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Atypical Femoral Fractures: Epidemiology, Etiology, and Patient Management

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Abstract

Purpose of Review—To review the definition, epidemiology, and putative pathophysiology of atypical femoral fractures and propose strategies for management of patients with atypical fractures as well as patients on long-term bisphosphonates without atypical fractures.

Recent Findings—Recent epidemiologic evidence shows that the absolute incidence of atypical femoral fractures is small compared to the incidence of typical hip fractures. However, long-term bisphosphonate use may be an important risk factor for atypical fractures, and minimal additional antifracture benefit has been demonstrated for treatment durations longer than 5 years for patients with postmenopausal osteoporosis. This review gives advice to aid clinicians in the management of patients with incipient or complete atypical fractures.

Summary—Extremely limited evidence is available for how best to manage patients with atypical fractures. A comprehensive metabolic approach for management of patients on long-term bisphosphonates will help to prevent oversuppression of bone remodeling that is implicated in the pathogenesis of these fractures.

Keywords

atypical fracture; bisphosphonate; osteoporosis; subtrochanteric fracture; diaphyseal fracture

I. Introduction

Bisphosphonates substantially reduce fracture risk in women with postmenopausal osteoporosis [1–3], and treatment durations of up to 10 years further reduce risk of clinical vertebral fractures [4]. Atypical femoral fractures in bisphosphonate-treated patients reported over the last 7 years have raised concerns about long-term safety of antiresorptive therapy. These fractures have a distinctive radiographic appearance and can occur spontaneously with or without prodromal pain. In light of uncertainty about the pathogenic mechanisms and controversy surrounding the association of atypical fractures with

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bisphosphonates, the management of patients with history of prolonged use of bisphosphonates is challenging. A comprehensive metabolic approach is necessary to prevent oversuppression of bone remodeling, which has been implicated in the pathogenesis of these fractures.

The purpose of this article is to review the literature on atypical femoral fractures from the past 18 months and to make recommendations for management of patients on long-term bisphosphonate treatment with or without incipient or complete atypical fractures. The American Society for Bone and Mineral Research (ASBMR) Task Force report established a provisional case definition and reviewed the literature on atypical fractures through 2010 [5]. This article focuses on new developments since the publication of the ASBMR report.

II. Definition

The earliest reports raising concerns about a possible link between bisphosphonate therapy and atypical fractures described unusual low-energy subtrochanteric or femoral shaft fractures in patients with severely suppressed bone turnover [6]. However, the association between these fractures and bisphosphonate therapy was unclear because some of the patients studied were taking multiple bone-active agents, including estrogen, bisphosphonates, and glucocorticoids [6]. A subsequent case series identified commonalities in the fracture morphologies of 70 patients with atypical subtrochanteric and femoral shaft fractures, including a simple transverse or oblique fracture with a periosteal stress reaction on the lateral cortex, and thick cortices in the proximal femur [7] (Figure 1a). The transverse morphology and subtrochanteric/diaphyseal location contrasts with the spiral subtrochanteric or intertrochanteric fractures seen typically in osteoporotic patients (Figure 1). The ASBMR task force defined major and minor features of atypical fractures (Table 1) [5]. All major features must be present to consider a fracture “atypical” and distinguish it from typical hip fractures, while minor features may or may not be present.

III. Epidemiology

This section describes 1) the overall incidence of subtrochanteric and femoral shaft fractures and the incidence of atypical femoral fractures and 2) the association between atypical femoral fractures and bisphosphonate treatment.

Incidence and Temporal Trends

The epidemiology of atypical femoral fractures is poorly understood compared to that of typical osteoporotic hip fractures. Furthermore, because no diagnostic code currently exists for atypical fractures, studies examining only diagnostic coding cannot distinguish atypical subtrochanteric fractures from typical subtrochanteric fractures; radiographs are required to identify features of atypia.

Fractures of the subtrochanteric and diaphyseal cortex, while less common than hip fractures, occur in a small fraction of osteoporotic patients, and an even smaller fraction is atypical. Fractures of the subtrochanteric, diaphyseal, and hip regions each account respectively for 3%, 3%, and 91% of all femoral fragility fractures [8]. Temporal trends in

the incidence of subtrochanteric and diaphyseal fractures differ from those of hip fractures. Multiple analyses of large US healthcare databases reported ~30% reductions the incidence of typical hip fractures in the decade since bisphosphonates were introduced in 1996, while incidence of subtrochanteric and femoral diaphyseal fractures were unchanged in both men and women [9] or increased by 20–40% in women [10, 11]. None of these investigations assessed radiologic features of atypia; thus, the relative proportions of typical and atypical subtrochanteric fractures are unknown in these studies.

