Atypical femur fractures

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Summary

Already from the late 1970s, some fractures of the subtrochanteric and diaphyseal region of the femur were defined "atypical" and described as "fatigue" fractures. In 2005, Odvina reported an unusual type of femoral fracture after the administration of alendronate as a result of a severely repressed bone turnover and Lenart defined femoral fractures occurring on the subtrocanteric or diaphyseal region in post-menopause women after alendronate therapy as "atypical" (AFFs). Hence the hypothesis that these fractures could be associated with the use of bisphosphonates (BP). Even with a "normal" dose of BP, the risk of fracture is highest if therapy lasts more than 5 years, although cases have recently been reported with short-term therapies.

However, many of the studies on this association did not consider the radiographic patterns and the atypical or typical radiographic definition did not evaluate the BP doses used and patient compliance; they just state if there was an association or not, and this had led to an underestimation of the real incidence of these fractures.

It is the latest revision of the diagnostic criteria made in 2013 by the American Society for Bone and Mineral Research (ASBMR) Task Force to determine that to be defined as AFF, a fracture localized along the femoral diaphysis just distal from the small trochanter to just proximal to the supracondylar region must have certain clinical and radiographic patterns. They also defined exclusion and minor criteria.

In general, incidence is still low. Considering the incidence of all femoral fractures of about 460/100,000 people-year, the sub-trochanteric ones represent 7 to 10% of these, and atypical ones are even rarer: 32 per million people-year and 5, 9 per 100,000 person-years in a retrospective study from 1996 to 2009. Morbidity and mortality are similar to neck or intertrochanteric femoral fractures.

However, AFF was also found in patients who had never used BP, so BP therapy could not be the only risk factor. Among them, recent attention has been given to hypoposphatasia, picnodisostosis with mutant catepsin gene, osteopetrosis, tumors, use of glucocorticoids (GC), high body mass index (BMI) and use of proton pump inhibitors (PPI).

About pathogenesis it seems that the accumulation of microlesions, the increase of mineralization with reduced heterogeneity of mineralization, accumulation of Advanced Glycation End-products (AGEs), reduced vascularization and reduced antiangiogenic effects, alterations of normal collagen reticulation and maturation variations of crosslinks of collagen are all factors involved.

Histological studies have demonstrated how these stress fractures occur: at the fracture site there are thin cracks that even micro-movements can distort and bring to their enlargement. In presence of predisposing conditions (femoral conformation, hypophosphatasia, use of GC ...) in BP patients, these cracks are trapped in free mineral deposits at the site of the fracture, particularly at intracortical level and act longer by suppressing just in that site where the remodeling processes are essential to healing. Initial alteration occurs precisely on the lateral cortex, which is subjected to increased stress in the subtrochanteric and diaphyseal region, causing a femur bending.

This observation has led to studies that have shown how femoral conformation plays a role in determining an increased risk of AFF. With a same BP therapy duration, for conformation characteristics, more is the lateral curvature of the femur and greater the knee valgus and more frequent are the AFFs; these features are more common in some breeds (Asiatic).

Recently AFF case reports have also been published with denosumab, a monoclonal antibody that similarly to BP has an anti-resorptive effect.

Some Authors and the ASBMR themselves have outlined guidelines for AFF diagnosis and management. Following patients who are taking BP therapy with DEXA is useful: evidence of certain pre-lesions to DEXA and the presence of prodromal symptoms are strong predictors of a subsequent fracture. Also useful is the dosage and monitoring of biochemical markers of bone remodeling.

With regard to surgical strategy, the use of an intramedullary nail is the best treatment. In cases of particularly curved femur it is more appropriate to use angular stability plates because in the case of incomplete

fracture the use of a nail may turn it into complete and because even in the case of complete fractures, the risk of non-union is higher.
To date, even stopping of BP alone in the AFF suspect and the use of teriparatide as supportive drug therapy are two key elements to enable proper AFF healing.

KEY WORDS: atypical; femur; fractures; bisphosphonates.

Introduction

Barcsa et al. first coined the term "atypical" in 1978 in their description of fatigue fractures (1). Nevertheless, Odvina et al., who suggested a prominent pathogenic role of severe bone turnover suppression caused by these drugs (2), published the first report of bisphosphonate-related femoral fractures in 2005. In 2008, Lenart et al. identified 15 postmenopausal women taking bisphosphonates (BPs) who sustained low-energy Atypical Femur Fractures (AFFs); all these patients shared a unique radiographic pattern defined as "a simple transverse or oblique fracture with beaking of the lateral cortex and diffuse cortical thickening of the proximal femoral shaft" (3, 4).
Bisphosphonates (BPs) reduce bone loss and prevent fractures in postmenopausal women with osteoporosis, in men with osteoporosis, and in patients receiving glucocorticoid (GC) therapy. In contrast to osteonecrosis of the jaw (ONJ), well-known potential complication of BP therapy, which came to attention in patients receiving high-dose BP therapy for malignancy (5), AFFs appear at low doses of BPs, most though not all patients with AFFs were receiving the lower doses of BPs typically used to treat osteoporosis or osteopenia (6).
In 2009, the American Society of Bone and Mineral Research (ASBMR) convened a multidisciplinary, international task force to develop a case definition (Table 1) so that subsequent studies reported on the same condition. The task force reviewed the English-language scientific literature on the epidemiology, risk factors, diagnostic imaging, and clinical management of AFFs and identified future areas for research. Based on its review of published and unpublished data and the widespread use of BPs in 2010, the task force concluded that the incidence of AFFs associated with BP therapy for osteoporosis was very low. That was true particularly if compared to the number of vertebral, hip, and other fractures that BPs prevented. They noted that a causal association between BPs and AFFs had not been established (7). However, the task force also expressed concern that risk may rise with increasing duration of exposure and that underreporting may mask the true incidence of AFFs.
The purpose of this paper is to provide an overview of the new definition, epidemiology, and putative pathophysiology of atypical femoral fractures and the strategies for management of patients with atypical fractures, based on the latest literature.

New definition of atypical femur fractures

Since publication of the report in 2010, several studies have been published on the epidemiology of and risk factors for AFFs and their relationship to BP therapy.
Therefore, the ASBMR reconvened the task force at the 2012 Annual Meeting of the ASBMR and drew up a final document with a new definition of AFFs, including reports published before March 10, 2013 (Table 2) (Figure 1).
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 4 of 5 major features have to be present. None of the minor features is required but has sometimes

Table 1 - 2010 ASBMR task force case definition of AFFs.

Major features (a)
Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
Associated with no trauma or minimal trauma, as in a fall from a standing height or less
Transverse or short oblique configuration
Noncomminuted
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
Minor features
Localized periosteal reaction of the lateral cortex (b)
Generalized increase in cortical thickness of the diaphysis
Prodromal symptoms such as dull or aching pain in the groin or thigh
Bilateral fractures and symptoms
Delayed healing
Comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia)
Use of pharmaceutical agents (e.g., BPs, glucocorticoids, proton pump inhibitors)

Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.
AFF = atypical femur fracture; BP = bisphosphonate.
(a) All major features are required to satisfy the case definition of AFF. None of the minor features are required but have been sometimes associated with these fractures.
(b) Often referred to in the literature as "beaking" or "flaring

Table 2 - Major and minor features for diagnosing atypical femur fractures (ASBMR Task Force 2013 Revised Case Definition of AFFs).

