

Atypical femoral fractures

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Summary

Bisphosphonates (BPs) represent the most widely used therapy for osteoporosis. Recently, a relationship between long-term treatment with BPs and a subset of atypical femoral fractures (AFFs) from below the lesser trochanter to the supracondylar line has been described. Many etiopathogenetic theories have been invoked to explain AFFs: reduced bone turnover and increased osteoblast bone apposition with accumulation of microdamage and decreased bone toughness with subsequent increased risk of micro-cracks and duration fractures, collagen fiber cross-linking and vascularization impairment.

Based on published studies, a task force of the American Society for Bone and Mineral Research has redacted the diagnostic criteria of AFFs by classifying them according to their major and minor criteria.

The treatment for displaced AFFs is osteosynthesis, but there is a lack of evidence for undisplaced AFFs and the duration of fracture treatment. BPs have a proven efficacy in osteoporotic fracture reduction as well as in the treatment of other bone diseases caused by the downregulation of osteoclast activity. BPs have an excellent benefit-to-risk ratio; however, minor adverse events, such as AFFs, occur in a variable percentage of patients treated over a long period of time.

KEY WORDS: atypical femoral fractures; bisphosphonates; surgical treatment.

Introduction

Osteoporosis is a chronic disease whose incidence is increasing due to the aging of the population (1, 2). This pathology requires

a long-term therapy to prevent fragility fractures. Currently there are several drug classes for the treatment of osteoporosis: estrogen, selective estrogen receptor modulators (SERMs) (such as raloxifene and bazedoxifene), antiresorptive drugs [such as bisphosphonates (BPs)], anabolic drugs [such as recombinant human parathormon (rh-PTH)], dual action drug (such as strontium ranelate) and monoclonal antibodies (such as Denosumab) (3-5). Nowadays, BPs represent the most widely used therapy for osteoporosis and other osteoclast-related bone diseases, such as Paget and bone metastases. BPs are also indicated in the therapy for Osteogenesis Imperfecta (6).

BPs are potent inhibitors of osteoclast-mediated bone resorption, with a demonstrated effectiveness in reducing the incidence of vertebral, femoral and other fragility fractures in both women and men (7).

The efficacy of BPs varies among patients. It is estimated that up to 15% of patients fail to respond to BPs therapy (8).

Moreover, some patients undergoing intravenous BPs treatment have experienced adverse events, such as atrial fibrillation, acute phase response, renal insufficiency and osteonecrosis of the jaw.

Recently, a relationship between long-term treatment with BPs and a subset of atypical femoral fractures (AFFs) from below the lesser trochanter to the supracondylar line (mostly at the subtrochanteric region) has been described. The first report was published by Odvina (2005) who described 9 cases in women having severely suppressed bone turnover who sustained AFFs and had been taking BPs for at least 1 year (9). Subsequently, several clinical cases and case reviews reported an association between low energy trauma, subtrochanteric or femoral shaft fractures and patients who had been treated with long-term BPs therapy.

Kim et al. reported an analysis based on data from the United States showing how rare AFFs are: of 33,851 patients treated with BPs, only 104 sustained an AFF, with an estimated occurrence of 1.46 per 1,000 treated patients per year (10).

In a cohort study using national healthcare data of the U.S., Abrahamsen et al. compared 39,567 patients taking alendronate from 1996 to 2005 with 158,268 untreated controls, reporting that subtrochanteric and diaphyseal fractures occurred at a rate of 13 per 10,000 patient/year in untreated women and 31 per 10,000 patient/year in women receiving alendronate (11).

Subtrochanteric or femoral shaft fractures are rare (10-30% of all hip/femur fractures) and many of them (about 75%) are usually associated with a high energy trauma. Subtrochanteric fractures account for approximately 3% of all femoral fractures in the elderly, but the morbidity and mortality are similar to hip fractures.

Etiopathogenesis

The etiopathogenesis of AFFs is still unknown; studies of the effects of BPs on bone metabolism suggest involvement of several biological mechanisms.

BPs have a strong affinity for mineralized tissue; they cause a chemical effect by binding strongly to calcium crystals and then inducing a cellular effect on the osteoclasts during bone re-

sorption. BPs have a long half-life, thus affecting osteoclast activity for several months after the end of therapy. By reducing bone turnover, BPs treatment leads to increased bone micro-damage and decreased bone toughness with a subsequently higher risk of micro-cracks and duration fractures (12).

