Atypical Femur Fractures

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Introduction

Low-energy femur fractures in patients receiving alendronate were first described in 2005 [1], followed by two case series in 2007 [2] and 2008 [3] reporting strong associations with alendronate. Since then, many articles have been published on atypical femur fractures (AFFs). The American Society for Bone and Mineral Research Task Force on AFFs analyzed 310 published cases in 2010 [4]. This was followed by a second report from the American Society for Bone and Mineral Research (ASBMR) Task Force in 2013, reviewing all the studies published between 2010 and 2013 [5].

Atypical femoral fractures, also known as bisphosphonate-related proximal femoral fractures, are an example of insufficiency fractures. Although the direct causative link remains somewhat controversial, it was reported as an uncommon complication of long-term use of bisphosphonates [6]. Atypical femoral fractures are stress or insufficiency fractures occurring in the femoral shaft, which may occur either unilateral or bilateral. The occurrence of atypical femur fractures has been described and linked to a negative side effect of antiresorptive therapy [7]. Considering the large population benefiting from this pharmacotherapy, the incidence of this fracture entity is rather low [8]. However, the difficult diagnosis caused by initially mild symptoms and slight radiological changes combined with a problematic therapy drives the need for guidelines to be established. The handling of the condition represents a challenge to the orthopedic surgeon not only regarding the surgical approach and the kind of osteosynthesis but also the short as well as the long-term patient's medical management, which should aim for avoidance of bone remodeling oversuppression [9]. Although the first encouraging steps have been made toward an evidence-based therapy [10], the results must be interpreted with caution, considering the rareness of such an event [11].

This chapter will provide the definition of AFF, terminology, and the difference between fatigue fracture, fragility fracture, insufficiency fracture, and atypical fracture. The chapter will expand to discuss epidemiology and pathogenesis of AFF, clinical features and diagnosis of atypical femur fractures, as well as management.

Definition

In the first ASBMR Task Force report [4], a provisional definition of AFF was published, with a subsequent update in 2014 [5]. These definitions have been used in studies for separating AFF from other fractures below the lesser trochanter

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Table 27.1 Comparison between the original and revised American Society for Bone and Mineral Research (ASBMR) atypical femur fracture case definition

Original	Revised (changes from 2010 are in underlined italicized font)
Major features	
The fracture located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare	*The fracture must be located along the femoral diaphysis 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	Associated with no trauma or minimal trauma, as in a fall from a standing height or less
Transverse or short oblique configuration	*Fracture line originates at the lateral cortex and is substantially transverse in orientation, although it may become oblique as it progresses medially across the femur*
Noncomminuted	Noncomminuted or minimally comminuted
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures only involve lateral cortex	Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures only involve lateral cortex
	Localized periosteal or endosteal thickening of lateral cortex at the fracture site ("beaking or flaring")
Minor features	
Localized periosteal reaction of lateral cortex ("beaking or flaring")	Generalized increase in cortical thickness of the *femoral diaphysis*
Generalized increase in cortical thickness of the diaphysis	Unilateral or bilateral prodromal symptoms such as pain
Prodromal symptoms, such as dull or aching pain in groin or thigh	Bilateral incomplete or complete femoral diaphysis fractures
Bilateral fractures and symptoms	Delayed *fracture* healing
Delayed healing	

of the femur. In comparison to the original definition, the newer one continues to require that the fracture must be located just below the lesser trochanter and above the supracondylar flare, but this is no longer listed as part of the definition. Instead, the fracture must have four of five of the major features (Table 27.1). Minor features (Table 27.1) 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.

Several studies have addressed the effect of the new ASBMR criteria on the diagnosis of AFF. In one review, implementing the newer ASBMR definition resulted in a decrease of about 50% of fractures no longer meeting the definition of AFF [12]. 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" (Fig. 27.1).

With regard to imaging techniques for diagnosis of AFFs, Critchlow et al. assessed the sensitivity and specificity of each radiographic criterion to identify an AFF [13]. Four independent experts representing different medical specialties within Kaiser Permanente Southern California compared radiographs from 55 AFFs and 39 non-AFFs. The most sensitive features distinguishing AFFs from non-AFFs were the lateral cortex transverse fracture pattern (mean 93.6%, range 85.5–98.2%), medial cortex transverse or oblique fracture pattern (mean 84.1%, range 72.7–98.2%), and minimal or noncomminution (mean 93.2%, range 89.1–98.2%). Specificity was greatest for lateral cortex transverse fracture pattern (mean 95.5%, range 92.3–97.4%). Luangkittikong and Unnanuntana [14] reported similar prevalence of AFFs with both criteria and that localized periosteal thickening of the lateral cortex was the most specific finding for bisphosphonates exposure in those with AFFs. In a study by LeBlanc and colleagues, two independent expert physicians applied the 2013 definition to radiographs previously categorized as AFFs by the 2010 definition [12]. The approximate 50% decrease in the number of fractures that met the 2013 than the 2010 ASBMR case definition (37