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 diaphysis
- 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

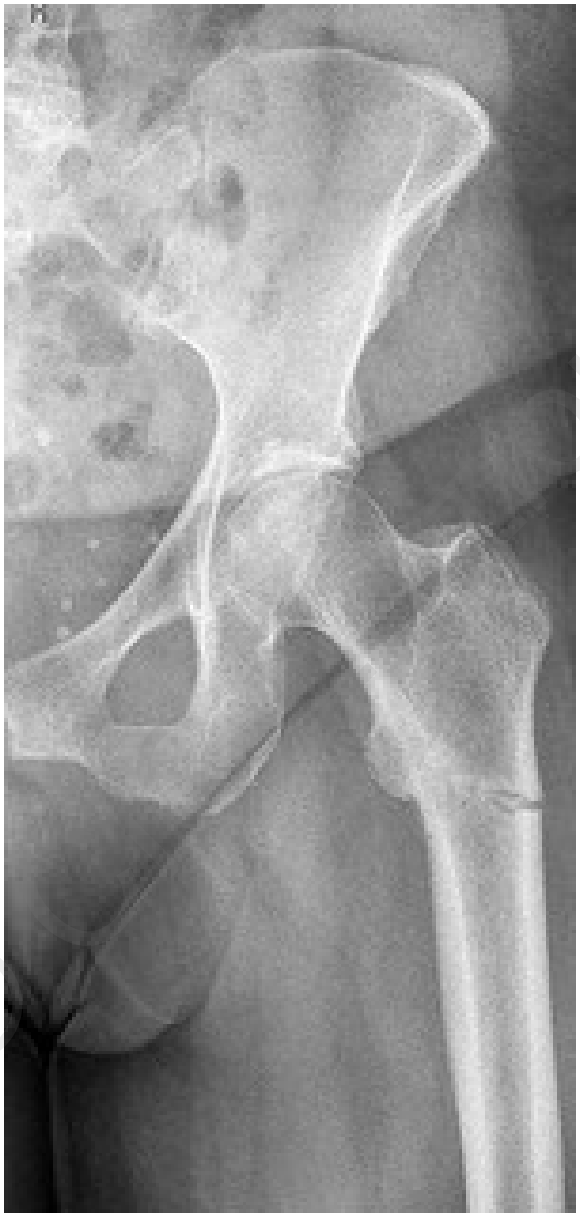

Figure 1 - Radiographic pattern of an atypical femur fracture.

been associated with these fractures. In the old version, to satisfy the case definition, all the major features had to be present.

As well as the old one, the new classification excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathologic fractures associated with primary or metastatic bone tumours and miscellaneous bone diseases (e.g., Paget disease, fibrous dysplasia).

Compared to the old version there are some changes in major and minor criteria.

About the fracture line, the term "short oblique" was not included, leading to a lack of precision of the old definition, which affected its specificity in classifying AFFs. However, the transverse nature of the fracture line is emphasized and it is specified that the transverse fracture may become oblique as it progresses medially across the femur. The precise definition of angle was not provided because it can be very difficult to measure angle in all cases, depending on the alignment of fracture fragments and projection of the X-rays.

The localized periosteal reaction of the lateral cortex is now specified to occur at the site of fracture and not "at or near" and has been moved from the minor to the major features. The language has been revised for greater precision to allow for inclusion of endosteal reactions based on the study by Mohan et al. (8) who observed multifocal endosteal thickening in patients with AFFs.

About the number of bone fragments, the fracture can also be minimally comminuted, cause the evidence of many orthopaedists on the task force have seen AFF cases with minimal comminution.

It has specified that bilateral fractures can be complete or incomplete.

The delayed healing is referred to the fracture.

The presence of comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and the use of pharmaceutical agents (e.g., BPs, glucocorticoids, proton pump inhibitors) are not anymore minor criteria, because it was deemed more appropriate for studies to seek these associations rather than to include them in the case definition.

Among the minor features, cortical thickening was retained despite the data on this was still inconclusive. Koeppen et al. (9) addressed whether patients with AFFs have thicker cortices than those with ordinary subtrochanteric and femoral

shaft fractures. They found no association between AFFs and generalized cortical thickening.

Epidemiology

The epidemiology of atypical femoral fractures is poorly understood compared to that of typical osteoporotic hip fractures. 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 (10).

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 of 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 (11) or increased by 20-40% in women (12, 13). None of these investigations assessed radiologic features of atypia; thus, the relative proportions of typical and atypical subtrochanteric fractures are unknown in these studies.

Other studies were conducted before the establishment of a definition for AFFs by the ASBMR task force, so that they lacked radiographic adjudication in differentiating the typical osteoporotic femur fractures from AFFs.

After the first case definition of AFFs in 2010, radiographs were reviewed and the fractures were categorized based on whether they met the definition for AFFs or not.

To date, two large datasets, in which radiographs were adjudicated for features of atypical fractures, have been analysed 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 (14). 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. This is the largest epidemiologic study to date of atypical femoral fractures that includes adjudication of radiographs for fracture morphology (10). Thus, even for bisphosphonate-users the absolute incidence of atypical fracture is low, approximately 1/30 of that of hip fragility fractures. Zeineb Mahjoub et al. (15) reported an incidence rate of AFF of 7.0 per 100,000 person-years, which is close to the incidence of 3.2 per 100,000 person-years in Geneva as reported by Meier et al. (16). In a population not exposed to BP, Dell et al. describe an incidence of 0.3 per 100,000 person-years. Nevertheless, in a population exposed to BP, the incidence rises to 55.0 per 100,000 person-years and from 1.78 to 107 per 100,000 person-years (depending on the duration of exposure), respectively (17).

Mohammad Kharazmi et al. (18) also evaluated age, sex and mortality. Patients with atypical fractures were younger than those with ordinary fractures and consisted of more women (93%) compared with ordinary fractures (81%). Endocrine disorders, neurologic diseases, and psychiatric diseases were less common in patients with atypical fractures compared with patients who had ordinary subtrochanteric or femoral shaft fractures. During 4013 person-years of follow-up with a mean of 4 years (maximum 7 years), 39 (23%) patients with an atypical fracture had died compared with 588 (62%) patients with an ordinary fracture. Those with an ordinary fracture had the highest rate of death early after the fracture event and 213 (22%) had died in the first year after the fracture. None of the patients with an atypical fracture died during the first year.

Ethyology and risk factors

The etiopathogenesis of AFFs is still unknown; several risk factors and biological mechanisms are involved in the development of AFFs.

Bisphosphonates

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 microdamage and decreased bone toughness with a subsequently higher risk of micro-cracks and duration fractures (19).

Studies of the effects of BPs on bone metabolism suggest the role of these drugs as a determinant factor in the pathogenesis, but according to a task force report from the ASBMR, this relationship has not yet been shown to be causal. Furthermore, many of the studies are observational.

Pharmaco-epidemiologic studies involving the monitoring of, detection of, evaluation of, and response to adverse drug events have used the well-known Bradford-Hill criteria. These criteria provide a better perspective on the lines of evidence in a given drug-disease association, thus helping to determine whether an apparent association between a medicine and an effect is likely to represent a causal relationship (20).

Bisphosphonates substantially increase the risk of atypical femoral fracture (with estimates of the odds ratio ranging from 2.29 to 139.33) (3, 10, 14, 21). Almost 40% of patients who sustained a subtrochanteric or femoral shaft fracture had used bisphosphonates for a significantly longer period than subjects who sustained an intertrochanteric or femoral neck fracture (odds ratio = 4.44, p = 0.002) (22). Despite these results, reanalysis of the data in three major randomized controlled trials showed no statistically significant increase in the risk of subtrochanteric femoral fracture in patients treated with bisphosphonates for as long as ten years (23). Given the mixture of results and the different methodologies used in these studies, it is difficult to demonstrate consistency of this association. Furthermore, not all fractures located in the femoral subtrochanteric or diaphyseal region of patients taking bisphosphonates are atypical. Only 17 to 29% of subtrochanteric or diaphyseal fractures can be classified as atypical fractures (7). Additionally, some atypical femoral fractures occur in patients who have not taken bisphosphonates (24, 25). Therefore, there is a lack of specificity for associating bisphosphonate use with atypical femoral fractures.

Studies have shown an increased risk of atypical femoral fractures in patients taking BPs for five or more years, suggesting a dose-response relationship (3, 22). Nevertheless,

Weaver et al. have shown that there is no dose-response relationship based on higher bisphosphonate dosage, but there appears to be a dose-response relationship based on the cumulative dose over time, which can be explained by the fact that bisphosphonates bind to bone for many years (26). Giusti et al. reported that the number of sub-trochanteric AFFs was higher in patients treated by BPs for longer than 5 years, whereas diaphyseal AFFs appeared to be more frequently observed in patients treated for less than 5 years (27).

