MANAGEMENT OF ENDOCRINE DISEASE

Atypical femoral fractures: risks and benefits of long-term treatment of osteoporosis with anti-resorptive therapy

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Abstract
Modern osteoporosis treatment began in the mid-1990s with the approval of amino-bisphosphonates, anti-resorptive agents that have been shown to decrease osteoporotic fracture risk by about half. In 2005, the first cases of atypical femoral fractures (AFF), occurring in the shaft of the femur, were reported. Since then, more cases have been found, leading to great concern among patients and a dramatic decrease in bisphosphonate prescribing. The pathogenesis and incidence of AFF are reviewed herein. Management and an approach to prevention or early detection of AFF are also provided. Denosumab, a more recently approved anti-resorptive medication has also been associated with AFF. Long-term management of osteoporosis and prevention of fracture are challenging in light of this serious but uncommon side effect, yet with an aging population osteoporotic fracture is destined to increase in frequency.

Introduction
As the population ages, the incidence of osteoporotic fracture will increase: in the European Union osteoporotic fractures are predicted to increase from about 3.5 million/year in 2010 to 4.5 million/year in 2025 (1). While hip fracture clearly leads to increased mortality and often loss of independence in those who survive, other osteoporotic fractures, particularly vertebral fractures, are also associated with increased mortality (2). Despite these facts, osteoporosis may not be considered a serious disorder; it does not cause symptoms until there is a fracture. Consequently, reports of side effects of osteoporosis medications may have an inordinate effect.
on initiation and persistence of therapy, whereas serious side effects from other drugs for other chronic diseases may be tolerated – because the other disorders are considered more ‘serious.’ In the mid-1990s alendronate was the first nitrogen-containing bisphosphonate shown to decrease fracture risk. Over time, risedronate, ibandronate, and zoledronic acid were approved and used widely for osteoporosis prevention and treatment. About 10 years after the bisphosphonates were first prescribed for osteoporosis, a report by Ovdina and colleagues (3) described unusual fractures of the femoral shaft in patients who had been treated with bisphosphonates for postmenopausal osteoporosis or osteopenia or glucocorticoid-induced osteoporosis. Soon thereafter other reports of such fractures were published (reviewed in (4)), which led the American Society for Bone and Mineral Research (ASBMR) to empanel an international task force to define and characterize what are now called atypical femoral fractures (AFF). The first task force report in 2010 (5) provided a definition, speculations on the pathophysiology, and early suggestions for management. A second task force report (6) modified the definition and provided more information about pathogenesis and treatment. This review will use the task force reports and subsequent publications from many parts of the world to provide an update on the incidence of AFF, the strength of the association with bisphosphonate therapy, the pathophysiology, and potential management modalities.

**Definition of atypical femoral fractures**

In the first ASBMR task force report (5), a provisional definition of AFF was published, with a subsequent update in 2014 (6). These definitions have been used in studies for separating AFF from other fractures below the lesser trochanter of the femur. The newer definition continues to require that the fracture must be located just below the lesser trochanter but above the supracondylar flare, but this is no longer listed as part of the definition. Instead, the fracture must have 4 of 5 of the major features (Table 1). Minor features (Table 2) may or may not be present. In the original definition, the lateral cortex periosteal reaction was considered a minor feature. In the newer definition, the lateral cortex reaction, resulting in so-called beaking or flaring, is now considered a major feature. Most recent studies use the updated version of the definition. Interestingly, in a recent review by LeBlanc and colleagues (7) of 372 femoral fractures, using the newer ASBMR definition resulted in a decrease of about 50% of fractures no longer meeting the definition of AFF. The most common reason for this was the change in the description of the fracture orientation. By the earlier definition, AFF had to have a transverse or short oblique configuration. In the newer definition, a major feature was: ‘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.’ In some respects, the findings of LeBlanc et al. are of concern because the incidence of AFF is still unclear. Calculating the number of typical fractures prevented vs the number of AFF potentially caused by bisphosphonate therapy depends on robust estimates of fracture incidence in untreated and treated individuals.

### Pathogenesis of atypical femoral fractures

AFF have been found in patients never exposed to bisphosphonates or denosumab, so one possible etiology is osteoporosis itself: AFF could be a type of osteoporotic fracture, perhaps not helped by anti-resorptive therapy. Arguing against this pathogenesis is the fact that cancer patients receiving bisphosphonates have also suffered AFF. In a recent report from Japan (8), two women with breast cancer developed AFF. One patient was only 52 but had been treated for breast cancer starting at age 36 and likely had early menopause because of other treatment. This patient had received intravenous bisphosphonate (pamidronate and later zoledronic acid) on a monthly...
Table 2  Definitions of atypical fractures – minor features.