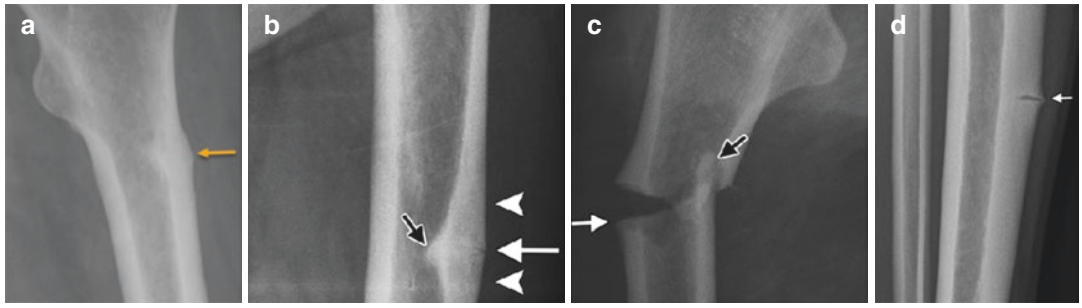

Fig. 27.1 Spectrum of radiographic abnormalities seen with atypical femoral fractures in three patients. (**a**) Plain X-ray left hip and femur anteroposterior, 64-year-old woman, showing enlargement of incomplete fracture and periosteal or endosteal thickening (arrow) of the lateral cortex ("beaking") of the femoral diaphysis, which is consistent with an atypical femoral stress reaction. (**b**) X-ray left hip, 66-year-old woman, AP view showing a transversely oriented fracture (white arrow) of the lateral cortex of the femoral diaphysis with associated endosteal beaking (black arrow) and adjacent cortical thickening (arrowheads), findings that are consistent with incomplete atypical femoral fracture. (**c**) X-ray right hip, 60-year-old woman, AP view, showing a noncomminuted fracture of the femoral diaphysis consistent with a complete atypical fracture. The fracture is substantially transverse (white arrow) in the lateral cortex but becomes more oblique with a medial spike as the fracture propagates medially (black arrow). Associated endosteal and periosteal beaking with thickening of the lateral cortex suggests that this complete fracture originated in the lateral cortex. (**d**) Plain X-ray right leg anteroposterior, 58-year-old women, showing stress fracture of the tibia bone

vs. 74) was primarily due to the more precise specification of transverse configuration. Twelve shaft fractures were reclassified as AFFs due to modification of comminution and periosteal/endosteal thickening criteria. In our opinion, radiographic studies that use the revised ASBMR case definition will capture the phenomenon more accurately [15].

Terminology

The overlap of various terminology words used to describe traumatic fractures may cause some confusion. This includes stress, fatigue, insufficiency, fragility, atypical, and pathological fractures, which can be an impediment to understanding, reporting, and grading these injuries [16, 17]. Stress fractures, in the broadest sense of the term, can be divided into fatigue fractures and insufficiency fractures. In clinical practice, fatigue fractures and insufficiency fractures lie along a spectrum, and in some cases, it can be difficult to differentiate between the two. However, understanding the biological and radiographic differences can lead to a better understanding of the underlying pathophysiology.

A fatigue fracture is a focal failure of normal bone caused by repetitive applied stress [16, 18, 19]. Fatigue fractures commonly occur when the patient engages in increased frequency, duration, or intensity of activity, such as when military recruits sustain "march fractures" of the metatarsal bones [20].

In comparison, an insufficiency fracture is a focal failure of abnormally weakened bone caused by repetitive applied stress [16–19]. The term fragility fracture likewise signifies a fracture in abnormally weakened bone; however, the term is often used in the setting of an isolated mechanical loading event rather than repetitive applied stress, and it applies most commonly in a patient with osteoporosis [21–49]. In clinical practice, the terms fragility and insufficiency are often used interchangeably with reference to osteoporotic fractures because, in many cases, it is not possible to distinguish the chronicity and magnitude of loading, resulting in fracture in diffusely weakened osteoporotic bone.

Although osteoporosis is by far the most common underlying metabolic disturbance resulting in fracture [17, 22], insufficiency fractures may arise from a variety of disorders that influence the ability of bone to withstand normal loading

forces, including disorders of bone mineral homeostasis (e.g., osteoporosis, hyperparathyroidism, diabetes mellitus, osteomalacia), bone remodeling (e.g., Paget disease, osteopetrosis, other sclerosing bone dysplasias), collagen formation (e.g., osteogenesis imperfecta, Marfan syndrome), the adverse effects of pharmaceuticals (e.g., glucocorticoid drugs, chemotherapeutic agents), and prior radiation therapy [19, 22–27]. However, in the absence of a known history of metabolic bone disease, differentiation between fatigue and insufficiency fractures is often arbitrary, and it is not always clear how to distinguish normal from abnormal bone.

Atypical femoral fractures occur in the lateral cortex of the femoral diaphysis (Fig. 27.2) and can be seen in patients undergoing long-term therapy with bisphosphonate medications. In distinction to stress and insufficiency fractures, where the terminology is somewhat imprecise, atypical femoral fractures are explicitly defined, and terminology should follow the established guidelines of the American Society for Bone and Mineral Research (ASBMR) [23, 25]. The imaging appearance of these fractures is similar to that of stress (fatigue) fractures; however, they should be considered as a form of insufficiency fracture because the bone can be excessively brittle and weakened.

The term pathological fracture generally is reserved for fractures through a focal neoplasm, which may be either benign or malignant [19, 26, 27], although this definition is also inconsistently applied, and pathological fracture through osteomyelitis has been described in the literature [28, 29]. This is in contradistinction to a fracture of a region of metabolic bone disease—whether diffuse, such as with osteopetrosis, or focal, such as with Paget disease—which generally should be referred to as an insufficiency fracture [30, 31] (Table 27.2).