Epidemiologic evidence supporting a relationship between bisphosphonate use and atypical fractures arises from two studies that adjudicated original radiographs to determine features of atypia (10, 28). 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.

The cause-effect relationship between bisphosphonate use and atypical femoral fractures is plausible given the hypothesized pathologic mechanisms involving bisphosphonate-induced microdamage accumulation, decreased spatial variation in the bone mineral density distribution, and decreased bone heterogeneity, as we will see when we talk about pathogenesis. In addition, the potential for a causal relationship between bisphosphonate use and the risk of atypical femoral fractures is supported by analogous examples of drug-enhanced fracture risk, including effects in patients taking corticosteroids, antiepileptic drugs, and antidepressants (29).

Femur geometrical features

Bone strength depends on a combination of its structural and material properties, both of which are modulated by bone turnover. Structural properties depend on the size and geometry of the bone, the microarchitecture and the amount of accumulated damage (30). Standing alignment of the lower limb results from the biomechanical interaction between its muscle and bone units, which is largely influenced by the geometry of the skeletal components. Variation in geometrical parameters can cause an imbalance in forces applied to the femur leading to different resistance to structural failure; for example, it has been shown that proximal femoral strength is decreased with a varus mechanical axis (31).

AFFs arise on the lateral aspect of the subtrochanteric and diaphyseal regions of the femur, which are subjected to high mechanical loads (32).

Because of this unique distribution, Morin et al. hypothesize that patients with AFFs have specific geometrical variations of their femur whereby baseline tensile forces applied to the lateral cortex are higher and might favor the appearance of these fractures when exposed to prolonged use of anti-resorptive agents such as bisphosphonates. Using the low irradiation 2D-3D X-ray scanner EOS™ imaging technology they had characterized and compared 3D femur geometric parameters, while in the standing position, between women who sustained BPs-associated AFF and women who had experienced similar duration of exposure to bisphosphonates but did not sustain AFF. Then they adjusted results for important predictors of femur geometric parameters such as ethnicity, age and height. They demonstrated that, compared to controls, those with AFFs had more lateral femur bowing and a wider hip knee shaft angle, indicating that for each degree increase in lateral femur bowing, from the femoral anatomical axis (0°), the risk of AFF was increased by 46%. Though not statistically significant, the hip-knee shaft angle showed a trend towards an association with increased risk of AFF. Women who sustained a sub-trochanteric AFF demonstrated a femoral neck shaft angle that was more acute (varus) than those with a fracture at a diaphyseal site (121.9° versus 127.6°) whereas femur bowing was more prominent in those with a diaphyseal fracture compared to those with a sub-trochanteric fracture (-4.3° *versus* -0.9) (33).

Many clinicians have noted anecdotally that patients who experience AFF have a femoral neck shaft angle at the lower limit of normal (120°); this lesser angle is seen more frequently in women and in individuals of Asian descent (34). Using 2 dimensional (2D) femur radiographs, Taormina et al. demonstrated the presence of a lesser femoral neck-shaft angle (varus geometry) in patients who had sustained BPs-associated AFF compared to controls also on bisphosphonates but without AFF (35).

Mahjoub et al. demonstrate that, in comparison with the controls, the patients with AFF were found to have an excessive femoral offset, a proximal femoral varus, a smaller femoral head diameter and smaller femoral neck. In addition, the presence of AFF was associated with thicker lateral and medial bone cortices at the level of the lesser trochanter and 50 mm below the lesser trochanter (15).

Chen et al. measured the lateral bowing angle of the femur in 17 patients with incomplete AFF and found that if the angle is ≤7 degrees, 63% of AFFs are located in the subtrochanteric region, and if the angle is >7 degrees, 100% of AFFs have a diaphyseal location (36).

Hypophosphatasia (HPP)

Patients with severe hypophosphatasia are known to sustain subtrochanteric fractures of the femur and there has been case reports of atypical femur fracture in a patient with hypophosphatasia taking bisphosphonates (37, 38).

Hypophosphatasia is a generally asymptomatic genetic condition with low alkaline phosphatase activity seen in up to 5% of adults. The severity of the disease is thought to be associated with the early age of onset. Clinical features include propensity to fracture, early loss of deciduous teeth, and pain. In particular, the most common fractures are stress fractures of metatarsals, associated of a hard healing delay and high risk of non-union. Low bone mineral density (BMD) and non-traumatic fragility fractures are typical signs of HPP in adult, often mistaken with osteoporotic fractures. The disease is caused by mutations in the tissue non-specific alkaline phosphatase gene (TNSALP, current gene symbol, ALPL). The low alkaline phosphatase activity results in a build-up of pyridoxal 5′ phosphate (PLP) and inorganic pyrophosphate. Inorganic pyrophosphate is chemically similar to bisphosphonates and an inhibitor of hydroxyapatite crystal growth and dissolution; therefore, it accumulates extracellularly and blocks skeletal mineralization causing osteomalacia (39, 40).

Hypophosphatasia presenting in adult life may manifest with bilateral femoral pseudofractures (Looser's zones or pseudofractures of Looser-Milkman) (41, 42) that are chronic and painful and usually occur laterally in the subtrochanteric diaphysis rather than within the medial cortex of the femoral neck typical of pseudofractures in more common forms of osteomalacia. Because there is no established medical treatment for hypophosphatasia, such pseudofractures are known to remain unchanged for years or to progress, but will not mend unless they go on to com-

pletion (often with low trauma) or receive intramedullary fixation (43). Whyte reported that similar femoral subtrochanteric pseudofractures occur in adults with X-linked hypophosphatemia (XLH), although in XLH they are more often located medially than laterally (44). As shown above, the lateral region of the femoral shaft sustained the maximum bending moment. Bisphosphonates are synthetic analogues of inorganic pyrophosphate that resist hydrolysis by alkaline phosphatase and then suppress skeletal turnover by blocking bone resorption while permitting some bone apposition. In a clinical vignette in 2009, Michael P. Whyte concluded that unmasking of hypophosphatasia in a carrier of a TNSALP gene defect or inadvertently treating XLH is probably not the explanation for the atypical femoral fractures that occur during alendronate therapy for postmenopausal osteoporosis. Whyte reported that the experience with hypophosphatasia and XLH bolsters the hypothesis that such fractures result from the pharmacological action of this bisphosphonate to suppress bone turnover (45).
Fundamental is not wrongly to diagnose HPP patients as osteoporotic patients, cause treatment with BPs increases risk of AFFs (46).

Age

AFFs occur in people younger than osteoporotic patients. Mahjoub et al. found in their study that the median age of the patients with AFF was 73.5 years (range, 65 to 81 years) *versus* 82.0 years (range, 69 to 88 years) of patients with osteoporotic fractures (15). Dell et al. (28) reported similar findings.

BMI (Body Mass Index)

Velasco et al. report that the BMI is higher in patients with AFF than in those with non-atypical femur fractures (47). While comparing a cohort of patients with AFF taking BP to another cohort taking BP but without any fractures, Taormina et al. noticed that the BMI was also higher in the AFF cohort (35).

PPI (Proton Pump Inhibitors) and GC (Glucocorticoids)

Yet Ing-Lorenzini et al. report long-term exposure to PPI in 7 out of their 8 patients with radiographically proven AFF (48). Fraser et al. (49) reported similar data.
Most (14, 16, 17, 50), though not all (10, 51), studies with radiographic review have reported significant association between GC use and AFFs, and two additional studies found an increased association that was not significant (52, 53).