These findings were clearly demonstrated by Mashiba and Komatsubara in animals models showing that suppressed bone turnover results in the accumulation of micro-damage and the reduction of bone toughness without a reduction in strength (13-15).

Human bone biopsies in patients who have taken BPs have shown conflicting results; an analysis of several studies with a total of 57 biopsies performed on the iliac crest or at the fracture site showed low bone turnover in the majority of patients but not in all of them. However, caution should be used when interpreting a biopsy at the fracture site because the fracture itself speeds up the remodelling processes (16).

Other theories of etiopathogenesis have hypothesized the involvement of collagen fibre cross-linking; BPs lead to increased mature collagen shaping, and greater bone stiffness and strength (17, 18).

Other authors have found that BPs reduce bone turnover, thus increasing bone mineralization and leaving the mineral part unmodified. This mineralization enhancement produces increased bone stiffness and strength (19, 20).

Moreover, Donnelly et al. compared the bones of 20 women taking BPs (with an average time of 7 years of treatment) with 20 naïve osteoporotic women. This study showed that the BP patients had more uniform bone tissue, especially in the cortical bone (21).

Another hypothesis for explaining the etiopathogenesis of AFFs is the vascularization impairment due to the BPs intake. Wood observed that BPs have an anti-angiogenic action (22); nevertheless, this finding was not confirmed by an animal study with clodronates (23). Other authors have found a vascularization reduction of up to 40% in mice treated with BPs and

have hypothesized that this reduction was due to osteoclastic activity inhibition (24).

Diagnosis

Approximately 70% of patients with a confirmed stress fracture report prodromal pain before diagnosis (16). Although AFFs are uncommon, they should always be suspected in elderly patients with chronic pain. The time between the onset of the pain and the diagnosis of an AFF varies from one week to 2 years (25).

When an AFF is clinically suspected, an X-ray should be carried out in both the antero-posterior and the lateral views. The data from case reports and case series show that BP-related AFFs present specific radiographic features (26).

Based on published studies, a task force of the American Society for Bone and Mineral Research (ASBMR) has redacted the diagnostic criteria of AFFs by classifying them according to their major and minor criteria (16) (Table 1). For the diagnosis of an atypical fracture, all major criteria are required; minor criteria could be either present or not. The X-ray characteristics of AFFs are listed in Table 2.

Unlike stress fractures, which usually involve the medial cortex of the proximal third of the femoral diaphysis, in AFFs, the fracture line starts from the lateral cortex (Figure 1 A, B). Moreover, stress fractures are commonly observed in athletes while AFFs are typical of elderly patients.

When groin or thigh pain is present with negative X-rays, it is necessary to perform a second level exam, such as bone scintigraphy, MRI or a CT scan.

Bone scintigraphy may show focal increased uptake at the lateral cortex; this feature should be unilateral or bilateral. MRI has greater sensitivity and specificity than scintigraphy. Similarly, a CT scan with thin section and multiplanar images makes this technique useful for identifying bony changes (16).

Table 1 - Diagnostic criteria for atypical femoral fracture (Task force for the American Society for Bone and Mineral Research) (16). Diagnosis requires the presence of all the major criteria. None of the minor criteria is required, but they could may be present concomitantly with major criteria.

Major criteria	Minor criteria	Exclusion criteria
Proximal fracture line under the lesser trochanter and distal fracture line above the femoral condyles	Periosteal reaction along the lateral cortex	Femoral neck fracture
No trauma or low-energy trauma	Increased cortical thickness	Intertrochanteric fracture with extension to the subtrochanteric femur
Transverse or only slightly oblique fracture line (angle < 30°)	Prodrome pain in the groin or thigh	Periprosthetic fracture
Non comminuted fracture	Bilateral fracture	Pathological fracture related to a primary bone tumor or bone metastasis
Complete fracture crossing from one cortex to the other, with or without a medical cortical beak or incomplete fracture (or fissure) involving only the outer cortex	Delayed healing	–
–	Co-morbidities: rheumatoid arthritis, vitamin D deficiency, hypophosphatasia	–
–	Concomitant treatments: bisphosphonates, glucocorticoids, proton pump inhibitors	–

Table 2 - X-ray characteristic of complete or incomplete fracture.