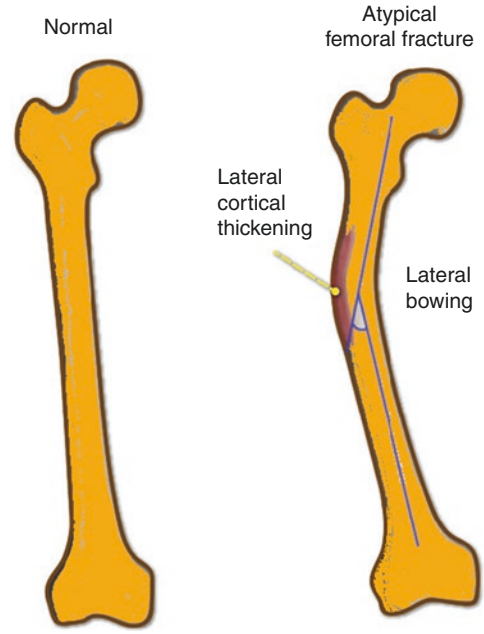

Fig. 27.2 Atypical femur fracture. Illustration showing the morphology of the femur and site of atypical femur fracture. Location of the atypical femur fracture in the femoral diaphysis as defined by the ASBMR: distal to the lesser trochanter—proximal to the supracondylar flare. (Quoted from Starr et al. [15] under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

Table 27.2 Characteristics of different types of stress fractures in contrast with pathological fracture

Stress fracture				Pathological fracture
Fatigue fracture	Fragility fracture	Insufficiency fracture	Atypical fracture	
Focal failure of a normal bone caused by repetitive applied stress Example: March fractures	Focal failure of abnormally weakened bone Isolate mechanical loading Example: Osteoporosis fracture	Focal failure of abnormally weakened bone Caused by repetitive applied stress Examples: bone remodeling disorders, collagen formation, drug induced (please see text)	Focal failure of abnormally weakened bone Occurs in the lateral context of the femoral diaphysis Usually in patients on long term bisphosphonate therapy *Has definition criteria	Fracture through focal neoplasm (benign/malignant) May occur though osteomyelitis

Epidemiology

In the second ASBMR Task Force report, AFF incidence was very low, ranging from 50 to 130 cases per 100,000 patient-years [31]. Their frequency was increased in patients on BPs, with a direct relationship between duration of BP exposure and risk of AFF [6, 31–40]. There was a significant association between glucocorticoid use and AFFs [31, 32, 35, 37, 39, 40]. Affected patients were approximately a decade younger than controls, a finding substantiated by a recent systematic review of 14 studies, in which 10 papers used the 2010 and 4 used the 2013 ASBMR definition [41]. The overall incidence of AFFs was low ranging from 3.0 to 9.8 per 100,000 person-years [41], the highest rate in a retrospective Norwegian fracture registry study that included periprosthetic fractures [42], which were specifically excluded in both ASBMR Task Force definitions. Other epidemiological studies have addressed relationships between AFF, BP use, and factors that may predispose certain patient populations to heightened risk. Most continue to report that AFF incidence is low, particularly compared to incidence of ordinary hip fractures [43–45].

AFFs in Osteoporosis Patients Treated with Denosumab

AFFs have been reported in osteoporosis patients receiving denosumab. While the majority of reports document extensive prior bisphosphonates exposure, as reviewed by Seiga et al. in 2016 [46] and reported by Ramchand et al. [47], AFFs have been reported in patients on denosumab with brief prior bisphosphonates exposure [48]. In the FREEDOM Trial open-label extension, two participants developed AFFs (0.8 per 10,000 participant-years), one after 7 years of denosumab exposure and one after 3 years of denosumab exposure [49].

AFFs in Osteoporosis Patients Treated with Romosozumab

Romosozumab is a monoclonal antibody that increases bone formation by binding to and inhibiting sclerostin and also decreases bone resorption. In the Fracture Study of Postmenopausal Women with Osteoporosis (FRAME), 1 of 3521 participants in the romosozumab group had an AFF after 3.5 months of exposure; that individual had a history of prodromal pain at the fracture site prior to enrollment [50]. In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study, 4093 postmenopausal women with osteoporosis and a fragility fracture were randomly assigned to monthly romosozumab or weekly oral alendronate for 12 months followed by open-label alendronate for another 12 months [51]. There were no AFFs during the initial 12 months in either group; in the second 12 months, two AFFs occurred in the romosozumab to alendronate group (< 0.1%) and four AFFs in the alendronate to alendronate group (0.2%).

AFF in Autoimmune Disease and Steroid Therapy

Autoimmune disease and glucocorticoid use, established risk factors for osteoporotic fracture, have both been linked to AFF [45]. In 125 Japanese patients (90% women) with long-standing autoimmune disease taking BPs and glucocorticoids, Sato et al. reported that localized periosteal thickening of the lateral cortex ("beaking") was present in 8.0% (15 femora, 10 patients) and new beaking developed in 10.3% (21 femora, 12 patients) over 2 years. A complete AFF at the beaking site occurred in one patient. Factors significantly associated with beaking included >4 years of BP therapy, longer duration of BP therapy (6.1 vs. 5.0 years), age 40–60 years, and diabetes [52]. They measured the height of the beaking reaction in 20 femora (12 patients), characterizing it as pointed or arched [53].

Beaking was considered "severe" if associated with pain, a complete AFF, or an incomplete AFF with a visible fracture line; the periosteal reaction was higher and more commonly pointed in the severe form.

AFFs in Cancer Patients Treated with Bisphosphonates and/or Denosumab

Edwards et al. retrospectively assessed the incidence of and risk factors for AFF in cancer patients followed at the MD Anderson Cancer Center over a 10-year period, both treated with oral and low-dose IV BPs for osteoporosis and with high-dose pamidronate and zoledronic acid for metastatic cancer [54]. As only AFFs that came to clinical attention were assessed, no absolute incidence rate was reported. Among 10,587 BP users, there were 23 AFFs compared to 2 AFF cases among 300,553 patients who did not receive BPs (OR 355.58; 95% CI, 84.1–1501.4, $p < 0.0001$). In cancer patients treated for osteoporosis, six AFFs occurred in patients on alendronate for a mean of 84 months and two AFFs occurred in patients on ibandronate for a mean of 36 months.