<table>
<thead>
<tr>
<th>Original ASBMR definition</th>
<th>Updated ASBMR definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral fractures</td>
<td>Bilateral fractures (may be complete or incomplete)</td>
</tr>
<tr>
<td>Prodrome of groin or thigh pain</td>
<td>Prodrome of groin or thigh pain</td>
</tr>
<tr>
<td>Increased cortical thickness of diaphysis</td>
<td>Increased femoral shaft cortex</td>
</tr>
<tr>
<td>Delayed fracture healing</td>
<td>Delayed fracture healing</td>
</tr>
<tr>
<td>Lateral cortex has localized periosteal reaction</td>
<td></td>
</tr>
<tr>
<td>Concomitant problems such as low vitamin D</td>
<td></td>
</tr>
<tr>
<td>Medical Rx such as bisphosphonates, glucocorticoids, proton pump inhibitors</td>
<td></td>
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basis for at least 10 years followed by more than 2 years of monthly denosumab at the 120mg dose. The second patient was 82 years old and had received monthly zoledronic acid for 9 years. Although both patients received anti-resorptives at much greater doses than those of osteoporosis patients, the two patients may have had osteoporosis before starting anti-resorptive therapy. More recently a larger review (9) of cancer patients on bisphosphonate therapy concluded that such patients were at higher risk for AFF than cancer patients not on bisphosphonates. However, from this review and earlier reports of AFF in patients not on bisphosphonates (10), it is not possible to know if such some of these patients had osteoporosis. So at this point, osteoporosis per se remains a potential contributor to the development of AFF.

The first report of AFF by Odvina and colleagues (3) suggested that severely reduced bone turnover due to bisphosphonates may have been the underlying mechanism for AFF. Since that time, there have been some investigations of bone turnover by histomorphometry and serum markers. In a very recent study (11), patients meeting the updated ASBMR definition of AFF were recruited for an open label study of teriparatide treatment. At baseline, only 1 of 14 subjects had a serum C-telopeptide (CTX) below the reference range, although 5 had levels of bone specific alkaline phosphatase below the normal range. Interestingly, after a mean anti-resorptive treatment duration of almost 9 years, the average T-score for spine and hip were −1 and −1.1 (calculated from the mean bone mineral density in g/cm²). At baseline, all 14 subjects had normal percent osteoid surface and osteoid width in iliac crest biopsies. Two subjects had no double tetracycline labeling at baseline; thus, the mineralized surface-to-bone surface ratio was reported in only 12 subjects. In 10 of 12, the ratio was lower than the reference range, although in one additional subject it was very close, and in the other subject, it was well within the normal range. Thus, there is obvious heterogeneity in bone histomorphometry, but we cannot conclude that severe suppression of bone turnover is a constant finding in patients with AFF. In another recent study (12), bone was obtained adjacent to the fracture site in women undergoing surgical repair. Using nanoindentation and vibrational spectroscopy, the authors showed that bone was harder and more mineralized in women with atypical fractures after bisphosphonate therapy, compared to women with typical osteoporotic fractures despite bisphosphonate therapy. The authors concluded that cortical toughness was diminished in patients treated with bisphosphonates who have experienced AFF. In a study of 8 patients with AFF, Schilcher and coworkers (13) examined the actual fracture area and found evidence that in the crack healing was attempted but not successful, as demonstrated by amorphous material without cells in the crack but living cells in adjacent tissue. They concluded that motion (perhaps the strains of standing and walking (14)) was enough to prevent healing of the crack. This group also disagreed (15) with a minor feature of the original ASBMR definition; they did not find evidence of a thicker femoral cortex in AFF patients. In this study (15), they found that cortical thickness, adjusted for age, measured 5 and 10 cm below the lesser trochanter was the same in patients with atypical and typical fractures.

In the ASBMR task force reports (5, 6), AFF were considered stress fractures because they develop over time (as manifested by prodromal pain) and appear to start in locations of stress on the lateral femur. Bisphosphonates may alter the ability to heal such fractures (6), but at this point, the pathogenesis of AFF is not settled.

