Atypical fractures of the femur: an updated overview from the laboratory to the operating room

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Summary

Atypical femoral fractures (AFF) are peculiar stress or insufficiency fractures typically occurring in patients with a prolonged period of bone turnover alterations, mostly associated to specific risk factors, comorbidities, or drug therapies. AFF are typically subtrochanteric or diaphyseal fractures, with a transverse or poorly oblique fracture rim, not comminuted, and generally not correlated to a clear traumatic mechanism. Their incidence is low compared to standard fractures, but they are challenging clinical issues to deal with. The treatment of AFF is based on the diagnosis: in case of an AFF, surgery is needed, but it is associated to a very slow healing and to frequent complications. If AFF are early diagnosed (before the fracture completes or as an impending fracture pattern), a conservative treatment based on the interruption of bone turnover modifying drugs, protected weightbearing, administration of bone stimulating agents, and the study of similar conditions in the contralateral femur is suggested. Surgical treatment includes intramedullary nailing or plating even if the former is suggested for its superior mechanical advantages with respect to the latter. The Authors present an update of the state of the art on this topic that is rare but still now challenging.

KEY WORDS: atypical fractures; vitamin D; bisphosphonates; teriparatide; intramedullary nailing; impending fracture; ASBMR.

Introduction

Atypical femoral fractures (AFF) are to date defined as spontaneous, not comminuted, subtrochanteric or diaphyseal femoral fractures with a transverse or poorly oblique fracture rim, generally involving patients with prolonged periods of altered bone turnover due to peculiar comorbidities or specific drugs therapies. Barcsa et al. firstly described a particular type of fatigue fracture in 1978 (1), but Odvina et al. suggested in 2005 a pathogenic role of the bone turnover suppression (2). Lenart et al. finally described specific features of such fractures as simple transverse or oblique fracture with lateral cortex interruption and local cortical thickening of the proximal femoral shaft (3). Several cases were then advised worldwide after these reports, inducing the American Society of Bone and Mineral Research (ASBMR) to review the literature and to propose a task force for a better evaluation and definition of AFF in 2010, further updated in 2014 (4).

Definition and epidemiology

To be defined as AFF, a femoral fracture should have specific features, following the criteria of ASBMR. Criteria have been divided in major and minor, and updated in 2014 (Table 1). The major criteria are: minimal energy or no trauma reported by patients; lateral cortex origin of the fracture rim with a transverse or poorly oblique inclination as the fracture progresses medially in the shaft; across the femur; non-committed or minimally comminuted; complete fracture associated to a medial spike; localized periosteal or endosteal thickening of the lateral cortex with specific aspect (“beaking” or “flaring”). Minor criteria are: cortical thickness of the femur; presence of prodromal symptoms (aching pain or in the groin or thigh); bilateral incomplete or complete femoral diaphysis fractures, and delayed fracture healing.

Moreover, exclusion criteria to distinguish AFF from other conditions have been characterized (mostly periprosthetic or pathologic fractures and peculiar bone diseases) (4). AFF are substantially rare fractures with an incidence of 3.2 and 50 cases per 100,000 persons/year (5). ASBMR task force puntuallised that only 17-23% of diaphyseal or subtrochanteric fracture have features to be related to AFF (4). Furthermore, oblique and transversal pattern of fracture is also a small part of the overall femoral fractures, accounting for the 3% of them (6). Lo et al. noticed that asian women showed a risk 8 time higher then caucasian women (7). In the period between 1996 and 2009 a healthcare US database found an incidence of AFF of 5.9 per 100,000 person/year (8). A large Swedish study reported an incidence of 55 AFF among 100,000 patients/year assuming bisphophonates (BPs), while in BFs-naïve patients the actual probability was of 1 AFF per 100,000 persons/year (6). Mahjoub et al. reported an incidence rate of AFF of 7 per 100,000...
Etiology, risk factors, and pathogenic mechanism

The etiology of AFF is not well known, while its pathogenic mechanism is now cleared. Several risk factors have been proposed, related to drug therapies, individual conditions, and specific diseases.

For many years, BF has been considered the major risk factor for AFF. Long-term therapy with such drugs may alter the bone turnover favoring the bone suppression (11-13). BF induces an increase of microdamages (occurring in the physiological bone metabolism) and collagen crosslinking, producing alterations of the collagen/bone ratio, and a decrease of bone heterogeneity, finally favoring bone tissue weakness (14). However, despite several studies showed an increase of the risk of AFF from 2.29 to 139.33 (6, 8, 15) in patients treated by BF, recent papers reveal that there is not any statistically significant difference (16), except in series of subjects undergoing a long-term therapy (17). It is now clear that in such cases it is not a matter of dose-response effects rather than a cumulative quantity over the years of treatment (18).