Compared to other bisphosphonates, the OR of an AFF was higher in patients treated with alendronate for osteoporosis (5.54; 95% CI; 1.60–19.112) and zoledronic acid was associated with a lower OR (0.34; 95% CI; 0.12–0.97). The authors hypothesized that the lower rate of AFFs in zoledronic acid users was because the drug concentrates in skeletal metastases and is less available to other skeletal sites [54]. However, there was a marked difference in duration of exposure between those treated with BPs for osteoporosis (84 and 36 months for alendronate and ibandronate, respectively) and those treated with zoledronic acid for metastatic cancer (5 and 14 months for zoledronic acid and pamidronate, respectively). Duration of exposure is an important risk factor for AFFs as time is required for suppressed remodeling to cause changes in bone material properties (collagen and mineralization) that may predispose to microcrack initiation and propagation [55].

Denosumab is used to treat metastatic skeletal disease and multiple myeloma at higher doses and with greater frequency than for osteoporosis (120 mg monthly vs. 60 mg twice yearly). Tateiwa et al. reported two AFF patients with metastatic breast cancer; one took BPs for 11 years before starting denosumab and one took only bisphosphonates [56]. In both, tomosynthesis, an older three-dimensional imaging technique that permits acquisition of higher-resolution images than conventional radiographs with lower radiation exposure than computed tomography, identified fracture lines within the area of cortical thickening that were not visible on radiographs [56]. Austin et al. reported two patients who sustained AFFs after receiving denosumab for metastatic cancer for 2 and 3.5 years without prior BP therapy [57]. Both experienced prodromal thigh pain, and in both, the fractures were initially attributed to skeletal metastases; neither patient had histological evidence of malignancy at the fracture site [57]. Yang et al. reviewed records of 253 patients at their cancer center who received at least 12 doses of denosumab for metastatic bone disease. During a median follow-up of 27 months, they identified one patient with a complete AFF (incidence 0.4%; 95% CI 0.1–2.2%) who received 70 doses of IV BP before receiving 28 monthly doses of denosumab [40]. They also reviewed all available radiographs in a subset of 66 patients with at least 21 monthly doses of denosumab; 2 patients had diffuse cortical thickening of the femoral diaphysis and localized periosteal reaction of lateral femoral cortex (incidence 4.5%; 95% CI 1.6–12.5%), confirmed on bone scan and magnetic resonance imaging [58]. These papers raise concern that clinical and subclinical presentations of AFF may be attributed to metastases and missed in cancer patients.

Periprosthetic AFFs

Two recent studies addressed periprosthetic fractures, which were excluded in the 2010 and

the 2013 ASBMR Task Force case definitions because they are associated with a known risk of femoral fractures. A retrospective Norwegian study of all patients greater than or equal to 65 years old treated at a single institution between 2004 and 2011 for subtrochanteric and diaphyseal fractures included patients with and without implants [59]. Of 217 fracture patients with evaluable radiographs, 17 fractures in 16 women were designated atypical by unspecified criteria. Their catchment area included 21,630 women aged ≥65 years, of whom 2214 were treated with BPs. AFF incidence was 9.8 (95% CI 5.2–14.5) per 100,000 person-years and 79.0 (95% CI 37.8–120.3) per 100,000 person-years in those receiving BPs. However, 8 of 17 fractures occurred close to implanted metal [9]. A more recent 10-year retrospective study of 15 North American centers defined characteristics of 196 patients with AFFs receiving long-term (> 2 years) BPs in whom the AFF was periprosthetic (PAFF, n = 21) or not periprosthetic (AFF, n = 175) [60]. Only periprosthetic fractures with atypical features (lateral cortical beaking or hypertrophy, transverse lucency in the lateral cortex, transverse orientation of the fracture in the lateral cortex, minimal comminution) were included. PAFFs took longer to heal and had higher mortality and significantly more complications. Compared to the literature, several features common to patients with ordinary periprosthetic fractures (history of revision surgery, infection, total hip replacement for previous low-energy hip fracture with/without femoral loosening) were not present in BP-treated patients with PAFFs. Prodromal pain was common in PAFF patients, but no data were presented [60]. While the ASBMR case definition for AFFs excluded periprosthetic fractures, emerging data suggest that they may occur. Physicians should be alert to the radiographic and clinical features and consider immediate cessation of BP therapy, imaging of the contralateral limb, protected weight-bearing, and close monitoring for signs of complete AFF or surgical fixation to stabilize the femur.

Pathogenesis of AFF

The fact that AFFs have been reported in patients never exposed to antiresorptive therapies such as bisphosphonates or denosumab, and the heterogeneity in bone histomorphometry found in AFF patients, it can be concluded that severe suppression of bone turnover is not a constant finding in patients with AFF. Several possibilities have been raised that the clinician should be aware of them. These include the following.

Stress or Insufficiency Fracture

The second ASBMR Task Force [5] considered AFFs to be stress or insufficiency fractures that 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, most likely attributed to prolonged suppression of bone remodeling. Long duration of bisphosphonates therapy may lead to osteon homogeneity with respect to tissue age and mineralization. In susceptible individuals, repetitive loading of the femur may lead to accumulation of microcracks within the cortex. Intracortical fracture repair, normally accomplished by targeted osteoclastic resorption of microcracks, which tends to aggregate in actively remodeling bone, is inhibited by bisphosphonates, thus leading to microcrack aggregation and propagation.

Hip Geometry and AFF

Some investigators have suggested that the geometry of the femur may play a role in the pathogenesis of AFF. Specifically, femoral anatomy, which may influence the position of maximal tensile stresses on the lateral femoral cortex. This suggestion was based on the propensity for AFFs to be bilateral and in the same location on ipsilateral and contralateral sides and the finding that anterior and lateral bowing were correlated with tensile stress adjacent to the fracture site [61].