Pathogenesis

The pathogenesis of AFFs remains unclear, although several mechanisms have been proposed. Some Authors have suggested that AFFs represent another form of osteoporotic fracture (24, 54).
However, several radiological and clinical features differ fundamentally from ordinary osteoporotic femur fractures and strongly suggest a distinct pathogenesis. The distinguishing radiologic features include the transverse orientation and general lack of comminution, which is unusual for a femoral fracture and is characteristic of brittle failure (also named fragility or insufficiency fracture), as well as localized cortical thickening at the fracture site, which is characteristic of stress fractures (also named fatigue fracture). The distinguishing clinical features include their bilaterality and prodromal pain.
The truth is that the AFFs have some features of stress and insufficiency fractures but the pathogenesis is unique though not entirely clear.
Bones subjected to repetitive loading that overwhelms the body's capacity for repair are at risk for developing a stress fracture, which imply abnormal, or excessive, loading of a normal bone.
Instead, insufficiency fracture implies normal loading of an abnormal or deficient bone.
Stress or insufficiency fractures develop most commonly in the lower extremities, which are more routinely subjected to higher loading than other skeletal sites.
AFFs differ in some aspects from exercise-induced femoral stress fractures, which usually initiate on the medial cortex of the femur, are located in the proximal one-third of the femoral diaphysis, and result in a more oblique fracture surface than do AFFs (55-58).
In contrast, AFFs initiate on the lateral cortex, are located between the lesser trochanter and the femoral condyles, and result in a smooth transverse surface.

Brittle fractures occur generally in the cervical or intertrochanteric region of the femur, present thin cortex on the lateral side and osteopenia, differing form AFFs, which can present a lateral cortex thickening and a localized periosteal reaction.
However as well as the AFFs, fragility fractures occur without or with low-energy trauma and comminution is possible.
In Table 3 the features of these types of fracture are summarised; we include for a complete differential diagnosis also the High-Energy fractures that occur in the sub-trochanteric and shaft region of the femur.
Various pathogenic mechanisms that could explain the relationship between prolonged BP therapy and AFFs have been the subject of extensive research (59).
Prolonged bisphosphonate treatment may be responsible for deleterious effects on bone quality by inhibiting bone remodelling at the cellular level.
Bisphosphonates bind tightly to bone surfaces shortly after dosing, and any BP is quickly eliminated from the body. The bisphosphonate reaches the intracellular compartment first when an osteoclast ingests bisphosphonate-containing bone. The intracellular bisphosphonate is toxic and inactivate the osteoclast.
Donnelly et al. (60) used Fourier Transform Infrared Spectroscopy (FTIR) to compare the physical properties of cortical and cancellous bone of the proximal hip in subjects with hip or femoral fractures who were BP-naïve with those who had taken BPs for a mean of 7 years. In those individuals on BPs they reported significantly more homogeneous crystallinity and collagen maturity (although not in overall matrix mineralization) and an increase in mineralization, suggesting greater uniformity of tissue composition in those individuals treated with BPs.
Altering both collagen maturity and cross-linking, BPs lead to an increased pyridinoline/deoxypyridinoline (PYD/DPD) ratio. This is associated with increased strength and stiffness of bone (61) as demonstrated in vertebral cancellous bone and tibial cortical bone from dogs treated with BPs for 1 year, compared with untreated controls (62, 63). On the other hand, reducing bone turnover also increases pentosidine levels, which are markers for advanced glycation end products

Table 3 - Common clinical and radiological foundings.

Features	AFFs	Osteoporotic Fractures	High-Energy trauma Fractures
Type of Trauma	No o Low-energy	No o Low-energy	High-energy
Prodromal Symtoms	Yes	No	No
Femur Region	Sub-trochanteric or shaft	Cervical or Intertrochanteric	Sub-trochanteric or shaft
Fracture Rime	Trasverse or short oblique (< 30°)	Long oblique or spiral	More fragments
Comminution	No or minimal	Possible	Present or segmentary
Cortical Thickening	Normal or thick in lateral side	Thin	Normal
Other Signs	Localized periosteal reaction or healing delay	Osteopenia	No

(AGEs), which are associated with tissue that is more brittle. Collagen in the extracellular bone matrix contains both enzymatic and non-enzymatic crosslinks. Enzymatic crosslinks, mediated by the actions of lysyl and prolyl hydroxylases, have a substantial impact on bone mechanical properties and are essential to stabilize the bone matrix. Non-enzymatic crosslinks are formed through the interaction of collagen and sugars in a series of glycation and oxidation reactions, leading to the formation of AGEs. Bisphosphonate treatment increased AGEs in the ribs of dogs (64) and such an increase has been associated in animals with deleterious effects on bone mechanical properties, including a lower threshold of energy to fracture (63). The bulk of evidence on the pathogenesis of these atypical fractures stems from animal models, with few studies of human bone. Furthermore, multiple biomechanical considerations and patient risk factors may play a role in the pathogenesis of these fractures.

Several studies in non-skeletal tissues have shown that BPs reduce angiogenesis (65). While direct suppression of angiogenesis by BPs was reported previously (66), it is difficult to make a distinction between the inhibition of new vessel growth and the suppression of osteoclastic activity because these two phenomena are usually coupled to each other.

Bisphosphonates reduce the rate of bone remodeling, therefore slowing the progression of structural loss in bone matrix. Bone matrix then undergoes more complete secondary mineralization rather than being removed and replaced with younger and less mineralized bone matrix (67), which paradoxically makes bones more brittle because it cannot absorb energy by deformation when loaded. Subsequently, microcracking (68) dissipate the energy applied to the bone. As seen in prolonged BP administration, microcracks propagate and lengthen with less resistance in homogeneously mineralized bone matrix (69). In addition, reduced removal of bone microdamage increases occurrence and propagation of microcracks and compromises the material strength of bone, leading to increased occurrence of stress fractures (70).

The anti-resorptive therapy stop the increased bone remodelling that predisposes to “insufficiency” under normal loading and then to bone fragility by suppressing osteoclast-mediated bone resorption, thereby interrupting the normally coupled resorption-formation process of bone remodelling. Since bone remodelling is essential for continuous bone renewal and repair of microdamage, severe suppression of bone remodelling can lead to microdamage accumulation and impaired stress fracture-healing (71, 72).

It should be noted, however, that microdamage accumulation alone does not explain the decline in bone toughness, as minimal association between changes in microdamage accumulation and bone toughness was found in preclinical studies (73, 74).

Studies on stress fractures induced in the rat ulna showed that BPs impair stress-fracture-healing by reducing the volume of bone resorbed and replaced during the remodeling process (75, 76). Several clinical reports also showed that a periosteal stress reaction and a transverse radiolucent line indicative of stress fracture usually preceded the complete atypical fracture in patients taking bisphosphonates, indicating a possible role for bisphosphonates in impaired stress-fracture healing (77-79).

However, there is no evidence that periosteal bridging is affected in any way, suggesting that normal osteoblastic bone formation is not suppressed when it is not coupled to prior resorption. This is consistent with several other studies that show that BPs do not affect the formation of initial fracture callus (80) nor affect formation of woven bone, which can also be a part of the fracture healing process (81, 82). Initial stabilization of a developing stress fracture occurs by endosteal or periosteal bridging of the crack, followed by repair by normal bone remodelling. This allows intracortical remodelling to repair the crack, ideally before a full fracture occurs.

Areas with microcracks are resorbed by osteoclasts and replaced with new bone by a process called “targeted remodeling”. If targeted remodeling is disturbed by anti-resorptive treatment, microcracks might grow, fuse and cause stress fractures. Periosteal and endosteal surface calluses develop in AFFs and do not seem to be impaired by BP treatment (83, 84). Complete repair of the fracture itself, however, occurs by normal coupled bone remodeling processes. BPs localize at sites of high bone turnover, including those sites at which stress fractures are forming, because of the increased blood flow associated with attempted remodeling and repair in these areas (85). As BPs suppress remodelling, they are also likely to affect adversely intracortical repair of a developing stress fracture in AFFs, allowing the crack to grow to critical size. Localization of an agent known to suppress coupled bone remodelling to a site that requires repair may be a precipitating event that allows the damage to progress to full fracture.