To date two large datasets in which radiographs were adjudicated for features of atypical fractures have been analyzed to estimate the incidence of atypical fractures. A low and stable rate of 5.9 atypical fractures per 100,000 person-years was observed over the period 1996–2009 in a large US healthcare database [12]. Incidences of 55 atypical fractures and 1510 hip fractures per 100,000 person-years were observed for bisphosphonate-treated patients and 1 atypical fracture and 740 hip fractures per 100,000 person-years were observed for bisphosphonate-naïve patients in a cohort study based on the Swedish national healthcare database [8]. Thus, even for bisphosphonate-users the absolute incidence of atypical fracture is low, approximately 1/30 of that of hip fragility fractures.

The incidence of atypical fracture may be higher in patients treated for cancer. In a cohort of 327 patients with metastatic bone disease who had received a minimum of 24 doses of intravenous bisphosphonates over a 3-year period, 4 atypical fractures (1.2%) were reported [13].

Association with Bisphosphonates

The association between atypical femoral fractures and bisphosphonate therapy is complex and somewhat controversial. Bisphosphonate therapy appears to increase risk of atypical fractures, with greater risk associated with longer durations of treatment and declining risk after cessation of treatment [8, 14]. However, atypical fractures have also been observed in patients who have never been exposed to bisphosphonates [8, 15]. Thus, while bisphosphonate treatment may be an important risk factor for atypical fractures, it cannot be the sole risk factor.

Analyses of large datasets to examine relationships between bisphosphonate use and subtrochanteric/diaphyseal fractures have yielded mixed results. Data from secondary analyses of randomized placebo-controlled clinical trials of bisphosphonates found no significant relationship between subtrochanteric/diaphyseal fracture and bisphosphonate use [16]. Similarly, a cross-sectional analysis of the Danish national health registry found no significant association between bisphosphonate use and subtrochanteric fracture [17]. A population-based cohort study from two American states found that risk of subtrochanteric fracture was not increased in bisphosphonate users compared with raloxifene/calcitonin users [18]. In contrast, a population-based, nested case-control study in Canadian women found an increased risk of subtrochanteric and diaphyseal fractures among women with more than five years of bisphosphonate therapy (OR 2.74, CI 1.25 – 6.02), and a reduced risk of typical femoral neck and intertrochanteric fractures (OR 0.76, CI 0.63 – 0.93) [19]. These studies primarily assessed diagnostic codes and did not review original

radiographs for features of atypical fractures; therefore atypical and typical subtrochanteric fractures were not distinguished.

Epidemiologic evidence supporting a relationship between bisphosphonate use and atypical fractures arises from two studies that adjudicated original radiographs to determine features of atypia. A large cohort study from the National Swedish Patient Registry showed that the relative risk of atypical fracture (n=59) with any use of bisphosphonates was 47.3 (95% CI 25.6 to 87.3), while the absolute risk was low, 55 per 100,000 person-years [8]. After drug withdrawal, the risk of atypical fracture declined by 70% per year since the last use (OR 0.28, CI 0.21 to 0.38). In an analysis of atypical fractures in a large California HMO, estimates of atypical fracture incidence increased with duration of treatment, from 2:100,000 per year with 2 years of oral bisphosphonates to 78:100,000 per year with 8 years of oral bisphosphonate treatment [14]. Thus, evidence to support a link between bisphosphonate use and atypical fractures is strongest in studies that include examination of radiographs for the specific morphology of atypical fractures. However, in a recent case-control study in which radiographs were reviewed, atypical fractures (n=10) occurred with equal frequency in bisphosphonate-treated patients and bisphosphonate-naïve patients [15]. In summary, the evidence on the association between bisphosphonate use and atypical fractures is mixed but on balance suggests increased risk of atypical fracture with prolonged bisphosphonate use.

IV. Etiology/Pathophysiology

Here we summarize recent studies in the context of the current understanding of the pathophysiology of atypical fractures, which is addressed in greater detail in a recent review [20]. Atypical fractures appear to initiate as stress fractures on the lateral cortex of the proximal femur (Figure 1), a site of high tensile loads due to bending [21]. The prodromal pain experienced by some patients with atypical fractures is consistent with an incipient stress fracture. The unusual transverse fracture morphology and lack of comminution also suggest a brittle tensile failure mechanism [5]. Multiple geometric and material factors may contribute to this process.

