Atypical femoral fractures and bisphosphonate use: current evidence and clinical implications

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Abstract: Osteoporosis is a disease characterized by a low bone volume and deterioration of the bone quality, which increases the risk of low-energy fractures. Bisphosphonate (BP) treatment increases the bone mass and reduces the risk of fractures in patients with osteoporosis by suppressing bone resorption. In spite of its clinical benefits, the long-term use of BPs has been linked to the occurrence of atypical femoral fractures (AFFs). Although the evidence had been controversial regarding the association between the occurrence of AFFs and BP use, more recent studies with radiographic adjudication have indicated the significant associations between them. However, the pathogenesis of AFFs is not completely understood. The most popular hypothesis has suggested that the suppression of bone turnover by BPs is responsible; however, some recent reports have implied the involvement of pathophysiological alterations of the bone quality and fracture repair process. In this review, we summarize and discuss the epidemiology, risk factors and pathology of AFFs.

Keywords: atypical femoral fracture, bisphosphonate, epidemiology, femoral geometry, lower limb alignment, pathogenesis, risk factor

Introduction

Bisphosphonates (BPs) reduce the incidence of vertebral and nonvertebral fractures and suppress the loss of bone volume in patients with osteoporosis [Harris *et al.* 1999]. However, BP therapy is associated with adverse effects because BPs inhibit osteoclast function and induce apoptosis, resulting in suppression of the bone turnover rate [Russell *et al.* 2007]. The prolonged use of BP therapy causes the accumulation of microdamage in bone [Mashiba *et al.* 2000], reduced heterogeneity of the organic matrix and mineral properties [Donnelly *et al.* 2012], increased advanced glycation end products [Saito *et al.* 2008], and a deterioration of bone quality, which can lead to atypical femoral fractures (AFFs). As AFFs occur even in patients without history of BP therapy [Tan *et al.* 2011], the risk factors for the development of AFFs are not only taking BPs, but also various other factors that affect bone remodeling.

The history and definition of AFFs

AFFs were first described by Odvina and colleagues in 2005 [Odvina *et al.* 2005]. They suggested that long-term BP therapy may lead to oversuppression

of bone remodeling, resulting in an impaired ability to repair skeletal microcracks and increased skeletal fragility. The American Society for Bone and Mineral Research (ASBMR) task force summarized the published reports regarding AFFs, and defined the major and minor features of these fractures [Shane *et al.* 2010]. In 2013, the case definition was revised by the ASBMR task force to clarify the features that distinguish AFFs from ordinary osteoporotic femur fractures (Box 1) [Shane *et al.* 2014]. In this revised version, localized periosteal ('beaking' or 'flaring') or endosteal thickening of the lateral cortex at the fracture site was added to the case definition (Figure 1), as these reactions near the fracture site had recently been reported [Neviaser *et al.* 2008; Lenart *et al.* 2009].

The characteristics of patients with AFFs

In 2010, the ASBMR task force summarized the characteristics of 310 patients with AFFs from the published literature [Shane *et al.* 2010]. The exposure of BP therapy among patients with AFFs was 93.9%, while 6.1% had no history of BP use. The majority of the patients used BPs for the treatment of osteoporosis (92.3%) and a minority used them

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Box 1. ASBMR Task Force 2013 revised case definition of AFFs.

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare

In addition, at least four of five major features must be present. None of the minor features is required but have sometimes been associated with these fractures

Major features*:

The fracture is associated with minimal or no trauma, as in a fall from a standing height or less

The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur

Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

The fracture is noncomminuted or minimally comminuted

Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ('beaking' or 'flaring')

Minor features

Generalized increase in cortical thickness of the femoral diaphyses

Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh

Bilateral incomplete or complete femoral diaphysis fractures

Delayed fracture healing

*Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (e.g. Paget's disease, fibrous dysplasia).