As well as in the pathogenesis of stress fractures fatigue

damage in the form of microcracks develops within the bone cortex and accumulates, also in the pathogenesis of AFFs the microcracks coalesce and without repair will eventually grow to a critical-sized defect that precipitates a fracture (86). Microcracks tend to accumulate in old bone that is unlikely to contain bisphosphonate, because bisphosphonates disturb only site of active targeted remodelling and only doses administered while targeted remodeling is going on will have this possibility. Sites with ongoing resorption also have an increased affinity for bisphosphonates in the circulation. The important role of ongoing treatment, rather than skeletal accumulation of bisphosphonates, is further supported by the observation that the risk of atypical fracture diminishes rapidly after cessation of treatment (in contrast, the reduction in risk of osteoporosis fracture seems to remain for years). This theory about ongoing treatment and atypical fracture is not falsified by the continuously increasing risk during long-term bisphosphonate treatment. The increase can be explained by an accumulation of areas with microdamage as long as targeted remodeling is inhibited. Finally, bisphosphonates are only weakly efficacious in areas with a pathologically increased resorptive activity. This is easily conceived, considering that each osteoclast will resorb some bone before it is inactivated by ingested bisphosphonate, and if new osteoclasts are continuously recruited, the bone will finally be lost.
The lateral cortex of the femur is known to sustain high levels of tensile stress due to bending (87), which may precipitate the damage in this location especially in those people with lower limb geometry that could exacerbate that effect (e.g., a bowed femur, Asian race), as explained in the paragraph related to epidemiology.
In Figure 2 it's presented a flowchart illustrating the potential pathogenesis of atypical femoral fractures (Figure 2).
In recent years, case reports of atypical femoral fractures have been reported where denosumab has been prescribed for treatment of osteoporotic fractures (88-90).
In these case reports, the Authors reported bilateral AFFs.
Denosumab is a potent anti-resorptive agent approved for treatment of osteoporosis. The osteoclasts are steered to the area where microcracks accumulate by receptor activator of nuclear factor kappa B ligand (RANKL), which is released by osteocytes residing at the site. Denosumab is a fully human monoclonal antibody directed against RANKL, thereby blocking osteoclast recruitment, activation and survival. While bisphosphonates are only in circulation shortly after dosing, Denosumab remains in the blood for months, so that several months after injection, osteoclast numbers are greatly reduced and there is virtually no resorption going on at all. Denosumab and weekly administration of bisphosphonates will both influence targeted remodelling, while bisphosphonates given once a year will only reach those areas of microdamage that are undergoing remodeling at the very time point of the injection. With denosumab, the ability to resorb bone usually recovers, at least partially, towards the end of the interval between injections. This might be sufficient for the skeleton to deal with areas of microdamage. It appears likely that denosumab confers a similar risk of atypical fracture through its effect on targeted remodeling. The possibility of a stronger effect of denosumab on bone resorption at sites with increased recruitment of osteoclasts could mean a higher risk of atypical fracture. Conversely, the recovery period between denosumab injections could mean a lower risk.
The published literature on osteoporosis and oncology does not offer clear insight into risk of atypical femoral fractures associated with denosumab.
The published phase II and III osteoporosis clinical trials with denosumab did not report atypical femur fractures. A randomized, double-blind, placebo-controlled, multicentre phase 3 study compared the effect of denosumab with alendronate on BMD and BTMs in 1189 postmenopausal women with T-scores less than or equal to -2.0 at the lumbar spine or total hip, without report of atypical femoral fractures (91).
The STAND trial (92) was a randomized, double-blind, double-dummy, multicentre, international study in 504 postmenopausal women ≥55 years of age with a BMD T-score between -2.0 and -4.0 who had received alendronate for at least 6 months. All subjects were randomized to either continued weekly alendronate or subcutaneous denosumab 60 mg every 6 months for 12 months. In subjects transitioning from alendronate to denosumab, clinical fractures occurred in 8 sub-jects (3.2%) in the denosumab group, and 4 (1.6%) in the alendronate group (p = .38). The distribution and type of fractures were typical for postmenopausal women with low bone mass.

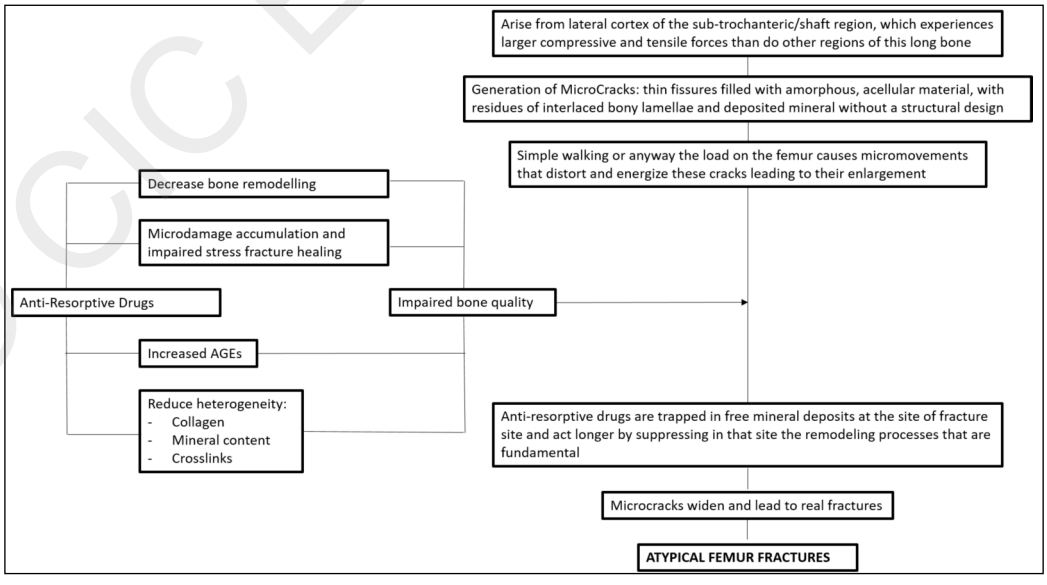

Figure 2 - Flowchart illustrating the potential pathogenesis of AFFs.

In the FREEDOM trial (93) subjects were randomly assigned to receive either 60 mg of sub-cutaneous denosumab or placebo every 6 months for 36 months. Three typical femoral fractures were seen in the placebo group and none in the denosumab group. Delayed healing was reported in seven subjects (2 denosumab, 5 placebo), including one with subsequent non union in the placebo group. Participants who completed the FREEDOM trial were enrolled in an extension trial to evaluate denosumab efficacy and safety for 5 years (94). Adverse events did not increase with long-term denosumab administration.
In conclusion, in light of the findings of the few case reports and articles in literature, atypical femoral fractures denosumab-linked are bilateral, occur after a treatment with BPs and appear to be associated with up to five years of continuous denosumab treatment.