Some investigators have suggested that the geometry of the femur may play a role in the pathogenesis of AFF. Specifically, femoral anatomy that increases tension on the lateral aspect of the femur may be important. In a study from Northern California (16), women of Asian ethnic background had a relative hazard ratio for AFF of more than 6, compared to Caucasian women. One potential contributor to this finding is that bowing of the femur may be seen in Asian women. In a report from Japan (17), a finite element analysis was applied to computed tomography (CT) of the femurs of women with AFF in the
subtrochanteric region, compared to those with mid-shaft AFF and no AFF controls. Anterior and lateral bowing were correlated with tensile stress adjacent to the fracture site. The authors also reported that the subtrochanteric AFF patients also had smaller femoral neck-shaft angles, compatible with a previous report (18). The prodromal symptoms of thigh or groin pain may be noted in many (perhaps the majority) of the patients who eventually have an AFF. Duration of therapy is also an important predictor of AFF (19). New bone densitometer software may provide low X-ray exposure images of the entire femoral shaft and extending the field of bone mineral density images by dual-energy X-ray absorptiometry (DXA) may also identify patients with early signs of AFF. This leads to potential ways a clinician might find patients at risk for AFF (Table 3), although AFF has been reported in patients who have discontinued bisphosphonates years prior to the fracture.

**Atypical fractures in other bones**

Brief case report: A 79-year-old man had osteoporosis related at least in part to chronic obstructive pulmonary disease and polymyalgia rheumatica requiring prednisone also had long-standing mild hyperparathyroidism. He had been treated for 5 years with weekly alendronate and was switched to monthly risedronate for 3 years hoping for better adherence to treatment. He was lost to follow-up, but almost 4 years after stopping risedronate, he received one infusion of zoledronic acid. Three months later, he experienced soreness in his calf while sitting in his recliner chair. He waited until his next appointment to have it checked. A transverse fracture of the fibula was found and treated conservatively because healing was noted on X-ray. This case illustrates that bones other than the femur may have atypical fractures, although there is no way to fulfill the ASBMR criteria in such cases. There have been published reports of non-traumatic fractures of the fibula (20) and ulna/radius (21) in patients on long-term bisphosphonate therapy for osteoporosis. Thus, the clinician needs to be aware of such possibilities.

**Management of atypical femoral fractures**

Typically, patients are referred to osteoporosis specialists or primary care clinicians after surgery for the AFF. In most cases, a medullary nail is placed to provide fixation of the fracture and allow healing. For patients with bowed femurs, an alternative nail entry site may be necessary (22), and lateral fixation has been suggested as an alternative (23). In any event, surgery followed by a rehabilitation program is necessary for those who have had a complete fracture; it is possible that the surgical technique will be refined over time. Medical management (5, 6) has been suggested as follows: discontinuation of anti-resorptive treatment, adequate dietary calcium, vitamin D supplementation if needed, consideration of teriparatide, particularly for patients with incomplete AFF who have not undergone surgery. The response to teriparatide has been variable (24). In a recent open label study, Watts and coworkers (11) performed iliac crest bone biopsies and clinical assessment in 14 patients treated with teriparatide for 2 years. Five had incomplete fractures (2 bilateral), 6 had unilateral complete fractures, 1 had bilateral complete fractures and 2 presented with complete unilateral fracture but developed a contralateral fracture during teriparatide therapy. Spine BMD was increased in most patients and stable in the remainder. In the hip, bone density remained stable throughout the teriparatide treatment.

**Avoiding AFF by optimization of long-term osteoporosis management**

The obvious way to minimize the incidence of AFF is to treat only those patients most likely to benefit from anti-resorptive therapy and choose other therapy for those patients who may be at higher risk for AFF. This is not easy. First, while osteoporosis is common, not all will suffer a fracture. As estimated by Hernlund and coworkers (1), by 2025, there will be 34 million individuals in the EU with osteoporosis and 4.5 million fractures. However, many of the fractures will be in people with osteopenia, not osteoporosis, as defined by DXA. Use of fracture risk calculators such as FRAX may be helpful to decide who should be treated. Age is an important risk factor such that the 80-year-old women with a DXA T-score of −2.5

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**Table 3** Potential indicators of patients at risk for AFF (in addition to anti-resorptive drugs).