Since the publication of the 2013 ASBMR Task Force [5], several reports were published supporting this concept. Saita et al. evaluated weight-bearing radiographs of 10 patients with 14 AFFs [62]. AFF locations were similar in those with bilateral fractures; the standing femorotibial angle (Fig. 27.3) was significantly larger (more varus) in those with diaphyseal than subtrochanteric fractures and larger than those with ordinary femoral fractures [62]. In other studies, femoral neck-shaft angle was smaller in AFF patients than healthy controls in other studies, also suggesting that more varus proximal femoral geometry predisposes toward AFF [63–65]. A femoral neck-shaft angle cutoff of <128.3° had a sensitivity of 69% and a specificity of 63% to predict AFF [65], although not observed in a Singaporean Chinese cohort [66].

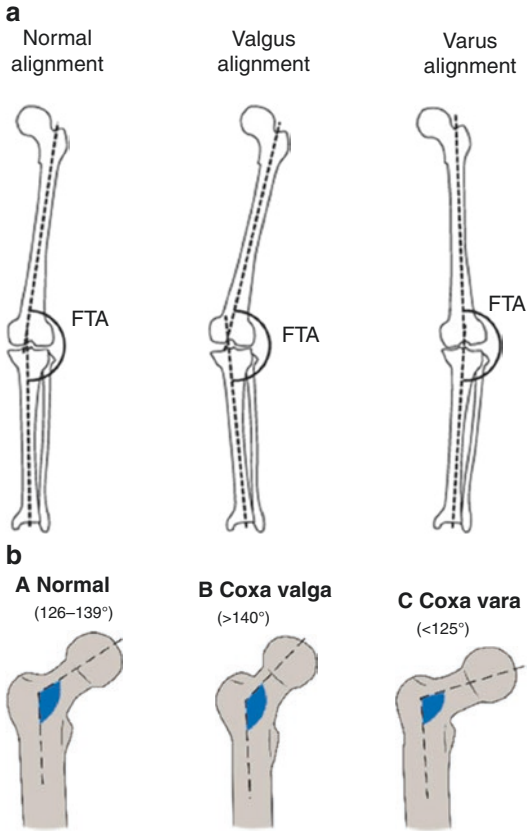

Fig. 27.3 (**a**) Femorotibial angle: the femorotibial angle (FTA) is the lateral angle between the axis of the femoral shaft and that of the tibial shaft. An increased FTA is called varus alignment while a decreased FTA is called valgus alignment. (**b**) Femur neck-shaft angle: a decreased femur neck-shaft angle is called coxa vara or varus alignment. An increased neck-shaft angle is called coxa valga or valgus alignment. (**c**) Femoral bowing angle: femoral bowing angle is the line that best describes the midpoint of the endosteal canal of the femoral diaphysis drawn in the proximal and the distal quarters. (Quoted from Starr et al. [15] under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

In their article, Starr and her colleagues [15] concluded that there is increasing evidence that the presence of a more varus femorotibial angle and lateral femoral bowing influences mechanical forces on the lower limb and the region of maximal tensile loading on the lateral femoral cortex, whereas the subtrochanteric AFF patients are more likely to have smaller femoral neck-shaft angles. Such biomechanical factors may account for the more proximal location of such fractures in individuals with more varus femorotibial angles.

Genetic Predisposition

The first evidence for a genetic influence on AFFs was reported by Roca-Ayats et al. [67]. Whole-exome sequencing in three sisters with AFFs and long-term bisphosphonate therapy revealed a novel p.Asp188Tyr substitution in the enzyme geranylgeranyl pyrophosphate synthase Asp188Tyr located in the genomic position g.235505746G → T on chromosome 1 (GRCh37/hg19). This mutation in GGPS1 affects a site within the enzyme that is inhibited by bisphosphonates, and this enzyme is key in the mevalonate pathway. This mutation would be expected to reduce enzyme activity and could predispose to AFF [67]. In a genome-wide search for nonsynonymous variants in coding region between 13 AFF patients with and 286 controls without AFFs, 21 genetic variants were more common in the AFF group [68–70]. Many cases had two or more at-risk variants, suggesting that the risk for AFFs may be polygenic and result from accumulation of at-risk genetic variants [71]. However, AFFs have been reported in bisphosphonate-naïve patients, in patients using other antiresorp-

tives [46], and in other genetic conditions with suppressed bone turnover [69, 70] or defective mineralization [71, 72].

Other Medications: Glucocorticoids, Proton Pump Inhibitors

Long-term use of both glucocorticoids and proton pump inhibitors has been linked to a variety of side effects, which also are related to bone metabolism. Proton pump inhibitor intake changes resorption and may lead to different forms of malnutrition, which has been associated with an increased general risk of fractures [73]. Furthermore, several studies also associated AFF risk with proton pump inhibitors (PPI) use [74]. However, there was no correlation with fracture location [75]. Similarly, long-term use of glucocorticoids is known to cause osteoporosis. Recommendations include treating with calcium and vitamin D plus an additional osteoporosis medication (oral bisphosphonate preferred) in adults at moderate-to-high fracture risk [76].

Since therefore the intake of bisphosphonates is frequently combined with glucocorticoids, the isolated influence of glucocorticoids is still under discussion. However, the importance of both medications in relation to the occurrence of AFF was rated by the ASBMR as high, so it was included in the definition as one of the minor criteria [77, 78].

