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Shohreh Ghasemi *

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Review Article

Mechanisms of Pathogenesis and Pathophysiology of Osteonecrosis of the Jaw (ONJ) and Atypical Femoral Fracture (AFF)

Shohreh Ghasemi *

Clinical Assistant Professor of OMFS Department of Augusta University, GA, USA.

***Correspondence Author:** Shohreh Ghasemi, Clinical Assistant Professor of OMFS Department of Augusta University, GA, USA.

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Abstract

In developing countries, osteoporosis, also known as osteonecrosis, and the resulting osteoporotic fractures cause significant morbidity, mortality and health care costs. In several randomized trials, pharmacological therapy for osteoporosis has been proven to lower the risks of hip fractures, vertebral, non-vertebral, and bisphosphonate medicines and have been linked to better survival in several studies. Anti-resorptive drugs can cause atypical femoral fractures (AFFs), a rare and often misdiagnosed treatment-related complication that has a significant impact on patients' quality of life.

Keywords: atypical femur fracture; anti-resorptive drugs; mronj; bone remodeling

Introduction

Anti-resorptive medications like as bisphosphonates (BPs) and denosumab have been used to reduce the risk of osteoporotic fractures for many years. Their long-term usage, on the other hand, has been linked to a higher risk of AFF [1-6]. The safety of these anti-resorptive medications has been questioned in the wake of reports of these rare but significant side effects, particularly in long-term users [6, 9]. The overall risk of AFF is low; on the other hand, increased awareness of AFF, as well as other questions raised about how to properly treat osteoporosis patients, has coincided with a significant decline in osteoporosis drug use and a plateau in a promising decline in osteoporosis fractures [1-12].

Denosumab and bisphosphonates (BP) are antiresorptive medications that have been utilized for quite a long time against the danger of osteoporotic femoral breaks. Nonetheless, their drawn-out use has been related to increased risk of AFF. The reports of these uncommon yet genuine results bring up issues about the wellbeing of these antiresorptive medications, particularly in individuals who consume these medications for quite a while. The high risk of AFF is low; However, public concern about AFF, along with other unresolved questions about how to properly treat osteoporosis patients in the long term, has coincided with a significant decline in osteoporosis medication use and, in any case, with an encouraging decrease in osteoporosis damage [12-18].

This has highlighted the concern of healthcare professionals and academics that many people who require pharmaceuticals are either inadequate or not taking them. The long-term effects of denosumab and bisphosphonates on AFF have still to be fully identified, and the developmental processes of AFF remain unknown. Although there is some evidence that risk syndromes and feasible precursors may have hereditary components, it is not possible to predict the onset of AFF. Since millions of osteoporosis patients use these sources around the world, this unpredictability poses a serious danger [18, 7].

Long term utilization of antiresorptive medications, specifically intravenous circulatory strain in malignancy treatment, likewise raises concerns in view of their relationship with an expanded danger of osteonecrosis. ONJ, which shows itself in a few phases of seriousness, is a crippling condition that influences the patient's wellbeing and personal satisfaction. Information on the system of activity of bisphosphonates as an antiresorptive specialist has extended fundamentally. Yet, less is thought about the specific pathogenesis and etiology of ONJ, particularly after reports that biologics, for example, inhibitors of angiogenesis and denosumab, are additionally connected through ONJ. Further advancement in appreciative this uncommon foundational confusion in people, which is particularly present in the oral cavity, will rely upon revealing the complex inclusion of various frameworks [19, 3, 7].

Recently, much consideration has been paid to the possibility of a association among low energy fractures and long-term use of bisphosphonates of the femoral shaft and subtrochanteric suture. These fractures were termed "atypical fractures" to differentiate them from "typical fractures" of the neck trochanteric and femoral zone induced by low-energy trauma. The most severe femoral shaft fractures occur as a consequence of severe high-energy traumas such as vehicle accidents or falls from significant heights. Unlike another PD complication, osteonecrosis of the jaw, atypical femoral fractures (AFF) are not linked to elevated blood pressure (ONJ) [11-19].