AFF, atypical femur fracture; ASBMR, American Society for Bone and Mineral Research.

for malignancy. The patients were female dominant and younger than the patients with typical osteoporotic femoral fractures. The median duration of BP therapy was 7 years. Prodromal thigh or groin pain was observed in approximately 70% of patients. Bilateral complete fractures and bilateral radiographic abnormalities, including cortical reactions, existed in 28% of the patients. The rate of delayed healing was 26%. Other systematic reviews were generally consistent with these findings [Giusti *et al.* 2010; Rizzoli *et al.* 2011; Donnelly *et al.* 2012].

Epidemiology

For the epidemiologic studies, there are two types of publications regarding the incidence of subtrochanteric (ST) and femoral shaft (FS) AFFs. In the first, the incidence of overall ST fractures was evaluated in registry-based cohort studies using a large database, such as the International Classification of Diseases codes [Abrahamsen *et al.* 2009, 2010; Kim *et al.* 2011; Hsiao *et al.* 2011]. Most of these studies were conducted before the establishment of a definition for AFFs by the ASBMR task force. They lacked radiographic adjudication in differentiating the typical osteoporotic femur fractures from AFFs. According to these studies, the rate of ST fractures among overall hip fractures was increased,

and the incidence of ST/FS fractures in female patients was between 10 and 35 per 100,000 person years. For instance, Wang and others described that the age-adjusted rates for hip fractures decreased by 31.6 % from 1996 to 2006; however, the number of ST fractures increased by 31.2% [Wang and Bhattacharyya, 2011]. Although this trend indirectly suggests a relationship between the increased use of BPs and the incidence of AFFs, the actual risk could not be estimated from these types of studies. In addition, Narongroeknawin and others [Narongroeknawin *et al.* 2012] investigated the validation of diagnostic codes for ST, FS and AFFs using administrative claims. They reviewed the records of 137 ST fractures (11 were AFFs) and revealed that the positive predictive value of administrative codes for defining AFFs was low and imprecise. Therefore, large database-based studies are helpful for estimating the incidence of AFFs, but they do not indicate the actual number of AFFs.

In the second type of studies, radiographs were reviewed and the fractures were categorized based on whether they met the definition for AFFs or not [Capeci and Tejwani, 2009; Lenart *et al.* 2009; Girgis *et al.* 2010; Giusti *et al.* 2011; Schilcher *et al.* 2011; Abrahamsen, 2012; Dell *et al.* 2012; Lo *et al.* 2012; Meier *et al.* 2012; Thompson *et al.* 2012; Saita *et al.* 2014a]. With regard to the

Figure 1. Lower limb alignment and location of AFFs [Saita *et al.* 2014b].

Standing full-length lower-limb radiographs in patients with subtrochanteric AFF (a) and femoral shaft AFF with bowed femur (b) are shown. Dotted lines indicate mechanical axes of lower limb. White arrows indicate fracture location of AFFs. In patient (a), the right femur sustained complete fracture, while the left femur sustained incomplete fracture with periosteal and endosteal focal hypertrophy in the lateral cortex. Mechanical axes path through knee joint in patient (a) but does not in patient (b). AFF, atypical femoral fracture.

incidence of AFFs amongst the overall ST/FS fractures, Lenart and colleagues reported that radiographic features of AFFs were present in 31.7% of ST/FS cases [Lenart *et al.* 2009]. In Australia, Girgis and colleagues reviewed the radiographs of 152 patients with ST/FS fractures, and confirmed that 20 patients (13%) had AFFs [Girgis *et al.* 2010]. In the Netherlands, Giusti and colleagues reported that the patients with AFFs comprised 16% (10/63) of ST/FS fracture patients [Giusti *et al.* 2011]. In Sweden, Schilcher and colleagues reviewed the radiographs of 1234 of the 1271 female patients who had a ST/FS fracture in 2008 and identified 59 (4.8%) patients with AFFs [Schilcher *et al.* 2011]. In the United Kingdom, Thompson and colleagues investigated 3515 patients with femoral fractures and identified 27 individuals with 29 AFFs, representing 0.8% of all hip fractures and 7% of FS fractures [Thompson *et al.* 2012]. In Japan, we reviewed the radiographs of 2238 hip and FS fractures, and