Donnelly et al. studied the physical proprieties of the bone after many years of treatment with BPs inducing an increase of the pyridinoline/deoxypyridinoline ratio, as other Authors demonstrated an increasing of the pendasidone levels and advanced glycation end products: both mechanisms produced a weakness and fragility of bone (19-21).

What is of paramount importance is on the other hand that the effects of BFs on the osteoporosis in the general population are dramatically fundamental with respect to the risk of AFF (22).

Subjects assuming specific drug therapies other than BF have been considered more prone to develop AFF, as proton pump inhibitors (PPI) (23, 24) and glucocorticoids, even the latter seem now much less involved (10, 25-27).

Recently, also other bone turnover influencing drugs as Denosumab showed an association with AFF: several case reports have been published, even if in most cases the patients affected by AFF showed a medical history of long-term therapy with BFs until 5 years. This may induce suspects about the increased risk of AFF related to BFs (28-31).

Risk factors related to local anatomy, physiology, and biomechanics of the involved subjects have also been studied. Specific geometrical features of the femur can also be a risk factor for AFF, influencing the intensity of maximal tensile stresses on the lateral femoral cortex, where the highest mechanical load physiologically concentrates, in case of altered bowing: also varus-valgus modifications of the head/neck axis alignment and a higher knee shaft angle may increase tensile stresses on the lateral femoral cortex (32-35). An interesting study revealed that a lateral femoral bowing angle lesser than 7 degrees is associated to an AFF in the subtrocanteric region, where a deformity over 7 degrees induces a diaphyseal AFF (36). Other anatomical risk factors are: excessive femoral offset, smaller femoral head diameter, thicker later and medial bone cortices (9).

Age is another parameter to be considered: patients affected by AFF usually have a mean age lower than fragility fractures subjects (73.5 vs 82 years old) (9, 10). Also BMI has been investigated in a population affected by AFF: AFF patients showed higher mean BMI values than the osteoporosis-related subjects (37).

Finally, some bone diseases are associated to an increased risk of AFF, as pycnodysostosis (38), osteopetrosis (39), rheumatoid arthritis (4), and hypophosphatasia (HPP). Specifically HPP is an often asymptomatic genetic condition with low alkaline phosphatase activity. In some cases, diffuse pain, early decidual tooth loss, and stress fractures and pseudo fractures (named as Looser-Milckman subtrocanteric fractures) (40-42). Sutton et al. suggested a genetic test for HPP in case of premature loss of primary dentition, recurrent delayed healing of metatarsal stress fractures, family history suggestive of HPP, or low serum ALP activity. In case of diagnosis of HPP, BPs should be avoided given the higher risk of AFF (43). Similarly, Marin and Brandi suggest that a mild form of HHP should be considered in adults subjects suffering for an AFF and exclusion of other clear disease, and consequently an antiresorption therapy should not be administered (44).

In the very last years, genetic evaluations focused peculiar cases of patients developing AFFs in BPs therapy, advocating also a molecular pathway inducing the altered metabolism of atypically fractured bones. Roc-a-Ayats et al. found an enzymatic mutation of geranyl pyrophosphate synthase (GGPS) is related with the occurrence of AFF (45). Another study reported a variant of collagen type I (COL1A2) as a potential cause of susceptibility to this kind of fractures (46).
Diagnosis

Prodromal pain in thigh or groin pain is reported in about 70% of stress fracture before diagnosis (47), even if the time between the onset of pain and AFF may be very long (up to 2 years) (48). Similar prodromal symptoms may affect the contralateral side in 28% of cases simultaneously or with a variable delay with the main side (4, 5). It is hard to suspect an AFF based on simple clinical criteria. When symptoms are more intense and joint function or gait are affected, a radiographic study is mandatory and often useful as ASBMR nowadays suggest. A transverse or oblique rim starting laterally and extending medially across the femur, a lateral cortical fracture angle ranging from 0 to 30°, a lack of comminution, and a localized periosteal or endosteal thickening of the lateral cortex are pretty clear signs of AFF (49-58) (Figure 1). Recently, Png et al. proposed a new scoring system using MRI and X-rays to detect a pre-fracture status in selected patients (50). CT scan may also be useful in cases of contraindications to MR (4, 50, 51). In the last years, the dual-energy X-ray absorptiometry (DXA) has been proposed in very early stages of bone alterations, often associated to prodromal symptoms (52). Biomarkers are modern tools of diagnosis in many pathologies, and also in AFF detection seem to have a role. N-terminal propeptides of type 1 procollagen are good markers of bone formation, whereas isoform 5b of tartrate-resistant acid phosphatase correlates to bone resorption. Undercarboxylated osteocalcin is another marker related to bone turnover, being lower in patients with AFF than other with non-atypical femoral fractures (51, 53-56). The guidelines proposed by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF) recommend the study of serum calcium and phosphorus levels, intact parathyroid hormone (iPTH), 25-OH Vitamin D, and biomarkers as C-terminal telopeptide, CTX or N-terminal propeptide of type-I procollagen, P1NP or bone alkaline phosphatase (51). According to what obtained, three groups of patients may be selected: “low turnover”, “normal turnover”, and “high turnover”. Low turnover subjects can be associated to anti-resorptive therapy (i.e. BPs) or genetic bone diseases (i.e. hypophosphatasia) (51). However, Giusti et al. demonstrated that bone resorption and formation markers were in large part of cases normal and decreased just in a very small percentage of patients with AFF (25).

