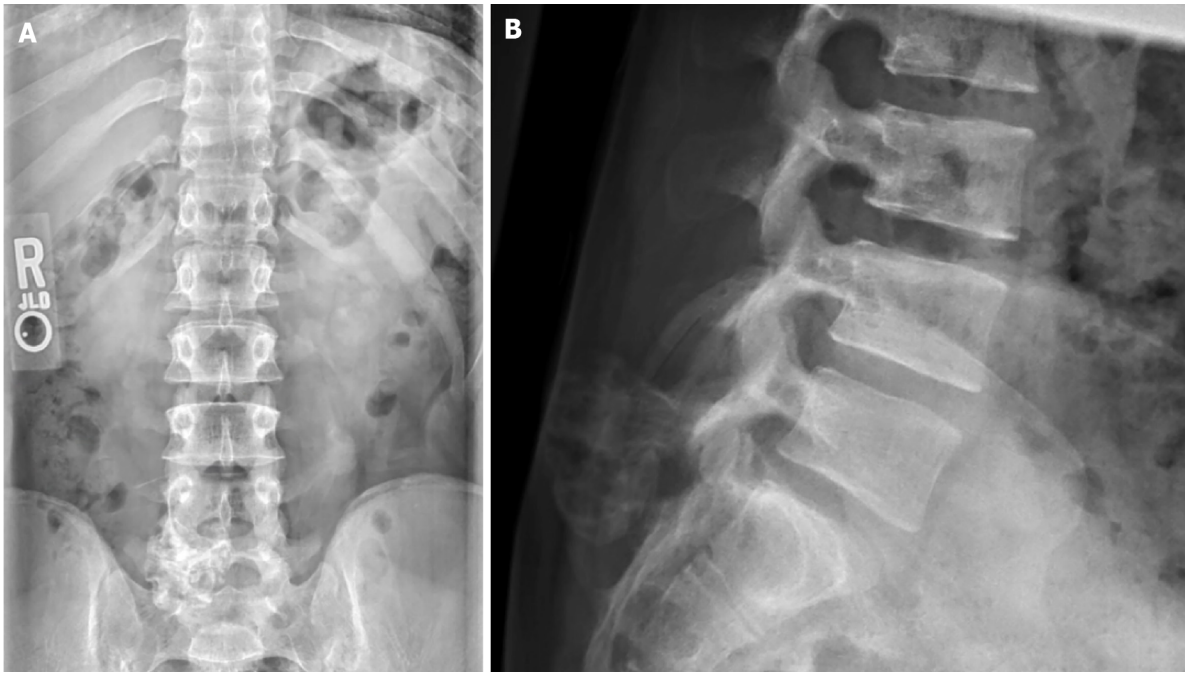

Figure 1 Anterior to posterior and lateral radiographs demonstrating calcified, pedunculated mass protruding from the posterior elements of the L5-S1 vertebral interval. A: Anterior to posterior radiograph; B: Lateral radiograph.