The American Society for Bone and Mineral Research (ASBMR) created an interdisciplinary special committee in 2009 and issued a position paper in 2010 as part of a systematic approach to further understanding AFF. The working committee defined AFF after evaluating published studies on imaging, epidemiology, clinical management practice and risk factors. It was established that the incidence of AFF was extremely low, especially when compared to the number of hip and spine fractures that may have been avoided if BP had been used. They also stated that, despite the lack of statistical power, a causal association between AFF and BP had not been proven. AFF is described as less traumatic or atraumatic fractures in the subtrochanteric area or diaphysis of the femur, according to a 2010 Working Group study [2, 8].

Intertrochanteric fractures with spiral subtrochanteric extension, as well as periprosthetic fractures, associated with primary or the metastatic bone cancer were eliminated from the AFF classification. Transverse or short oblique shapes, as well as non-comminuted incomplete fractures affecting just the lateral cortex, were all major hallmarks of AFF. Complete fractures, on the other hand, penetrate both cortical layers and may have a medial extrusion. Localized periosteal reaction or lateral cortex curvature, widespread thickening of the cortical layer of the femoral shaft, bilateral fractures and symptoms, and delayed healing owing to certain drugshistory of prodromal pain, and medical conditions are all minor indicators. All major criteria must be present for a fracture to be classified as "atypical," although minor traits may be lacking in certain circumstances [11]. In September 2011, the Food and Drug Administration (FDA) conducted a study of the situation. Atypical fractures are relatively slight or unusual, according to the report [12].

Discussion

Incidence of AFF

In a case report published in 1978, Richardson with his colleagues discovered atypical stress fractures in women who are on premenopausal stage connected to osteoporosis. This was before the widespread usage of highly potent bisphosphonates. In 1985, McClung and Orwoll discovered a similar type of stress fracture in people with osteoporosis and low bone turnover. Bisphosphonates were approved for the treatment of acute and chronic osteoporosis in the United States in the mid-1990s, and they were widely utilised. In 2005, Odvina and colleagues reported nine people who had spontaneous non-spinal fractures while using alendronate, four of which were femur fractures. The researchers concluded that significant suppression of bone turnover during long-term alendronate treatment might result in fractures. Femoral stress fractures are abbreviated as AFFs [16-19].

Wang and Bhattacharya reported an analysis of average femur fractures and AFFs associated with bisphosphonate usage in the United States more than ten years after bisphosphonate-based medicines were first introduced in the United States in 2011. They determined that with bisphosphonate treatment, for each 100 commonplace osteoporotic femoral cracks forestalled, there was an expansion of one subtrochanteric break due to fragility. In another evaluation, Meyer and associates found a 47% decrease in exemplary cracks, yet an expanded danger of AFF. 10.7% each year with long haul utilization of bisphosphonates. These creators likewise found that more drawn-out bisphosphonate treatment was related with a more serious danger of AFF. According to a study, contralateral cracks were seen in just about 33% of patients with AFF [9, 3].

Measurable characteristics associated with atypical femoral fractures

In order to develop a clinical profile and determine which individuals are vulnerable, it is required to quantify the indicators that are considered part of the etiopathology of atypical femoral fractures. One of the features of atypical, according to case reports and a series of investigations, is cortical thickening at the place of a fracture. However, because cortical thickness varies across the diaphysis, as well as with sex, race and perhaps age research examining this trait must identify particular locations for investigation and measurement [12, 15].

As a preliminary step in assessing the importance of cortical thickness in the pathophysiology of atypical fractures, the normal range for sex, age, and shaft location should be evaluated. It is also significant to prospective study the incidence of other characteristics identified in association with atypical femur fractures, like as:

- Frequency of periosteal reactions (e.g., callus) associated with a fracture, including the frequency of such reactions in the contralateral femur without fracture
- Bilateral fracture rates and symptoms
- Frequency and duration of prodromal hip pain

Pathophysiology of AFF

Although several pathways have been hypothesized, the etiology of AFF is still unknown. Stress fractures develop when bones are subjected to recurrent stress that surpasses the bone's ability to heal. The radiological characteristics detected in AFF correlate to stress fractures. Anti-resorptive medicines that inhibit bone remodeling can result in the buildup of irreversible micro-damage, which can lead to stress fractures. Variations in lower and hip extremity geometry may play an influence on the development of AFF and, specifically, may dictate where stress fractures of the hip occur [4, 8, 9].