Bone Material Properties in Patients with AFFs

Bones are exposed to a variety of mechanical forces, including compressive, tensile, bending, shearing, and torsional forces (24). The immediate response of bone or any other structural material to mechanical forces is determined according to the interplay of two primary factors—the ability of the material to absorb a mechanical load (stress) and the ability to deform under those forces without failure (strain) (Fig. 27.4). At low load levels, a bone readily deforms within its elastic range, and the bone returns to its original shape and structure when the load is released. As mechanical load increases, the bone deforms beyond its elastic range (into the plastic range) and microcracks are formed. A fracture occurs when there is accumulation of microcracks outpacing the body's capacity for repair (e.g., stress, fatigue, or insufficiency fracture), when there is a single force exceeding the failure load of the bone (e.g., traumatic fracture), or when there is a combination of these two [30].

Spontaneous or low-trauma fractures of the femur bone are unusual. Femur is rich in cortical bone and physiologically adapted to withstand large, repetitive forces. Although antiresorptive therapies increase bone mineral content, prolonged exposure may cause some changes in cortical bone material properties with potentially deleterious effects on bone strength. These effects may vary according to the bisphosphonates medication class. In a four-point bending study of femur bones from osteoporotic sheep exposed to raloxifene, alendronate, zoledronate, or teriparatide for 1 year, alendronate was associated with reduced fatigue life (fewer cycles of stress before failure) and lower modulus loss at failure (reduced tendency for a material to bend) [79].

Biopsies of the proximal femoral cortex were compared among five groups of postmenopausal women undergoing surgery for fracture or total hip arthroplasty: bisphosphonate-treated with AFF, bisphosphonate-treated with ordinary osteoporotic fractures, bisphosphonate-treated without fractures, bisphosphonate-naïve with typical osteoporotic fractures, and bisphosphonate-naïve without fractures [55]. By vibrational spectroscopy and nanoindentation, the **b**isphosphonate-treated AFF group had higher tissue mineral content and more mature collagen (characteristics associated with bone that is harder and more brittle) than bisphosphonate-treated women with ordinary osteoporotic fractures. In addition, bisphosphonate-treated patients had increased propensity for crack initiation and decreased deflection of crack paths at osteon borders. This study showed that normal mechanisms by which bones dissipate energy and retard crack propagation were impaired by bisphosphonates; together

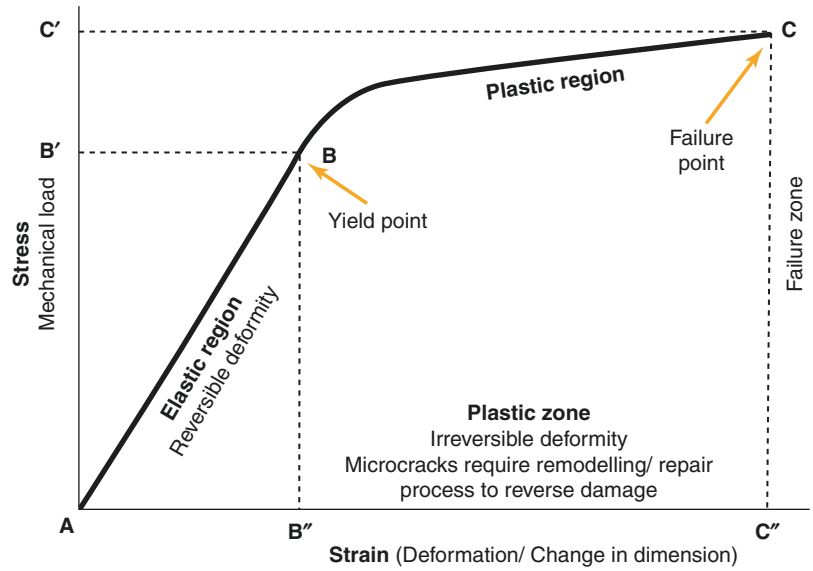

Fig. 27.4 Stress–strain curve**.** The yield point represents the mechanical load required to cause irreversible plastic deformation of a material. In bone, multidirectional forces above the yield point result in microcracks that initiate the bone remodeling and repair cascade. A stress fracture occurs when the rate of microcrack formation exceeds the repair capacity of the bone. The failure point represents the mechanical load required for gross failure of the material. In bones, this is the force required to produce an acute traumatic fracture

with increased uniformity of mineralization, this could lower resistance to fracture and explain the transverse fracture morphology seen in AFFs.

In contrast, bone microarchitecture does not appear to influence AFF pathogenesis. Zanchetta et al. used high-resolution peripheral quantitative computed tomography (HR-pQCT) to evaluate microarchitecture among BP-treated AFF, BP-treated and BP-naïve patients without AFFs [80], finding no difference in any volumetric or microarchitectural index. However, as HR-pQCT measures bone microarchitecture at the radius and tibia, it could miss local changes in the femur.

Mechanisms of Impaired Fracture Healing in AFF

Normally, bone microcracks heal by targeted remodeling in which osteoclasts resorb damaged tissue and osteoblasts form new bone. Suppression of remodeling, typical of bisphosphonate-treated patients, has been documented in AFF patients by bone turnover markers, iliac crest biopsies, and fracture site biopsies [5, 6, 59]. Schilcher et al. performed micro-computed tomography (CT), infrared spectroscopy, and histomorphometry on cortical biopsies including the fracture line in eight patients, four with complete AFFs, and four with incomplete AFFs [81]. In the incomplete AFFs, the fracture gap varied from 150 to 200 μm wide and contained amorphous, nonmineralized, acellular necrotic material. Bone adjacent to the fracture gap demonstrated evidence of remodeling with osteoclasts, resorption cavities, and woven bone, with no evidence of remodeling or callus within the gap [81]. The investigators hypothesized that local strains related to low-impact activities such as walking prevented cell survival and delayed healing [81, 82]. Radiographic new bone deposition with bridging was observed within resected cortical deficits in all cases, within the expected time frame for cortical bone [83].