found 14 AFF cases (3.5%) in 402 ST/FS fractures [Saita *et al.* 2014a]. According to these radiographic adjudication studies and large database studies, the incidence of AFFs can be estimated between 0.3 and 11 per 100,000 person years. Similarly, in the United States, Feldstein and others investigated the incidence of new femur fractures between 1996 and 2009 in female patients over 50 years old and male patients over 65 years old, and revealed that the incidence of AFFs was 5.9 per 100,000 person years [95% confidence interval (CI) 4.6–7.4], with 1,271,575 person years observed [Feldstein *et al.* 2012]. In Switzerland, Meier and colleagues reported that the incidence rate of AFFs was 3.2 cases per 100,000 person years [Meier *et al.* 2012].

These studies with radiological adjustment indicate that the absolute incidence of AFFs is relatively low, but there is an association between BP use and the incidence of AFFs.

Risk factors

There have been some case-control studies with radiographic adjudication which have compared the typical osteoporotic fractures with AFFs [Girgis *et al.* 2010; Schilcher *et al.* 2011; Feldstein *et al.* 2012; Meier *et al.* 2012; Warren *et al.* 2012; Saita *et al.* 2014a]. In Australia, Girgis and others reviewed 152 femoral fractures (not including hip fractures) that occurred in 152 patients (mean age, 78 years old) from June 2003 to May 2008 [Girgis *et al.* 2010]. Twenty of the 152 fractures (13%) were classified as AFFs, and 17 patients (85%) in this group were current oral BP users. However, 3 patients (2.3%) were taking BPs of the 132 patients with typical femoral fractures. The relative risk of a patient with AFF being on a BP was 37.4 (95% CI 12.9–113.3; $p < 0.001$). Several additional risk factors were associated with AFFs. These included a history of a low-energy fracture [odds ratio (OR) 3.2; 95% CI 2.1–17.1; $p < 0.001$], the use of glucocorticoid (GC) therapy for more than 6 months (OR 5.2; 95% CI 1.3–31.0; $p = 0.01$), active rheumatoid arthritis (OR 16.5; 95% CI 1.4–142.3; $p < 0.001$), and a level of serum 25-hydroxyvitamin D less than 16 ng per milliliter (40 nmol per liter) (OR 3.5; 95% CI 1.7–18.7; $p < 0.001$).

In Sweden, Schilcher and others reviewed the radiographs of 1234 of the 1271 female patients who had a ST/FS fracture and identified 59 patients with AFFs [Schilcher *et al.* 2011]. A total of 78% of the patients with AFF and 10% of the controls had received BPs, corresponding to a multivariable-adjusted OR of 33.3 (95% CI 14.3–77.8). The duration of BP use influenced the risk (OR per 100 daily doses 1.3; 95% CI 1.1–1.6). After drug withdrawal, the risk diminished by 70% per year since the last use (OR 0.28; 95% CI 0.21–0.38).

In the United States, Feldstein and others reviewed 122 typical FS fractures and 75 AFFs [Feldstein *et al.* 2012]. The adjusted ORs of ever having a BP dispensed in patients with AFFs *versus* nonatypical FS fractures was 2.11 (95% CI 0.99–4.49). The ORs for exposure to GCs and proton pump inhibitors (PPIs) were also explored, and were not significantly different between the groups.