Variations in the morphology of the femur, such as flexed pedicle deformity, the varus angle, femoral shaft short diameter, have been proven in studies to determine the locations of greatest stress in the femur. This can help pinpoint where stress shifts can lead to cracks. Bisphosphonates also impact the characteristics of bone structure, such as glycation and collagen end products, and long-term bisphosphonate usage causes an increase in tissue mineral density, which may enhance fracture propagation following a stress fracture. Furthermore, there may be a hereditary susceptibility to producing stress alterations inside the hips in patients who take antiresorptive medicines [12, 17, 14,20].

Pathophysiology: proposed mechanisms

Although the pathogenesis of AFFs is uncertain, its epidemiological relation to bisphosphonate medication has led to numerous theories. Bisphosphonates affect collagen development and polymerization, resulting in increased bone strength, a higher pyrinoline (PYD)/deoxypyridinoline (DPD) ratio, but also stiffness. However, decreasing bone remodeling also increases pentosidine, which interacts with collagen through oxidative non-enzymatic cross-linking, resulting in increased accumulation of the end-product of glycation, resulting in decreased strength. Both effects increase the stiffness of the die and therefore reduce the load-carrying capacity. Strengthening due to increased mineralization of the matrix and crosslinking of pentosidine reduces plasticity; the structure becomes more fragile [6, 9 ,10].

In addition, more uniformly mineralized bone tissue contributes to the occurrence and spread of fracture fractures. Thus, suppressing remodeling increases the stress on the microcracks, allowing the cracks to elongate and reducing their removal. The preferential absorption of bisphosphonates in locations of significant bone remodeling, such as stress fractures, might accelerate the buildup of microdamage. Bisphosphonates might possibly impact intracortical healing of a developing stress fracture which including AFF by blocking remodeling at these local locations, letting the injury to progress to a complete fracture [14, 13, 11].

In most AFF cases, iliac crest biopsies revealed a reduction in bone metabolism, as would be predicted with bisphosphonate therapy, but this was not the case in all cases. Both reduced and enhanced bone remodeling have been observed in AFF biopsies taken around the fracture site, albeit

the latter might be due to a recent fracture and not suggest an underlying pathogenic mechanism of AFF [2].