Atypical Fractures in Other Bones

Atypical insufficiency fractures have been linked mainly to the femur bone. On the contrary, atypi-

cal fractures of other bones are much less common. There are only few case reports available that describe insufficiency fractures occurring in other bones. Atypical fracture of the tibia bone is the most commonly reported fracture. Fractures of the tibial diaphysis [84–86] and metaphysis [87, 88] of patients on long-term bisphosphonate therapy were published as case reports. The diagnostic guidelines outlined by the American Society for Bone and Mineral Research (ASBMR) delineate the criteria for atypical insufficiency fractures [89, 90]. However, this definition is strictly limited to femoral fractures and is not designed for fractures in alternative sites. Most of the atypical fractures reported in other bones apart from the femur meet all major and multiple minor ASBMR criteria for atypical fractures. In one study, key features include presenting with bilateral transverse, noncomminuted tibial fractures following no trauma, with delayed fracture healing and prodromal pain for several months leading up to the fracture [91].

Furthermore, there have been published reports of nontraumatic fractures of bones other than the tibia, in patients on long-term bisphosphonate therapy for osteoporosis, including the fibula [92] and ulna/radius [93]. Thus, the clinician needs to be aware of such possibilities as atypical fractures potentially associated with antiresorptive therapy can occur in weight-bearing long bones other than the femur.

Clinical Features and Diagnosis of Atypical Femur Fractures

Avoiding AFF by identifying patients at risk of developing AFF (Fig. 27.5), optimizing osteoporosis management, and recognizing impending fractures are challenging and require a high index of suspicion for any patient with a history of osteoporosis, especially, but not exclusively, if currently or recently treated with bisphosphonates (AFF has also been reported in patients who have discontinued bisphosphonates years prior to the fracture [31]) or other prophylactic medication and complaining of thigh or groin pain, even if they received treatment for only a brief period. When suspicious of incomplete AFF, careful radiographic exploration for features suggestive of impending fractures on hip and pelvic radiographs should occur. In patients with a complete fracture, the contralateral side should also be radiographed and carefully inspected for transverse fracture lines in lateral cortex, beaking, and other characteristic signs of atypical femoral fracture since 40% or more have bilateral involvement [94–96]. The sensitivity and specificity for these signs are generally high, especially for transverse fracture lines, lack of comminution, and localized periosteal or endosteal thickening of the lateral cortex (“beaking”) [97].

In cases with normal radiographs on the contralateral side, but where there is still clinical suspicion, computed tomography (CT) should be considered since fracture lines, not visible on radiographs, might be diagnosed. Lee et al. [98] have shown that patients with a subsequent AFF have a thicker lateral cortex in the subtrochanteric region of the femur on CT before the fracture event than bisphosphonate users who did not sustain a femoral fracture and than bisphosphonate-naïve patients. Thus, CT might be used for the early detection of AFF in long-term bisphosphonate users. Periosteal and endosteal edema can be visible using magnetic resonance imaging (MRI) and might also be indicative of an impending fracture and might be used in conservative follow-up of impending fractures [99].

Management of Atypical Femoral Fractures

Early Detection of AFFs

Extended femur scanning by DXA has been suggested as a tool for screening the patients for atypical femur fractures [100]. When prolonged treatment with antiosteoporotic medication is necessary, it is reassuring for physicians and patients to assess the patient for the possibility of an incomplete AFF. DXA has the advantage of being able to detect incomplete AFF in patients

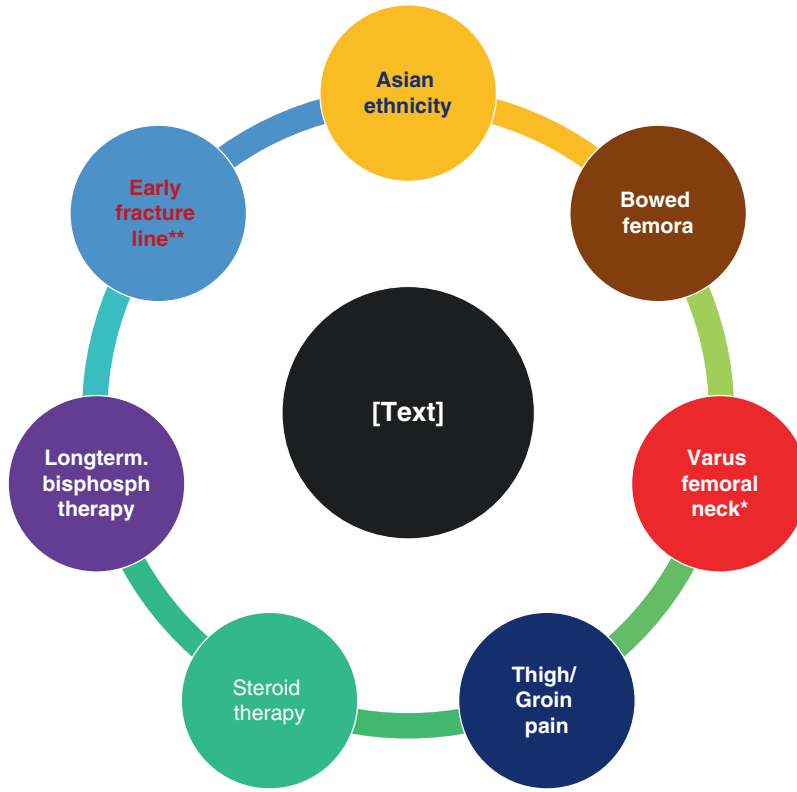

Fig. 27.5 Potential indicators of patients at risk for AFF (in addition to antiresorptive drugs). *Varus femoral neck/shaft angle. **Signs of early fracture line or periosteal reaction on image of femur

on antiresorptive treatment with negligible radiation exposure and without additional costs when DXA is performed for follow-up evaluation. Therefore, extended femur scans by DXA could be considered a clinically relevant screening method because early identification of AFFs has therapeutic consequences.