At the whole-bone geometric level, a striking feature of atypical fractures is the thick cortices often observed bilaterally in radiographs of the femora. In the absence of material changes, thick cortices would be expected to strengthen the femur, and no evidence suggests that bisphosphonates cause periosteal or endosteal apposition. Indeed, the change in subtrochanteric cortical thickness over 5 years was not different between long-term alendronate users and bisphosphonate-naïve controls [22]. Therefore, while bisphosphonates are unlikely to affect cortical thickness, some other, genetically influenced geometric property (e.g., curvature of the femur), may contribute to high tensile loads on the lateral cortex. Populations with bowed femurs are expected to have greater bending stresses and be at greater risk for stress fracture initiation in the lateral femoral cortex.

At the material level, bisphosphonates alter tissue properties by reducing turnover, thereby increasing tissue age, i.e., time since tissue formation. In the organic matrix, bisphosphonate treatment allows accumulation of nonenzymatic crosslinks (advanced glycation endproducts), which is associated with reduced bone toughness [23], and increases the

maturity of the enzymatic crosslinks [24]. Bisphosphonate-treated tissue from the lateral proximal femur had a narrower distribution of cortical collagen maturity and crystallinity compared to bisphosphonate-naïve tissue [25]. Similarly, nanomechanical analysis of iliac crest biopsies revealed narrower distributions of elastic modulus and hardness in cortical tissue of patients with severely suppressed bone turnover relative to controls [26]. Reduced heterogeneity of tissue properties may be associated with reduced toughness, although this relationship has not yet been established directly for human bone. Finally, the proximal lateral femoral cortices of patients with atypical fractures had 8% greater tissue mineral content than patients with typical fractures [25], consistent with the brittle failure pattern observed at this highly mineralized site [27].

Moreover, the formation of and failure to repair microdamage may also contribute to the pathophysiology of atypical fractures. Microdamage accumulation has been observed preclinically with bisphosphonate treatment in a canine model [28, 29] and more recently in an ovine model [30]. A recent case report described six patients with multiple myeloma who developed metatarsal stress fractures while receiving monthly IV pamidronate and zoledronic acid for a median duration of 7.5 years [31], suggesting that patients receiving high doses of bisphosphonates for malignant disease may be at elevated risk of developing stress fractures. Bisphosphonates also have the potential to inhibit healing of stress fractures by binding preferentially to microcrack surfaces and preventing the remodeling process essential to removal of microdamage. Rat models of bisphosphonate treatment in the setting of stress fractures demonstrated reduced extent of repair and delayed repair [32, 33]; similar data in humans are unavailable.

Suppression of bone turnover with long durations of bisphosphonate treatment could cause a loss of material toughness or microdamage accumulation that might impair the tissue's ability to resist fracture. However, direct evidence for this putative pathophysiologic mechanism has not yet been established.

V. Management of Patients with and Without Atypical Femoral Fractures

There are no controlled studies evaluating medical and surgical treatment protocol in patients with atypical femoral fractures. Therefore, our guidelines are based on the recommendations outlined by the ASMBR task force [5], which represent the consensus of the clinicians and basic scientists who served on the task force.

Management of patients with atypical femoral fractures

Management of patients with atypical femoral fractures includes fracture fixation and initiation of medical management. An intramedullary reconstruction full-length nail is preferred because fractures treated with intramedullary nails heal by endochondral repair, which allows for stabilization via callus formation, while plate-screw constructs generally preclude the endochondral repair process. Although minimal data are available on healing of atypical fractures, preliminary evidence suggests that healing may be impaired. The outcome of intramedullary nail fixation was poor in a case series of 16 patients with bisphosphonate-related atypical femoral fractures, 7 of which (53%) required secondary operative

procedures [34]. Surgical intervention must therefore be followed with careful medical management.

Following diagnosis of atypical femoral fracture from radiographic evaluation, bisphosphonate therapy should be discontinued. Patients should receive daily calcium supplementation of 1000–1200 mg/day, and 25-hydroxyvitamin D should be corrected to a minimum of 30 ng/mL. Teriparatide should be initiated postoperatively to increase bone turnover and BMD in patients previously taking bisphosphonates [35, 36].

Surveillance of patients with atypical femoral fractures throughout the healing process is essential because bilaterality is a minor feature of these fractures, and incipient stress fractures in the contralateral limb may propagate when weight bearing is reduced in the fractured limb. Radiographs of the contralateral femur must be evaluated for evidence of a stress fracture. A technetium bone scan or magnetic resonance image (MRI) should be considered if a stress fracture is suspected (Figure 2). If the patient has minimal pain, bone marrow edema, and no clear fracture line on a radiograph, a period of conservative therapy may be considered. Teriparatide, reduced activity, and reduced weight bearing should be implemented to prevent progression to a complete fracture until there are signs of healing from the plain radiographs or MRI. Prophylactic intramedullary nail fixation should be considered when there is a moderate to severe pain of the affected limb; persistent pain or persistence of the fracture line on radiographs after 3 months of conservative treatment; or progression of the fracture line observed from serial radiographic examination (Figure 2) [37]. Two recent case series indicated that most patients initially treated conservatively without teriparatide eventually required surgical intervention [37, 38].