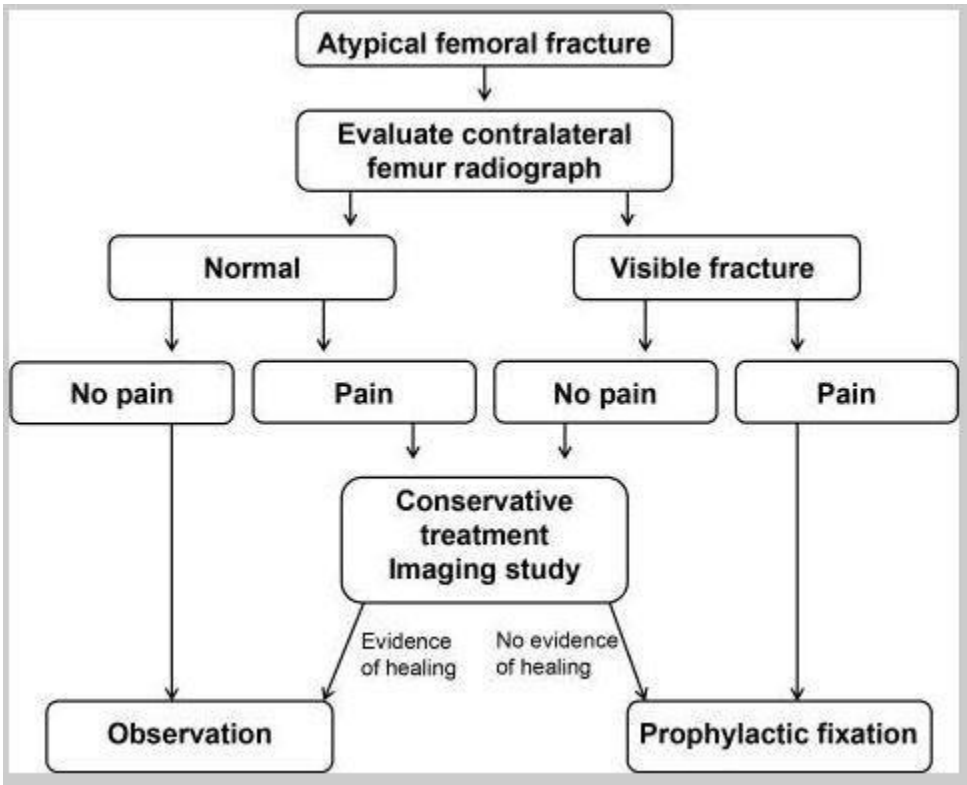

Figure 1: Atypical Femoral Fracture

Risk factors for AFF

AFFs are uncommon, despite the widespread use of denosumab and bisphosphonates for the treatment of osteoporosis. Most people with osteoporosis who are treated with antiresorptive medications for a long time do not exhibit stress changes in the femur. Women on antiresorptive drugs have a considerably higher chance of having AFF than males, according to observational studies, and they tend to be younger than those with conventional osteoporotic fractures. Asian women tend to be more likely than white women to have AFFs. This might be related to changes in lower limb geometry across these groups. Low blood vitamin D levels, concurrent use of numerous antiresorptive bone medications, rheumatoid arthritis, concurrent use of glucocorticoids, and relatively young age at commencement of bisphosphonate treatment are all risk factors for AFF [20, 21, 15].

AFFs can sometimes be detected before a major fracture of the maxillofacial femur becomes disastrous. AFF or stress alterations in the contralateral femur are seen in around one-third of individuals with diagnosed AFF. This allows for the detection of AFF before it becomes a full fracture, when it may be treated [12, 14].

The 2014 ASBMR Working Group Report outlines recommended AFF management. After AFF is found, bisphosphonates should be stopped, according to the report. Denosumab should also be avoided in patients with AFF since it is a powerful antiresorptive medication. Calcium and vitamin D supplements should be maintained. Secondary causes of osteoporosis and underlying metabolic bone disease should be assessed in patients with AFF. If required, testing for uncommon genetic illnesses linked to AFF, such as hypophosphatasia, should be considered [17, 16].

General practitioners and orthopedic surgeons work together to treat these fractures. Because alternative surgical fastening procedures have a high failure rate, complete AFFs require intramedullary nail surgery. Fracture healing is generally delayed, and nonunion is a common complication. Depending on the symptoms of the limb, the length and depth of the fracture line, and the patient's request, patients with incomplete AFF may be considered for preventative IM nailing [1, 3].

Patients with AFF can be safely treated with anabolic bone medications such teriparatide and abaloparatide. Teriparatide has been found to improve bone mineral density and reduce the incidence of fractures in osteoporotic individuals at high risk of fractures in randomized controlled studies. Even so, there isn't any evidence that it helps with AFF recovery. It is, nevertheless, suggested as a first-line treatment for people who have undergone AFF, particularly in those who are at high risk of traditional osteoporotic fractures [17].

AFF is an uncommon but potentially fatal side effect of antiresorptive medications. The use of antiresorptive medications for osteoporosis, as well as the length of use, increases the chance of developing AFF, and some patient variables appear to enhance the likelihood of developing AFF when using these treatments. Bisphosphonates and denosumab, on the other hand, remain first-line and very effective treatments for those at high risk of fractures. According to the ASBMR Working Group study, every AFF used to treat antiresorptive drugs prevents one osteoporotic fracture [18].

Conclusion

BPs reduces the risk of non-spinal and spinal bone fractures, such as typical and extensive hip fractures and intertrochanteric fractures, significantly. There is, however, evidence of a relationship between long-term blood pressure medication usage and a certain form of femoral and subcutaneous shaft fracture. on the other hand, typical femoralfractures are a matter of concern, and additional information is considered necessary, both to help identify individuals at high risk and to determine the

length of BP medication. By modifying the BP labeling, doctors and patients should be aware of the likelihood of bilateral nature and atypical femur fractures. Given the rarity of atypical femoral fractures, new procedural and diagnostic codes for atypical femoral fractures should be created to aid future research, a worldwide registry should be created, and case registrationquality should be enhanced.

Animal models should be developed, monitoring should be expanded, and more epidemiological data should be collected to determine the exact prevalence and risk factors of this ailment, as well as research into surgical and medicinal therapy options.

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