Imaging pattern

In the case definition of the ASBMR the radiological fracture pattern is indicated as transverse rim in its orientation, although it may become oblique as it progresses medially across the femur.
Based on convention, a “transverse” fracture line is generally taken to be at 0° to 30° deviation from the perpendicular to the long axis of the femoral shaft; a short oblique fracture is taken to be at >30° to 60° deviation; and a long oblique fracture is taken to be >60° to 90° from this same reference. Unpredictable crack progression, resulting in variable lengths of the medial cortical spike, can affect the assessment of the obliquity of the overall fracture angle. Alvin C. Ng. et al. (95) demonstrated that the determination of fracture angles in suspected AFFs is best assessed using only the component that is restricted to the lateral cortex, the most likely site of fracture initiation in AFFs.
They compare lateral cortical fracture angle (LCFA) versus overall fracture morphology/angle (OFM/OFMA) in determining the transverse morphology of AFFs. They also compare the inter-individual measurement variability of LCFA versus OFMA when assessing AFFs and explore fracture angle differences between AFFs and non-AFFs using both LCFA and OFMA methodologies to determine the best cut-off angles for distinguishing between fracture types. The mean OFMA and LCFA were significantly different between AFFs and non-AFFs. However, the difference appeared to be much greater when LCFA was employed, suggesting that it was a much better discriminating measurement. Even if the angle of the overall fracture morphology, ie, OFMA was objectively measured, there were important problems with this approach of assessing the fracture line beyond the confines of the lateral cortex. Depending on the path of fracture propagation, the medial portion of the fracture may be of variable lengths and shapes. Furthermore, the variable nature of the falls with the varying combinations of twisting, bending, and shearing forces contribute to the myriad possible configurations of the medial spike. Therefore, by incorporating the medial spike in the measurement of the fracture angle and consequently the fracture morphology, the assessment can be skewed quite dramatically in some cases. Their results suggested that using the LCFA and a cut-off of 0° to 30° to determine transverse morphology was the more precise and accurate method when assessing suspected AFFs.
Liana Tripto-Shkolnik et al. (96) investigate the feasibility of case findings by the coding system and the reproducibility of radiological evaluations in two hospitals in Israel and compare BP exposure of atypical fractures (AF) patients to a control group with typical (intertrochanteric of femoral neck) fractures. Fractures were classified as atypical or not atypical according to ABSRM published criteria.
They reported, among the 198 patients who fulfilled the search criteria, 38 AF as classified by initial radiological opinion. Subsequent radiological opinion judged 16 as not atypical. Of the AF patients, 80% were exposed to BP. Of those, 81% continued to receive BP treatment for 2.4 years after AF. Only one AF patient was discharged with suspected AF diagnosis. In the control group, 27% were exposed to BP prior to fracture ($P < 0.001$).
Recently, radiography and magnetic resonance (MR) imaging have been used as tools for detecting pre-fracture lesions and prognosticating future occurrences of fractures (97, 98). Considering the low incidence of atypical subtrochanteric fractures (ASFs) in bisphosphonate users, however, routine screening for pre-fracture lesions on any imaging device warrants debate. In contrast, bisphosphonate users typically undergo dual-energy X-ray absorptiometry (DXA) annually or biennially to track changes in BMD at many institutions.
Sungjun et al. (99) retrospectively assess how often and how early hip DXA images show pre-fracture lesions in patients with ASF and determine whether DXA images with assessment of prodromal symptoms could be used for early ASF prediction. They reported among the 33 hips in the ipsilateral group, 20 (61%) with serial DXA images showed focal cortical change, and 13 (39%) showed negative results. Among the 20 hips in the ipsilateral group that demonstrated focal cortical change, six showed external periosteal changes, 11 showed internal medullary changes and three showed combined external-internal callus formation. They conclude that detection of prefracture lesions occurred earlier with the addition of DXA hip images. Observation of focal cortical changes on DXA images and the presence of prodromal symptoms together showed superior cumulative detection rates compared with the presence of prodromal symptoms alone.
Bone scintigraphy may show focal increased uptake at the lateral cortex; this feature should be unilateral or bilateral.
Magnetic Resonance Imaging (MRI) has greater sensitivity and specificity than scintigraphy. If MRI cannot be performed, computed tomography (CT) could detect the cortical fracture or lucency and associated new bone formation with thin section and multiplanar images. As cortical thickenings suggestive of fatigue fractures are found in a patient, MRI or CT is necessary to further investigate the nature of the lesion. MRI detects a cortical fracture line and associated bone marrow oedema or hyperaemia, which indicates a fatigue fracture and/or associated new bone formation. If cortical lucency is detected from CT or MRI, then the lesion should likely be considered an incomplete AFF. If no cortical lucency is present but marrow oedema is present, then such lesions could be considered a stress reaction (7).

Histological pattern

Schilcher et al. (100) between 2008 and 2013, collected bone biopsies including the fracture line from 4 complete and 4 incomplete atypical femoral fractures and evaluated their histology pattern.

The predominant founding in all incomplete samples was that the gap contained an amorphous, non-mineralized material with no discernible cells, most probably protein precipitate and detritus with new-formed woven bone and osteoclasts adjacent to the fracture line, signs of bone remodelling.
A callus reaction was found on both the endosteal and the periosteal aspect of the fracture, with the periosteal bony callus interrupted where the fracture reached the periosteal surface. In this site, there was only soft tissue, and the callus formation is therefore unlikely to have provided mechanical stability.
Areas with empty osteocyte lacunae were found, mainly at a distance from the fracture line.
The "mineral-to-matrix ratio" was close to 0 in the amorphous material in the fracture, whereas it ranged from 3 to 5 in the surrounding bone. This was due to high amounts of organic matrix (amide I absorption) without much mineral (phosphate) in the amorphous material.
The fact that there were no signs of remodeling or callus formation within the fracture gap itself, despite the cellular activity in the adjacent tissue, are compatible with the idea that normal gait produces strains in the fracture gap that are too large for cell survival.
Furthermore because the fracture surfaces are not covered by cells, the mineral in these areas is more accessible to circulating bisphosphonate acting and making them particularly resistant to resorption. The Authors demonstrated that even 1.5 years after cessation of treatment, only a few remodeling units had succeeded in bridging the gap, and these still did not provide sufficient mechanical stability to relieve pain on weight bearing.
They conclude that atypical femoral fractures show signs of attempted healing at the fracture site. The narrow width of the fracture gap and its necrotic contents are compatible with the idea that micromotion prevents healing because it leads to strains within the fracture gap that preclude cell survival.
Other Authors have conducted histological analysis, but the findings have been inconsistent.
Somford et al. have described the bone near the fracture, but not the fracture itself (101).
Kajino et al., as well as Lorenzini et al., investigated a biopsy only from a complete fracture including the fracture surface, finding immature bone on the periosteal surface and a bridging periosteal callus reaction, a fracture gap filled with blood, and a total absence of remodeling in the cortical bone respectively (48, 102).

Biomarkers pattern

Iizuka et al. (103) measured the levels of bone turnover markers (BTMs) within 24 h after trauma in Japanese patients with atypical femur fractures (AFFs) and typical femur fractures (TFFs).
They collected the serum BTM levels, including N-terminal propeptides of type 1 procollagen (P1NP), isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b) and undercarboxylated osteocalcin (ucOC). P1NP is used as a biochemical marker to assess bone formation (104). TRACP-5b has been used as a biochemical marker to assess bone resorption (105). High serum levels of ucOC have been reported to reflect high bone turnover (106) and low bone mineral density (107) and lead to fragility hip fractures (108).
The use of BPs was more frequently observed in patients with AFFs than in patients with TFFs. The levels of P1NP, TRACP-5b and ucOC were significantly lower in patients with AFFs than in patients with TFFs. Furthermore, the level of TRACP-5b was found to be significantly lower in patients with atypical subtrochanteric fractures than in atypical diaphyseal fractures. Moreover, the levels of P1NP and TRACP-5b were found to be significantly lower in patients with AFFs than in patients with TFFs in a subgroup analysis of BPs users. The use of BPs was considered to be a factor associated with AFFs. Their results indicate that the severe suppression of bone turnover is associated with the pathogenesis of AFFs and The extent of the influence of suppressed turnover on the pathogenesis of AFFs may differ depending on the fracture site.
Other study (27, 97, 109) did not demonstrate any suppression of BTM levels in most AFF patients; this may be explained by the time at which the BTM levels were measured or the type of BTMs that were studied.

Clinical patterns

Approximately 70% of patients with a confirmed stress fracture report prodromal pain before diagnosis (7).
Although AFFs are uncommon, they should always be suspected in elderly patients with chronic pain. Pain occurs in the thigh or the groin and can be of variable duration and severity. This presentation is typical of insufficiency stress fracture, but this one more frequently occurs in young, sportive people. Vigorous evaluation by appropriate imaging techniques is mandatory in patients on BP therapy presenting with pain in the thigh and/or worsening on standing. The time between the onset of the pain and the diagnosis of an AFF varies from one week to 2 years (27). Giusti et al. reported a similar incidence of prodromal pain in people on BP therapy according to the duration of bisphosphonate therapy and type of fracture: 60.0 *vs* 67.4% if duration on BP therapy is <5 or >5 respectively and 62.5 *vs* 60.0% if the fracture occurs in sub-trochanteric or shaft region of the femur respectively (27).
Among minor criteria of ASBMR, it has noted the possibility to have a bilateral fracture. AFF affect the contralateral leg in 28% of cases (110). A contralateral AFF could be simultaneous (111) or could occur at variable time after the first event, ranging from 1 month to 4 years (27). Several case reports pointed up the importance of this aspect cause the management and the therapies of AFFs may change (112, 113). Therefore, adequate RX study of the contralateral femur after the index AFF is mandatory, as recommended also by the EMA and the FDA (114). Technetium bone scintigraphy or magnetic resonance imaging (MRI) should be considered if a stress fracture is suspected.