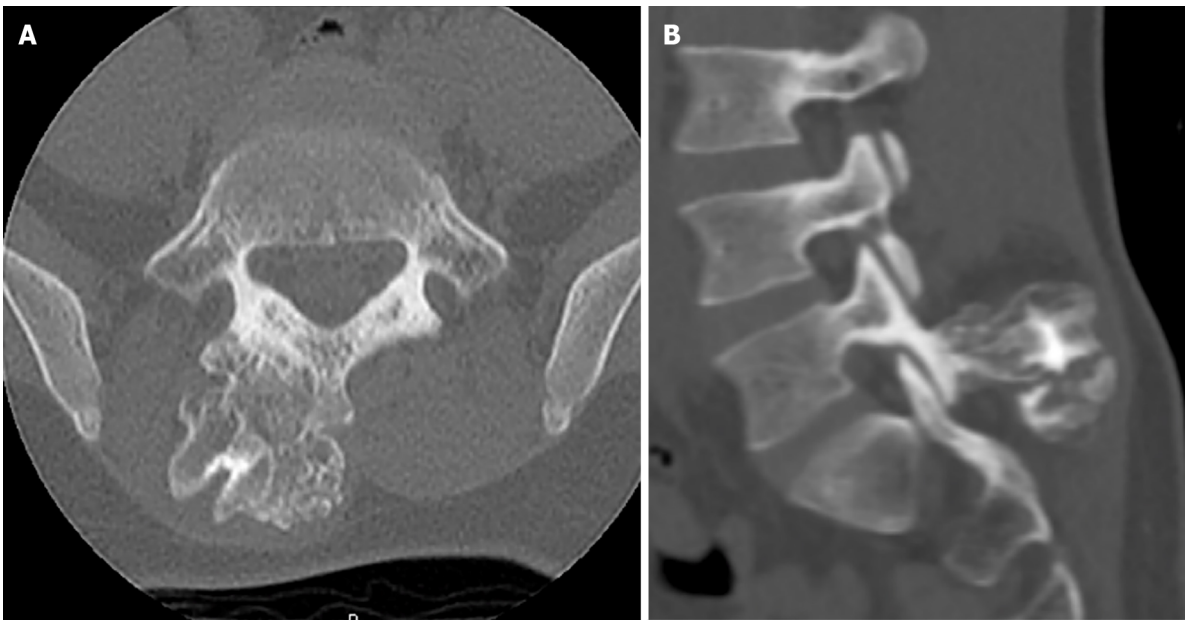

Figure 2 Computed tomography imagines. A: Axial computed tomography imaging demonstrating osteochondroma protruding from right spinous process/Lamina junction; B: Sagittal computed tomography imaging at the level of the L5/S1 facet joint depicts mass involvement of the right inferior articular process of L5. An ultrasonic bone scalpel was used to remove the mass *en bloc* from the articular process without disrupting the facet capsule.

Patients typically present with axial pain which may be exacerbated with certain positions or activity like the patient in this study. Neurological manifestations from cord compression are rare but have previously been reported[16]. Initial radiographic evaluation may reveal a spinal lesion composed of a cortical protuberance in continuity with the medullary canal. Advanced imaging is recommended to aid in diagnosis. CT imaging provides detail of the osseous and cartilaginous margins whereas MRI can provide the thickness and architecture of the cartilaginous cap. A cartilage cap > 3 cm thickness can indicate malignant transformation[1,4].

Lumbar involvement of these exostoses is rare, perhaps due to increased stiffness of the lumbar spine when compared to the cervical spine and therefore less microtrauma to the epiphyseal cartilage. Osteochondromas occur within the posterior elements of

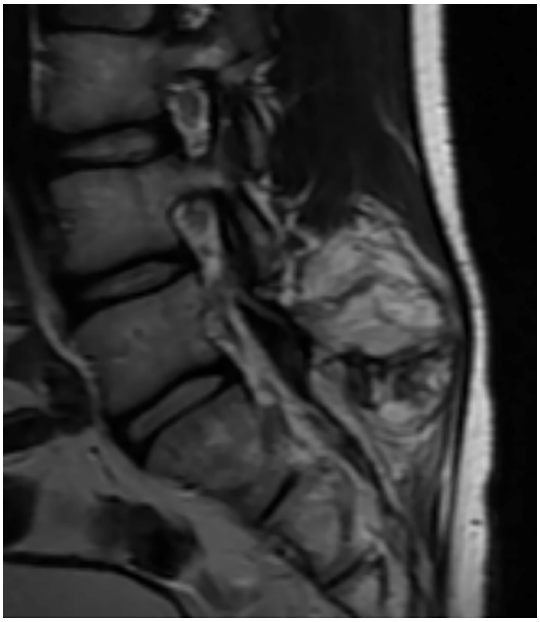

Figure 3 Sagittal T2 magnetic resonance image demonstrating the well-defined 1.5 cm cartilaginous cap of the lumbar osteochondroma extending into the right paraspinal musculature.

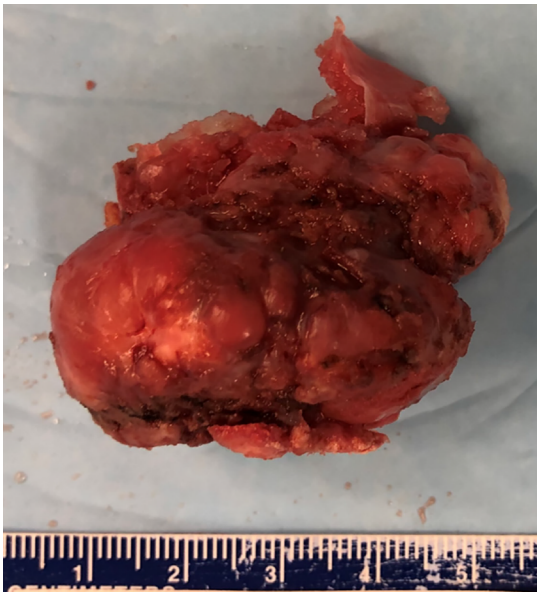

Figure 4 Gross specimen of excised lumbar mass measuring 3.8 cm × 3.5 cm × 2.5 cm with cartilaginous cap and smooth muscle margin.

the spine and may become symptomatic with growth into the paraspinal musculature [17]. A review of lumbosacral osteochondromas performed by Kuraishi *et al*[16] noted radicular symptoms in 4 out of 5 cases. In that series, involvement of the L4 inferior articular processes resulted in an L5 radiculopathy whereas involvement of the superior articular process of S1 corresponded with an L5 radiculopathy.