Management

The first and crucial step toward an appropriate management of AFF is its identification. An accurate clinical history is essential, focused on comorbidities, risk factors, and ongoing therapies. The clear indication of a trauma or the analysis of bone turnover examinations are essential as above mentioned.

Management is based on the clinical pattern of patients: subjects with risk factors alone (prevention therapy), with non-displaced or incomplete AFF and/or prodromal symptoms (conservative/medical and in case-surgical therapy), and with a complete AFF (surgical therapy).

In all types of the previous mentioned patterns, the suspension of the antiresorptive treatment, calcium and vitamin D supplementation, and the prescription of bone forming drugs (teriparatide) associated with radiologic screening of both femur are mandatory (4, 58, 59).

Preventive treatment

The assessment of benefits and risks before proposing to a patient a BPs treatment is essential to avoid unnecessary complications. As above mentioned, BPs are very useful and efficient in the prevention of fragility fractures but with specific indications (57, 58). The optimal duration of BFs therapy is not however yet clear. Some studies showed that there is a continued release of BFs after a prolonged administration also during years after suspension (45, 60, 61). The World Health Organization fracture risk assessment tool (FRAX) and the study of the bone turnover markers showed a great utility in such assessment (62). Patients with low risk of osteoporosis-related fractures do not need a treatment over 5 to 10 years after the first dose; on the other hand, subjects with higher risk of fracture should perform a prolonged BFs therapy but washout periods of 1 to 3 years should be suggested every 5 to 10 years of treatment by a tailored approach (63). Vitamin D and calcium administration should always be continued, even in the BFs washout periods.

A close X-rays surveillance should be performed in both femurs as ASBMR recommend (64). Limiting intense activities and efforts, physical activities for muscular tone maintenance, balanced diet, yearly bone markers evaluations, and periodic DXA studies should be proposed (4, 65). MRI may be suggested in case of prodromal signs or alterations in one or more of the previous factors: in such cases, patients should be treated as in case of presence of AFF (66, 67).
**Conservative and medical treatment**

Conservative and medical treatment are indicated in patients with incomplete AFF and/or prodromic symptoms without comorbidities (51). Limitation in the weight-bearing by specific walking devices may be unnecessary given the risk of poor activity levels of subjects: on the other hand, a physical maintenance avoiding efforts or activities with risk of trauma are discouraged until bone oedema (usually found at a MRI study) is resolved. A parathyroid hormone therapy should be used (59). Teriparatide effects on AFF bone metabolism have been found as intense two years after treatment with clear signs of cortical thinning and bone union coupled with pain resolution (68).

If symptoms do not rely and no radiographic improvements are obtained, a prophylactic (preventive) intramedullary nailing is indicated (47).

**Surgical treatment**

Complete symptomatic, incomplete (symptomatic or not), and impending contralateral AFF should undergo a surgical treatment. Even if plating and screws or intramedullary nailing have been both proposed over the years, there is a clear evidence that nailing is mechanically superior to plate (34, 45, 54, 67). Plates have higher rates of failure due to the inhibition of endochondral ossification (47, 59) and different lever arm with respect to nails; moreover, nailing provides an over-reaming of the medullary canal before nail placing enhancing the ossification (47, 51).

Several nails are available, but better results were associated to cephalomedullary nails (59). However, plate fixation should be considered in cases of narrow medullary canals or significant bowing of the femur (59, 69). Various reports evaluated good fixation and healing by plates but the overall need of revision surgery was higher with respect to intramedullary fixation (70), specifically related to non unions or delayed union: in such cases, plate removal and long intramedullary nailing was the best choice (71) (Figure 2).

Whatever the choice of fixation device, the healing of a AFF is slower than standard fragility fractures and rates of non union and delayed unions are significant (72). Finally, fixation device rupture is not uncommon in healing complicated cases as reported in several series (11, 13, 59).

AFF are still now challenging patterns of fracture that should be suspected in a large part of the population affected by bone metabolism diseases, excluded in subjects presenting risk factors, and treated in a preventive fashion if early diagnosed.

**References**


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