Meier and others identified 39 patients with AFFs and 438 patients with typical fractures in 477 patients (aged 50 years and older) with ST/FS fractures between 1999 and 2010 hospitalized at a single university medical center [Meier *et al.*

2012]. Of the patients with AFFs, 32 (82.1%) had been treated with BPs compared with 28 (6.4%) in the typical fractures group (OR 66.9; 95% CI 27.1–165.1). The ORs (95% CIs) for AFFs were 35.1 (10.0–123.6) for less than 2 years of BP use, 46.9 (14.2–154.4) for patients who had used BPs for 2–5 years, 117.1 (34.2–401.7) for patients who had used BPs for 2–9 years and 175.7 (30.0–1027.6) for patients who had received BPs for more than 9 years compared with no use.

In New Zealand, Warren and others reviewed the radiographs of 195 patients with ST/FS fractures [Warren *et al.* 2012]. There were six AFFs, which they compared with 65 typical fractures. Of the patients with AFFs, 3 (50%) had been treated with BPs compared with 15 (23%) who had been treated in the typical fractures group (OR 5.5; 95% CI 0.97–31, $p = 0.07$). The ORs for exposure to GCs was 4.9 (95% CI 0.74–32.7; $p = 0.13$),

In Japan, we conducted a case-control study in 10 patients with AFFs and 30 patients with low-energy typical ST/FS fractures [Saita *et al.* 2014a]. BP exposure was 90% in the AFF group, whereas it was 14.3% in the typical fracture group. A fracture location-, age- and gender-matched (1:3) case-control study revealed that the administration of BPs, GCs and suffering from a collagen disease were significant risk factors for developing AFFs (OR 36.0, 95% CI 3.8–342.2; OR 13.0, 95% CI 2.3–74.1; and OR 9.0, 95% CI 1.6–50.3, respectively).

In a prospective study, Dell and others reviewed all femur fractures that occurred between 2007 and 2011 in 1,835,116 patients older than 45 years at Kaiser Southern in California [Dell *et al.* 2012]. The results showed that 142 patients had AFFs; of these, 128 (90%) had BP exposure. There was no significant correlation between the duration of use (5.5 ± 3.4 years) and age (69.3 ± 8.6 years) or bone density (T score -2.1 ± 1.0). There were 188,814 patients who had used BPs. The age-adjusted incidence rates for an AFF were 1.78/100,000/year (95% CI 1.5–2.0) with exposure from 0.1 to 1.9 years, and increased to 113.1/100,000/year (95% CI 69.3–156.8) with exposure from 8 to 9.9 years. They concluded that the incidence of AFFs increases with a longer duration of BP use.

Wang and others followed 522,287 new BP users for their adherence to oral BPs among all Medicare fee-for-service female beneficiaries from 2006 to 2010 [Wang *et al.* 2014]. They found that the

adjusted hazard ratio (HR) of ST/FS fractures for the highly compliant *versus* the less compliant users became significant after 2 years of follow up (HR 1.51, 95% CI 1.06–2.15) and reached the highest risk in the fifth year (HR 4.06, 95% CI 1.47–11.19). However, the age-adjusted incidence rates for intertrochanteric (IT)/femoral neck (FN) fractures were significantly lower among highly compliant beneficiaries compared with less compliant users (HR 0.69, 95% CI 0.66–0.73). Therefore, adherence to oral BPs needs to be monitored for a possible risk factor for AFFs. These studies show that those who are more compliant with BP therapy have fewer IT/FN fractures, but more ST/FS fractures, suggesting that BPs may have a negative effect on the ST/FS fracture.

Under other conditions, several studies indicated that there was an association between GC use and AFFs [Girgis *et al.* 2010; Dell *et al.* 2012; Meier *et al.* 2012; Saita *et al.* 2014a], while some reports [Schilcher *et al.* 2011; Feldstein *et al.* 2012] did not. Female gender and a younger age are also considered to be significant risk factors [Abrahamsen *et al.* 2009; Nieves *et al.* 2010].