Given our patient's history of a suprasellar pineal germinoma requiring chemotherapy and radiation, the spinal lesion was potentially radiation-induced. Pediatric oncology literature describes osteochondroma growth as a complication of both localized radiation therapy as well as total body irradiation[18]. The proposed pathogenesis is radiative damage to the epiphyseal plate resulting in immature cartilage fragment migration to the epiphysis and periosteal layers. These cartilage fragments expand during subsequent maturation and ossification. Radiation-induced osteochondromas have been reported in the ulna, tibia, and hands[18-20]. To our knowledge, this is the first detailed case report of a spinal osteochondroma in a

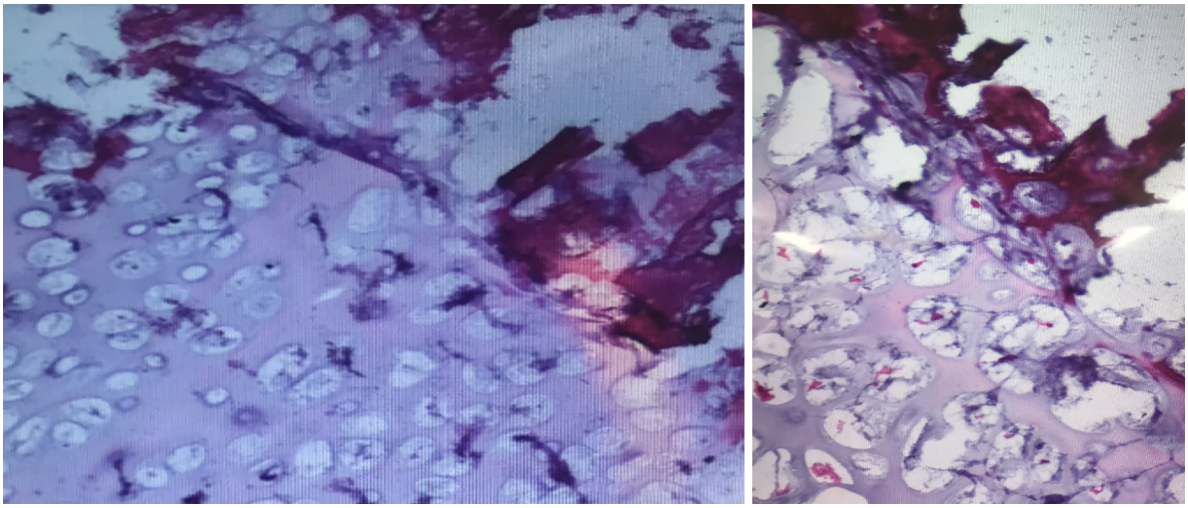

Figure 5 Histology of excised mass demonstrating mature cartilage, fibrous perichondrium, and trabecular bone without evidence of cellular atypia or malignant transformation; consistent with osteochondroma.

pediatric patient with previous radiation treatment.

Painful lesions or those causing neurologic deficit require surgical intervention. If resection entails destabilizing the spine, instrumentation and arthrodesis should be considered. The goal of surgery should be complete resection of the lesion[21]. Surgical nuance of our lumbar osteochondroma excision was the use of an ultrasonic bone scalpel. The ultrasonic bone scalpel amplifies electrical signals that oscillate a blunt blade, allowing for targeted resection of cortical bone without violation of soft tissues [22]. Given the location of our patients osteochondroma with abutment of the right L5 interspinous ligament and right L5-S1 facet capsule, excision of the mass without violating the soft tissues prevented posterior spinal destabilization requiring subsequent instrumentation and fusion.

CONCLUSION

Osteochondromas of the spine are a rare but treatable condition. For symptomatic lesions, complete resection is largely curative without adjuvant therapy. The patient in this case report was pain free at his post-operative visits without signs or symptoms of recurrence or complication. He returned to work as a manual laborer at 3 mo. Further reports of patients diagnosed with osteochondromas and a history of childhood radiation will enable better understanding of radiation-induced osteochondromas and the rates and locations at which they occur.

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