Transverse fracture line
Cortical thickening (focal or diffuse), particularly in the lateral cortex
Focal cortical thickening may produce an appearance of cortical "beaking" or "flaring" adjacent to a transverse fracture line
In a complete fracture, an oblique component may be observed as a prominent medial spike



Figure 1A - A-P: X-ray of a 63 year old female under treatment with BPs for 5 years. The X-ray shows cortical thickening and beaking of the lateral cortex; a transverse fracture line is present.



Figure 1B - Lateral view which shows a duration fracture and femoral shaft narrowing.

Treatment

There is a lack of data in the literature regarding the appropriate surgical treatment. In the case of displaced fractures, the treatment should be reduction and surgical fixation. A contralateral femoral X-ray should always be carried out in order to eventually identify a contralateral AFF. If osteosynthesis is considered the treatment of choice for displaced AFFs, few data exist regarding the treatment of undisplaced AFFs.

Shane et al. have suggested that, when in the presence of an AFF, treatment should be guided by symptoms; asymptomatic patients should reduce their activity level, patients with slight groin or thigh pain should avoid weight bearing by using crutches. After 3 months of conservative treatment, when no symptomatic or radiological improvement occurs, a prophylactic fixation should be considered. In patients with moderate or severe pain and risk for fracture dislocation, prophylactic surgery should be performed (16).

For incomplete fractures intramedullary nail fixation seems to be easier; in the literature, no evidence exists as to which is the correct surgical technique for dislocated AFFs.

Despite the fact that Grady et al. (27) have reported two failures of AFFs healing after intramedullary nailing, other authors have reported good results, even if some additional procedures were required (28).

As BPs inhibit bone remodelling, in complete fractures, intramedullary nailing is preferred to open reduction and internal fixation with a plate and screws which leads to direct fracture healing where osteoclast activity is mandatory.

In the pharmacological management of patients affected by AFFs, the serum levels of calcium and vitamin D should always be assessed; when levels are low, standard supplements should be prescribed. Due to the possible etiopathogenesis of AFFs, all antiresorptive drugs should be suspended. Finally, in the literature, there are case reports in which the use of anabolic drugs, such as teriparatide, have improved fracture healing (29-32).

Conclusion

Bisphosphonates have a proven efficacy in the reduction of osteoporotic fractures as well as in the treatment of other bone diseases which benefit from a decrease in osteoclast activity. BPs have an excellent benefit-to-risk ratio; however, minor adverse events, such as AFFs, occur in a variable percentage of patients who have undergone long-term treatment.

In an analysis on 11,994 patients, Abrahamsen et al. showed that only 7% of patients with a subtrochanteric fracture of the femur had taken BPs (33).

Giusti et al. reported 141 atypical femoral fractures in women treated with BPs. In their study, 24% of the patients who sustained an AFF had been under treatment with BPs for less than 3 years and 75.9% had at least one major chronic disease: rheumatoid arthritis (10.3%), asthma (14.9%), diabetes (10.3%) or chronic obstructive pulmonary disease (10%). Moreover, 60% of the patients were using at least one drug other than BPs: estrogen (11.8%), proton-pump inhibitors (38.9%), more than 25% were on long-term oral glucocorticoid treatment and approximately 10% were using inhaled glucocorticoids (25).

The European Medicines Agency stated that AFFs are a class effect of BPs, but that the benefits arising from their use continue to outweigh its risks (34).

There is no rationale for withholding BPs therapy from patients with osteoporosis, although continued use of BPs beyond a treatment period of 3 to 5 years should be reevaluated annually. Consideration should be given to stopping (at least temporarily) BPs therapy in patients who are reassessed to be at low or

low-moderate risk (no incident fractures, T-score of 2.0 or higher, and no other major risk factors) after a 3 to 5 year therapeutic period (35, 36).

The possibility to predicting the risk of adverse drug reactions is essential for chronic bone disorders requiring long-term treatment. Moreover, various effective therapies are currently available and, therefore, selecting the best treatment option for each individual patient is a reality.

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