Pathogenesis

The mechanisms underlying the development of AFFs have not been fully understood. The characteristics of radiological features of AFFs, such as focal hypertrophy of the lateral cortex, periosteal and endosteal callus formation and the transverse fracture line at the lateral cortex, suggest that fatigue damage accumulates within the bone cortex for a long period and that AFFs are stress or insufficiency fractures. A concentration of mechanical stress on the bone leads to the formation of microcracks, which heal by bone remodeling *via* the initiation of osteoclastic bone resorption, followed by osteoblastic bone formation to replace new bone. The pathogenesis of BP-associated fractures seems to be related to the alterations of this tissue repair process as a result of the continuous suppression of the bone turnover rate [Mashiba *et al.* 2000]. Ettinger and others proposed the mechanisms underlying the pathogenesis of AFFs by reviewing the evidence that support suppression of bone turnover contributing to reduce bone material quality [Ettinger *et al.* 2013]. They hypothesized that long-term decreased bone turnover causes tissue brittleness that initiates cracks, increases homogeneity of osteonal and interstitial structures, and impairs targeted repair by bone metabolic units. These pathogenic changes result

in unimpeded crack progression and lead to the development of AFFs.

A reduction of the bone turnover by BP treatment alters the bone mineral and matrix properties. Saito and others revealed that BP therapy causes an increase in advanced glycation end products of the extracellular bone matrix, deteriorating the mechanical properties of the bone [Saito *et al.* 2008]. Prolonged BP therapy causes the accumulation of microdamage to bone and reduces the heterogeneity of the organic matrix and mineral properties [Donnelly *et al.* 2012]. These changes reduce the bone repair ability, which results in the accumulation of local microdamage especially at the site of maximum mechanical force.

Several reports have investigated the histology of patients with AFFs, and the ASBMR task force summarized them in 2010 [Shane *et al.* 2010]. Most of them performed transiliac bone biopsies on samples from patients with BP-associated AFFs, and observed reduced or absent populations of osteoclasts and osteoblasts, which were expected following BP treatment. However, few reports have examined femoral bone biopsies. Jamal and others reported a histomorphometric analysis of a biopsy from a femur of a patient with AFF and revealed normal lamellar bone texture, no evidence of adynamic bone, and no impairment of the mineralization [Jamal *et al.* 2011]. They suggested that the cause of AFFs associated with BP use is not related to the oversuppression of bone turnover. More recently, Schilcher and others reported the histology of the femur in the patients with eight AFFs [Schilcher *et al.* 2014]. They found that AFFs appear to consist of a microcrack at the lateral cortex with its main direction perpendicular to the long axis of the bone. The surrounding bone shows signs of remodeling, mainly represented by the presence of osteoclasts, resorption cavities and woven bone facing the crack. They also evaluated the osteocyte lacunae and found that half (4/8) of the AFFs consisted mainly of empty lacunae. They found that the bone facing the crack of the AFF shows signs of remodeling, though there were no signs of remodeling or callus formation within the fracture gap itself. They hypothesized that normal gait produces strains in the fracture gap that are too large for cell survival and ongoing BP treatment suppresses bone resorption allowing smaller cracks to coalesce to larger cracks and ultimately form a stress fracture. We also experienced the case of a patient with an AFF whose histology of

the femora revealed an increase of the woven bone and mainly empty lacunae (data not shown).

These findings suggest that the pathophysiology of AFFs is related to the impairment of the bone repair process, where microcracks need to be remodeled to new bone, and suppression of osteoclast function may cause unfavorable effects on this process.

Femoral geometry and biomechanical considerations of the lower limb

It is notable that AFFs also occur in BP-naïve individuals, suggesting that the pathophysiology cannot be entirely explained by BPs. Based on investigations of the radiological features in AFFs, it has been suggested that increased tensile stress on the lateral cortex would explain the ST and diaphyseal distribution of AFFs [Png *et al.* 2012].