Management of patients on long-term bisphosphonate therapy without atypical fractures

Bisphosphonates are generally safe and effective when used for the durations of the original clinical trials (typically 3–5 years) [1, 3]. For durations longer than 5 years, the FDA currently recommends periodic review of the medical management of patients on long-term bisphosphonate therapy, although the elements of those reviews are still under debate [39]. These patients should be monitored for signs of femoral stress fractures as well as for markers of bone turnover to avoid oversuppression of remodeling. Relevant markers include serum or urine N- or C-telopeptide of collagen cross-links (NTX, CTX) for bone resorption and bone specific alkaline phosphatase or aminoterminal propeptide of type I collagen (PINP) for bone formation. In addition, patients should be monitored for evidence of stress fractures, particularly prodromal pain in the thigh or groin, because bisphosphonates bind preferentially to sites of microdamage formation, and localized oversuppression of bone turnover and damage accumulation could potentially occur even with normal systemic levels of bone turnover markers. Finally, fracture risk should be assessed by considering individual patient risk factors such as age, history of glucocorticoid use, and family history of fragility fracture.

Bisphosphonates should be discontinued in patients without a clear indication for antiresorptive therapy, such as those with normal or mildly osteopenic BMD (Figure 2). Patients with moderate-high fracture risk may consider a drug holiday of 1–2 years after 5 years of bisphosphonate treatment. No data from large trials examining drug holidays and

fracture risk are available; therefore, treatment must be tailored to the patient, and careful monitoring is required. Minimal additional antifracture benefit to 5 years of alendronate treatment beyond the initial 5 years of treatment has been demonstrated in meta-analyses of clinical trials of alendronate [40], although an additional 5 years of treatment reduced risk of clinical vertebral fractures [4]. This protective benefit must be balanced against the slightly increased risk for subtrochanteric or femoral shaft fractures observed in postmenopausal women who have been receiving bisphosphonate therapy for durations longer than 5 years [40]. An alternative medication such as raloxifene may be given during the holiday from bisphosphonates; anabolic agents should be reserved for the setting of fracture healing or declining BMD despite bisphosphonate therapy. Drug holidays are not recommended for patients at the highest risk of fragility fractures, including those receiving glucocorticoids or chemotherapy. These patients may require serial measurements of bone turnover markers and monitoring for stress fractures.

Conclusion

The absolute risk of atypical femur fracture is low compared to the risk of typical hip fractures in bisphosphonate users, but current epidemiologic evidence suggests that long-term bisphosphonate use may be an important risk factor for atypical fractures. Long-term bisphosphonate users must be monitored for biochemical markers of bone turnover and evidence of stress fractures in the proximal femur.

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Summary

- Bisphosphonates are generally safe and effective in reducing fracture risk in postmenopausal women when used for the duration of the original clinical trials (5 years).
- The absolute risk of atypical femur fracture is low compared to the risk of typical hip fractures in bisphosphonate users.
- Current epidemiologic evidence suggests that long-term bisphosphonate use (> 5 years) may be an important risk factor for atypical fractures.
- Long-term bisphosphonate users should be monitored for biochemical markers of bone turnover and evidence of stress fractures in the proximal femur.
- In patients with atypical femoral fractures, bisphosphonates should be discontinued, and teriparatide should be initiated postoperatively to increase bone turnover and bone density.

Figure 1. Radiographs showing a1) a stress reaction (arrow) on the lateral proximal femoral cortex and a2) an atypical subtrochanteric fracture sustained autramatically in the same patient 48 hours later; and b) a typical spiral subtrochanteric fracture.

Figure 2. Proposed guidelines for management of patients on prolonged bisphosphonate therapy with and without atypical femoral fractures [5].

Table 1

Major and Minor features for defining atypical femoral fractures [5]

	Major features	Minor features
Fracture history	• No or minimal trauma	• Prodromal pain in the groin or thigh • History use of other pharmacologic agents such as glucocorticoids or bisphosphonates
Location	• Subtrochanteric or femoral shaft	• Bilateral
Configuration	• Transverse or short oblique • Noncomminuted • Medial cortical spike	• Localized periosteal reaction of the lateral cortex • Generalized cortical thickening • Signs of delayed healing