Management

Differentiating AFFs in two major subtypes depending on bone turnover is useful for orthopaedic surgeons to make a more appropriate diagnosis and perform a better medical and surgical management of these fractures. Whereby, fractures can occur in a state of severe suppressed bone turnover (SSBT) or not.

A thorough patient history, clinical examination and analysis of appropriate bone biomarkers can offer a general idea of the underlying bone metabolism. The guidelines published by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF) recommend collecting serum calcium and phosphorus levels, intact parathyroid hormone (iPTH), 25-OHVitamin D and at least one resorption (i.e. the C-terminal telopeptide, CTX) and one formation bone biomarker (i.e. N-terminal propeptide of type-I procollagen, P1NP or bone alkaline phosphatase) (115).
However, it is advisable to complete the evaluation of bone health through DXA and a complete metabolic assessment, even after hospital discharge.
Being dependent on the results of the aforementioned evaluations, we could distinguish patients in "low turnover", "normal turnover" and "high turnover". BRAFF should theoretically occur in low turnover group. However, Giusti et al. found that both bone formation and resorption biomarkers,
were in the normal range in most cases (79 and 69.7% respectively) and were decreased only in a small percentage of cases (14 and 18.2 % respectively) (27). Anyway, these findings are susceptible to misinterpretation considering that most of these evaluations were obtained around the time of fracture, in a period when the bone was healing and turnover would be expected to be elevated. Thus, the patients with fractures probably had a false-normal turnover, which should be more correctly considered as a hidden low bone turnover.
In case of a low bone turnover AFF, the fracture might be associated to anti-resorptive therapy (i.e. BPs) or genetic bone disease (i.e. hypophosphatasia). In this group as well as in case of false-normal turnover, there is a rational to stop anti-resorptive therapy, and to consider anabolic drugs according to ASBMR (110).
However, medical therapy should be tailored for all patients, particularly in those with "high turnover", considering that this condition could change the diagnosis of AFF towards other bone disorders (i.e. Paget's disease of bone).

Conservative treatment

Conservative treatment is an option only in case of patient with incomplete fractures with no or minimal pain or severe comorbidities. If there is minimal pain, the patient can be observed with limited weight bearing through use of crutches or a walker for 2-3 months. If symptomatic and radiographic improvement is not achieved after the period, prophylactic nailing should be considered, because these patients may progress to a complete fracture. If periosteal thickening is observed without associated radiolucency, limited weight bearing may be continued for another 3 months and reassessed. Reduced activity should be continued until there is no bone oedema detected on MRI or no increased activity detected on bone scan (7, 110).
It is mandatory to stop the ongoing anti-resorptive therapy.
However, stopping BPs administration after >5 years therapy has to be accurately weighed.
Patients who discontinued BPs therapy had a contralateral AFF incidence of 19.3% in the following three years, compared with 41.2% if the BPs were continued (116). Schilcher et al. observed that the risk of AFF fell by 70%/year after discontinuation of BPs (117). The risk of a contralateral atypical femoral fracture decreased by approximately 53% (p = 0.042) if bisphosphonates were discontinued after the index atypical femoral fracture (118).
Pharmacological treatment is essentially based on administration of calcium and vitamin D supplements, together with bone anabolic drugs such as teriparatide, as we see later.
Recommendations for optimal treatment include a daily calcium intake of 1000 to 1200 mg/day (119). Although current recommendations from the Institute of Medicine state that 400 to 800 IU/day of vitamin D3 is adequate (119), many experts and studies have shown these recommendations to be insufficient (120-122). The minimum adult intake of vitamin D3 should be 1000 to 2000 IU/day (123).
Nonetheless, the results of conservative treatment are usually poor. Ha et al. published the results of 14 cases of AFF treated by observation and analgesics. Ten patients eventually needed a surgical treatment, and none of the 4 others had total pain relief or signs of complete healing (124). Banffy et al. reported only one successful outcome in 12 conservatively treated incomplete AFF using a protocol consisting of partial weight bearing and observation (125). However, other Authors reported good results using conservative treatment protocols that included avoiding weight bearing, vitamin D and calcium supplementation, and bone forming agents, such as teriparatide or strontium ranelate (126-133).
Because of suppressed bone turnover, healing of BP-associated AFF is also usually delayed.
Many case reports and case series have shown the effectiveness of teriparatide (TPTD) in both complete and incomplete AFF. Teriparatide, a recombinant form of parathyroid hormone (PTH) and an anti-osteoporotic agent with potent bone-forming effects, enhances bone healing in patients with delayed healing or non-union. It has been experienced also in periprosthetic fracture treatment. (134, 135). Yanfei L. Ma et al. (136) evaluated the effects of teriparatide on cortical histomorphometric variables in post-menopausal women with or without prior alendronate (ALN) treatment. They reported that endocortical and periosteal mineralizing surface (MS/BS %), periosteal bone formation rate (BFR/BS), mineral apposition rate (MAR) and the number of intracortical forming osteons were significantly lower in the ALN-pretreated patients than in the TPTD group. In the ALN-pretreated group the percentage of quiescent osteons decreased and, in contrast, forming and resorbing osteons were increased. Most indices of bone formation remained lower in the ALN-pretreated group compared with the TPTD group at study end. Endocortical wall width was increased in both ALN-pretreated and TPTD groups. Cortical porosity and cortical thickness were significantly increased in the ALN-pretreated group after teriparatide treatment. They conclude that 24 months of teriparatide treatment increases cortical bone formation and cortical turnover in patients who were either TPTD or had previous ALN therapy.
Gomberg et al. (137) treated a 63-year-old woman with thigh pain and bilateral AFFs who taken BPs for 13 years. After 6 months of daily TPTD, her pain diminished, MRI revealed less oedema around the fracture, and after 16 months, there was complete healing and relief of pain. Similarly, Carvalho et al. (138) described a 77-year-old woman whose AFF closed after only 1 month of TPTD. Reddy et al. (139) reported a case of a 70-year-old man with prostate cancer who was treated with androgen deprivation therapy and 4mg intravenous zoledronic acid monthly for 2 years. He complained of thigh pain and was found to have a transverse femoral shaft fracture. An orthopaedic nailing procedure pro-

duced a further fracture. After 2 months of TPTD therapy, there was full healing. Thus, discontinuation of BP therapy and TPTD treatment has been associated with fracture healing.

Moreover, the unpublished clinical experience of bone experts is that only some patients appear to respond to TPTD. Variable response to TPTD was reflected in several reports of medical treatment of AFFs presented at the ASBMR Annual Meeting in 2012. Mastaglia et al. (140) described a 57-year-old Argentine woman who had been treated with alendronate for 7 years and sustained a non-healing femur shaft fracture. Her pain improved after 10 days of TPTD and healing was complete after 3 months. However, Bock and Felsenberg (141) reported that only one of three German patients with AFF responded to 2 years of TPTD.

The prospective study of Chiang et al. (142) shows the advantages of using TPTD in AFFs that have inherent difficulty in achieving fracture healing. The results from the study of Miyakoshi et al. (129) show that TPTD administration shortens the union time and reduces the incidence of delayed or non-union in surgically treated AFFs while it is undetermined in non-surgical cases. The series of Saleh et al. (130) shows that incomplete fractures without radiolucent lines are responsive to TPTD alone whereas those with radiolucent line needed intramedullary nailing. These results imply that TPTD works best when the fracture site is stable, either inherently or with surgical fixation.

Although there is a lack of level 1 studies on the evidence of TPTD in promoting bone union in AFFs, the available literature revealed that TPTD works positively in AFFs and is a viable treatment option for enhancing fracture healing in AFFs.