The femur geometry determines the tensile force on the lateral cortex, while bowing of the femur concentrates the mechanical stress on the diaphysis of femora. Oh and others [Oh *et al.* 2014a] evaluated the bone morphology using a CT-based finite element method and revealed that patients with bowed AFFs showed a marked concentration of diffuse stress on the anterolateral surface, suggesting that tensile stress due to a bowing deformity may induce AFFs. Similarly, Sasaki and others reported that the femoral curvature was significantly higher in patients with AFFs in comparison with the control group, suggesting that an increased femoral curvature might be a causative factor for AFFs, especially in the older population in Japan [Sasaki *et al.* 2012]. Since femoral shaft bowing and age were significantly correlated in female patients, but not in male patients [Karakas and Harma, 2008], the bowed femora in older female patients may predispose these patients to the development of AFFs not only in BP users but also in BP-free cohorts [Oh *et al.* 2014b]. Recently, Taormina and others conducted a case-control study in which the prefracture radiographs of 53 BP users who developed AFFs were compared with those of 43 asymptomatic chronic BP users and 64 patients with intertrochanteric fracture [Taormina *et al.* 2014]. They found that BP users who developed fractures had more acute/varus prefracture neck-shaft angles, a shorter hip axis length and narrower center-edge angles. A receiver operating characteristic (ROC) curve analysis (area under the curve = 0.67; 95% CI 0.56–0.79) determined that a cutoff point for the neck-shaft

angle less than 128.3° yielded 69% sensitivity and 63% specificity for the development of an AFF. They concluded that an acute/varus angle of the femoral neck and a narrow center-edge angle were associated with the development of AFFs in long-term BP users. They recommended that physicians should regularly evaluate patients by radiography to assess the potential risk of AFFs.

An examination of the lower extremities in patients with AFF was performed in two studies. First, we evaluated the standing lower limb alignment in 10 patients with AFFs and found that the mechanical axes of the lower limbs, represented by the femorotibial angle (FTA), correlated with the fracture height ($r=0.82$; 95% CI 0.49–0.94) [Saita *et al.* 2014b]. This revealed that FS-AFFs occurred in subjects with larger FTA (183.3°), while ST-AFFs occurred in subjects with smaller FTA (172.8°), suggesting that the lower limb alignment would determine the fracture location (Figure 1). Second, Morin and others investigated the femoral geometrical parameters of 25 patients with AFFs exposed to BPs [Morin *et al.* 2013]. Lower extremity examinations were performed in the upright weight-bearing position using the EOS low irradiation 2D–3D X-ray scanner (EOS imaging, Paris, France). They showed that subjects with AFF tended to have shorter lower limbs, smaller femur neck-shaft angles, larger hip-knee shaft angles and greater femoral torsion compared with a normal reference cohort. Compared with female patients with FS-AFFs, those with ST-AFFs tended to have a smaller femur neck-shaft angle (122.8° *versus* 127.9°; $p=0.09$) and a larger femoral offset which was defined as the distance from the center of rotation of the femoral head to a line bisecting the long axis of the femur (4.2 cm *versus* 3.8 cm; $p=0.08$).

These studies indicated that biomechanical factors, such as the femoral bone geometry and lower limb alignment, are related to the location where the mechanical stresses are concentrated. Therefore, malalignment or age-related changes in the lower limbs would be one of the risk factors, for the accumulation of the microcracks in the lateral cortex and progression to AFFs.

Conclusion

The recent literature indicates that the absolute incidence of AFFs is low, but there is an association between long-term BP use and the incidence of AFFs. Although the pathogenesis of AFFs has not been fully understood, long-term suppression

of bone remodeling would cause a deterioration of the bone microarchitecture, reduce the bone repair process and lead to the accumulation of microdamage resulting in the progression of AFFs. Geometrical factors related to the femur and lower limb alignment are related to the concentration of mechanical force. Physicians should recognize the risk factors for the development of AFFs, as well as signs of AFFs, in order to provide adequate treatment for patients. More research will provide better evidence related to these topics and can contribute to establishing evidence-based treatment for AFFs.

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Conflict of interest statement

The authors declare no competing interests.

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