| Asian ethnicity | Bowed femora | Varus femoral neck/shaft angle | Prodromal symptoms: thigh or groin pain | Long duration of anti-resorptive therapy | Glucocorticoid therapy | Signs of early fracture line or periosteal reaction on image of femur |
has a much greater chance of fracture than a 55-year-old woman with the same T-score. Fracture risk calculators help keep individuals at low short-term fracture risk from premature treatment. In the past, patients with osteopenia were started on bisphosphonates to prevent osteoporosis. Often their risk for typical osteoporotic fracture was low in the ensuing 10-year period, but some younger postmenopausal women suffered AFF from long duration bisphosphonate treatment. Thus, one way to decrease AFF incidence is to use bisphosphonates or denosumab only in patients at higher risk for fracture in the next 5 or 10 years. This is done by history, physical examination, a few laboratory tests and DXA testing. Each country or medical system may determine just what level of typical fracture risk should lead to treatment. In the United States, the National Osteoporosis Foundation has used FRAX for calculation of 10-year fracture risk and has recommended treatment if the hip fracture risk is 3% or greater or if the major osteoporotic fracture risk is 20% or greater (25). This was based on cost-benefit analysis (26), especially because hip fracture is very expensive in the United States. However, intervention thresholds will be different in other countries, and the fact that generic oral bisphosphonates are now very cheap changes any cost-benefit analysis. Black and Rosen (27) did an analysis of the number needed to treat to prevent one typical fracture and the number needed to harm (by atypical fracture). For 1000 women at risk for fracture, 100 fractures would be prevented with bisphosphonate treatment for 3 years. Even with a relative risk of AFF as high as 12 (compared to patients not on bisphosphonates), only 1.25 AFF would be experienced in 1000 women treated for 3 years. While this is comforting, osteoporosis usually needs to be treated for more than 3 years, and as described by another task force from the ASBMR (28), there are very few studies of longer term treatment of osteoporosis. The task force recommended that after 5 years of oral bisphosphonate therapy or 3 years of annual intravenous bisphosphonate therapy, postmenopausal women should be assessed for continued high fracture risk. Those remaining at risk (due to femoral neck T-scores remaining below −2.5) should be considered for continuation of therapy with reassessment again in 2–3 years. Those women who have had a good response to bisphosphonates and no longer seem to be at high risk for fracture could be considered for a drug holiday again with reassessment at 2–3 years. Intravenous zoledronic acid appears to suppress bone turnover for more than a year (29), leading to the recommendation (30) that some (29) have recommended that intravenous bisphosphonate infusions be spaced so that all bisphosphonate patients receive an initial 5-year course of treatment. In any event, there are no data on what to do after 10 years of bisphosphonate treatment. The NOGG Guideline (31) agrees in general with the approach of the ASBMR task force on management up to 10 years. The Italian Association of Clinical Endocrinologists generally concurs as well (32). Again the problem is that after 10 years of treatment fracture risk may remain, and there are no studies on which to base a therapeutic plan.

**Time for a new treatment paradigm?**

Bisphosphonates were the first modern drugs for osteoporosis and have become the standard of care, particularly now that generic oral bisphosphonate therapy is very inexpensive. For the patients likely needing long-term treatment, perhaps a new approach is needed. In the DATA-SWITCH study (33), teriparatide for 2 years followed by denosumab for 2 years led to much better bone response than denosumab for 2 years followed by teriparatide for 2 years. Teriparatide and the newly approved abaloparatide have not been considered first-line therapy because of two factors: they require daily subcutaneous injections and they are much more expensive than oral bisphosphonates. Because of concerns about potential osteosarcoma risk, use of these drugs has been limited to two years per lifetime (34), although there has been no safety signal noted as of yet. Even in glucocorticoid-induced osteoporosis, for which a study (35) showed fewer fractures in patients treated with teriparatide than with alendronate, the American College of Rheumatology still recommends oral bisphosphonates. Despite this, a case can be made to treat high-risk patients who will likely need very long-term therapy with an anabolic agent first, concordant with recommendations of the American Association of Clinical Endocrinologists (36). Increasing bone mass and improving microarchitecture with an anabolic drug before starting a bisphosphonate might change the risk for fracture when the patient is assessed after 5 years of anti-resorptive therapy. With this paradigm, it is likely that more patients will be eligible for a drug holiday. In the recent two-year VERO study (37), teriparatide treated postmenopausal women had fewer morphometric and clinical vertebral fractures than women treated with risedronate, providing more support to the use of anabolic therapy for osteoporosis. If AFF is related to duration of bisphosphonate exposure, as has been shown by some (38) but not all (39) studies, then lowering fracture risk for
some patients by this 7-year plan (2 years anabolic therapy followed by 5 years of bisphosphonate treatment), might lower the AFF risk. After the drug holiday, another course of anabolic therapy (perhaps one year) could then be followed by re-institution of bisphosphonate treatment. While a plan such as this has some theoretical appeal, it would be almost impossible to conduct a prospective study to demonstrate its efficacy. In addition, with the high price of anabolic agents, gaining clinical experience with this type of approach will be very challenging.

Conclusion
Osteoporosis is a common, chronic and serious disorder. Hip and vertebral fracture lead to increased mortality, and the seriousness of osteoporosis is underappreciated. The approach of anabolics first and bisphosphonates second for high-risk patients who likely will need prolonged therapy and for lower risk patients postponing bisphosphonates until they have significant fracture risk (e.g., do not treat osteopenia in those with low 10-year risk by FRAX), the incidence of AFF is likely to decrease. Until newer methods to treat osteoporosis are developed, creative management strategies, avoidance of treatment for those at low risk and careful monitoring of treated patients are the only tools currently available to minimize the incidence of AFF.

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