The ASBMR task force recommendations define conservative treatment as limiting or avoiding weight bearing and strenuous activities in addition to medical management of the underlying disorder. From the low-quality evidence available, still the ASBMR task force summarizes the medical strategy of AFF as follows: it is reasonable to discontinue BPs, adequate calcium and vitamin D intake should be ensured, and teriparatide should be considered for those who appear not to heal with conservative therapy (110).

Surgical treatment

Surgical treatment is indicated for complete AFF or symptomatic incomplete AFF.

AFFs fractures are usually treated with intramedullary (IM) nailing or plating. IM nailing is the treatment of choice for most Authors in both complete and incomplete AFF. This preference is explained by the fact that a fracture treated by IM nailing heals by endochondral repair, whereas a conventional plate-and-screw construct generally precludes the endochondral repair process.

Furthermore, IM nailing is invoked as a preventive approach.

When IM nailing is chosen, over-reaming of the medullary canal by at least 2.5 mm larger than the nail diameter is recommended (7). Several Authors recommend the use of long cephalomedullary interlocking nails, considering that stress fractures usually occurred both above and involving an IM interlocking nail used to treat a prior AFF fracture (143, 144).

Extreme caution is advisable when performing IM nailing in very bowed or narrow femora, because of increased risk for distal fractures and diaphyseal comminution (145, 146). Hyung Park et al., with a simulation of a 3D printed model reported some surgical tips when a IM nailing is used in severely bowed femurs in atypical femur fractures:

1. Implant choice
   - smallest radius of curvature
   - smallest diameter
   - the opposite side of laterally bended nail (if not available, a straight nail with GT entry point)
2. Reaming of thickened lateral cortex
3. Using Poller screws & positioning the distal part of the nail laterally and anteriorly in the distal femur
4. Back-strike technique to reduce gap, if the presence of gap (147).

However, it is difficult to insert a nail into a femur in incomplete AFF patients with severely curved femurs, and complete fracture is sometimes caused on placing an intramedullary nail (8). Bone union may be delayed if this occurs.

Fixation with a locking plate could be a substitute in order to avoid the complications and technical difficulties associated with IM nailing (148). A long locking plate could be a good option when choosing plate fixation, particularly in the case of fractures associated with sever suppressed bone turnover, in which healing by second intention through a more elastic construct may adequately stimulate fracture healing. Plate and screw constructs are however associated with a high complication rate in AFF (7, 145). Therefore, their use in AFF is more restricted than IM nailing, even if some reports have proven their reliability in selected incomplete and complete AFF (148-150).

The outcome of surgical treatment in patients with bisphosphonate-related atypical femoral fractures is poor, compared to other fragility fracture (151). Weil et al. showed that seven (44%) of sixteen fractures treated with IM nail fixation required secondary operative procedures (152).

Of the 42 BP-associated femoral shaft fractures reported by Prasarn et al., the two most common complications were hardware failure (13%) and intraoperative fracture (21%) (145).

Another cause of concern is the effect of bisphosphonates on fracture healing.

Although some studies suggested a potential negative effect of bisphosphonates on the fracture-healing process, current evidence shows conflicting results (7, 111, 124, 153). Visekruna et al. reported on three patients with atypical subtrochanteric fractures, one of whom had no radiographic evidence of union at twenty-two months (126). Conversely, Ha et al. reported that ten atypical femoral fractures all healed, with osseous union after internal fixation during the follow-up period of twelve to sixty months (124). These differing results may be due to differences in preoperative status and in the medication type or dose used in these patients.

Prevention

Assessment of the benefits and risks before BP treatment is essential to avoid unnecessary complications, such as AFF. Once administered, bisphosphonates accumulate in the bone

and continue to be released for months or years after treatment is discontinued.

BP therapy is strongly indicated, even if not always necessary (154, 155), to protect patients from rapid bone loss and increased fracture rates associated with organ transplanta-

tion, endocrine disorders, or chemotherapy for breast or prostate cancer, and when aromatase inhibitors and glucocorticoids are first used.
The optimal duration of BP treatment is still unclear.
Data from the Fracture Intervention Trial Long-term Extension (FLEX) study showed that the fracture risk in postmenopausal women who discontinued alendronate after five years of treatment was not higher than in those who continued alendronate for a total of ten years, despite a moderate decline in bone mineral density at both the spine and femoral neck and a rise in bone markers in the former. However the incidence of clinical vertebral fractures was significantly lower in those on 10 years of continued alendronate versus those who stopped after 5 years (156). Instead, a reduction in non-vertebral fracture incidence was limited to women without a fracture history but with femoral neck T scores that were 2.5 or less (157).
For risedronate, the extension of the Vertebral Efficacy with Risedronate Therapy (VERT)-North America study showed that one year after discontinuation of a three-year protocol of risedronate treatment, BMD decreased (but remained higher than baseline and higher than in the former placebo subjects) and BTM increased (to levels no different from those in the former placebo subjects). Despite these changes, the incidence of new morphometric vertebral fractures was 46% lower in the former risedronate group compared with the former placebo group (158). This information supports the hypothesis that there is continued release of bisphosphonate from bone resulting in statistically significant and clinically important fracture prevention following discontinuation of bisphosphonates. Thus, there may be some lingering effects on bone even after bisphosphonates are discontinued.
Continued use of BP therapy over 5 years need annual re-evaluation, assessing factors such as BMD, fracture history and newly diagnosed disorders.
Furthermore, it has to be considered that there are differences in binding affinity and anti-resorptive potency of each bisphosphonate, which has a unique profile of the speed of onset and offset of its effect, as well as a unique degree of bone turnover suppression.
Patients has to be stratified on the basis of the fracture risk to establish management guidelines for prolonged bisphosphonate therapy.
Fracture risk can be estimated with use of the World Health Organization's fracture risk assessment tool (FRAX) as well as bone turnover markers (159).
Patients at low risk of osteoporosis-related fractures do not need medical treatment.
Patients who are at moderate risk but in a high-turnover state should be managed as if they have high risk of fracture. For these patients, continuation of BP therapy for 5-10 years or beyond could be necessary. As these patients are known to be at high risk of future fracture, discontinuation of BP treatment is not advised but a "drug holiday" for 2-3 years (if moderate risk) or 1-2 years (for high risk) should be strongly considered. Patients should nevertheless take daily calcium and vitamin-D supplements and alternatively, other medications such as denosumab or teriparatide may be provided during the holiday from bisphosphonates.
In general, the drug holiday should be continued until there is substantial loss of bone mineral density, marked increase in bone turnover markers, or the occurrence of a new fracture (160).
However, recent or multiple fractures suggest assessment for underlying secondary causes and re-evaluation of the treatment plan.
As an AFF occurs, the contralateral femur has to be evaluated.
In case of incomplete contralateral fractures, further treatment depends mostly on the associated symptoms. If the patient has thigh or groin pain, prophylactic surgery is advised. On the other hand, when the patient is asymptomatic, conservative treatment may be attempted for the first 2 or 3 months, with strict observation in order to quickly perform prophylactic surgery if signs of fracture progression or non-union occur (116).
In asymptomatic incomplete fractures associated with a simultaneous contralateral complete fracture, prophylactic surgery could be the gold standard to allow early weight bearing, but the ultimate decision depends on patient's preferences.
In individuals with a negative X-ray examination of the contralateral femur, clinical observation should remain strict. If thigh or groin pain appears during follow-up, further investigations such as a bone scan or MRI is highly recommended.
If imaging findings are compatible with diagnosis of a fracture, a conservative treatment cycle for up to 2-3 months may be initiated. If pain worsens or becomes persistent, prophylactic surgery should be considered. In this case, fracture healing could be evaluated repeating MRI or bone scans (130). On the other hand, if these imaging studies show no signs of fracture, a follow, up possibly through serial DXA scans, may be performed.
In patients who have already sustained an AFF, careful evaluation of DXA scans of the contralateral femur is mandatory, performing a long femur scan, that does not alter proximal femur BMD measurements (161, 162).

Conclusion

Atypical fractures are uncommon, and with a correct indication (but only then), anti-resorptive drugs prevent many more fractures than they cause.

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