Between October 2011 and January 2013, 257 patients over age 50 who had been on bisphosphonates for over 5 years had a dual-energy X-ray absorptiometry (DXA) scan of the femur scan with the region of interest (ROI) extended distally from 15.3 to 22 cm. Cortical beaking was detected in 19 (7.4%); all had follow-up radiographs and seven (2.7%) had radiographic evidence of incomplete AFFs [101]. A subsequent study by the same investigators used single-energy (SE) DXA technology to image the entire femur between May 2013 and September 2014; none of 173 patients on bisphosphonates for over 5 years had cortical beaking, suggesting declining prevalence of AFFs possibly due to contemporaneous declines in bisphosphonates prescribing from 2009 through 2014 [102]. Between 2006 and 2014, Van de Laarschot et al. performed bilateral extended femur scans in 282 patients on long-term bisphosphonates [103]. Ten incomplete AFFs were diagnosed in nine patients (3.2%); one was a false positive and two patients did not have follow-up X-rays of the femur. Khosla et al., in a perspective published in the *Journal of Bone and Mineral Research*, noted that SE DXA is a promising new technology that can detect localized periosteal reactions and may be useful to monitor patients who require long-term BPs for impending AFFs [104].

Extended femur scans can easily be implemented as a screening tool for incomplete AFFs when a follow-up DXA is performed for therapeutic evaluation and they should not be limited to symptomatic patients. The exposure to irradiation should not represent a negative point. DXA has the advantage of utilizing very low irradiation exposure dose compared with conventional radiography [105, 106]. It is estimated that the effective radiation dose of a unilateral dual-energy

extended femur scan with a maximum length of 33.6 cm is ~0.37 μSv compared with ~10 μSv of one anteroposterior X-ray of the femur [107].

The extended DXA scans of the femur are carried out with the region of interest (ROI) extended distally from 15.3 to 22 cm to depict the lesser trochanter down to the supracondylar flare. Femur scans should be assessed for beaking (also called flaring), which is defined as localized periosteal or endosteal thickening of the lateral cortex, by visual inspection. If beaking was visible on DXA and evaluation of previous X-rays or other medical images did not explain this abnormality, an additional X-ray of the femur should be ordered to confirm the presence of incomplete AFF. Incidental findings such as irregularities of the medial cortex should be reported as well because they may lead to additional diagnostics. The patient's medical records should be checked for the occurrence of a complete or incomplete AFF in the past based on the available clinical correspondence and/or radiographs of the femora [100].

However, it should be kept in mind that prospective studies on the natural course of established incomplete AFFs are lacking and that it is also unknown if and how soon AFFs still may develop when there is absence of beaking at this moment. Furthermore, AFF by extended femur scan will necessitate decision-making for preventive surgery versus conservative treatment. In a recent study by Min and colleagues, a novel scoring system was proposed to predict the occurrence of a complete fracture among patients with incomplete AFF [108]. A score of 9 or higher indicates a high risk of an impending complete fracture and warrants prophylactic fixation.

Prophylactic Treatment

Impending fractures, as defined by the ASBMR, have an elevated risk of progressing to a complete fracture as high as 28.3% within 6 months after diagnosis. Subtrochanteric location, functional pain, and a radiolucent line of more than 50% of the lateral cortex were identified as risk factors for occurrence of a complete fracture [108]. Prophylactic surgical treatment with cephalomedullary nail seems to be effective, particularly in those with extensive cortical defects and pain and/or marrow edema on magnetic resonance imaging (MRI), which are predisposed to delayed or nonunion or to progress to complete AFFs without surgical intervention [109]. It also seems that fractures heal faster when treated surgically with a consequent shorter hospital stay. Progression to complete fracture and pain refractory to nonsurgical treatment reduce the success rate of nonsurgical treatment of incomplete fractures to approximately 50% [110].

The ASBMR recommends that patients with incomplete fractures and no pain, or those with periosteal thickening but no cortical lucency, should limit weight-bearing and avoid vigorous activity. Reduced activity should be continued until there is no bone edema detected on an MRI or no increased activity detected on a bone scan [6].

In the study carried out by Min and colleagues [108], a practical scoring system was developed to identify impending complete fracture among incomplete atypical femoral fractures. The proposed scoring system (Table 27.3) appeared accurate, reliable, and valid. The system can be useful to determine how to treat incomplete atypical femoral fractures. In planning the treatment of incomplete atypical femoral fracture, the problem lies in accurately distinguishing between nonpending fractures that can be treated without surgery and impending fractures that require prophylactic fixation. Results of the study revealed that a score of 7 is suggestive (probability of fracture, 8%) of an impending fracture, whereas a score of 8 is diagnostic (probability of fracture, 15%). When a score of 9 or more is obtained, the probability of fracture warrants prophylactic fixation. Conversely, incomplete atypical femoral fracture with a score of 7 or less may be treated conservatively. Patients who had painless incomplete AFF should be informed that pain might be a prodromal symptom for the progression to a complete fracture, and follow-up evaluations should be done frequently. During the follow-up, physicians should recalculate the proposed scor-

Table 27.3 Scoring system to predict the occurrence of a complete fracture among patients with incomplete AFF [108]

	Score		
Variable	1	2	3
Site	Others	Diaphyseal	Subtrochanteric
Pain	None	Mild	Functional
Contralateral	Complete	Incomplete	Intact
Radiolucent	Focal change	<1/2 of diameter of the involved femur	≥1/2 of diameter of the involved femur

ing system according to the changes of pain intensity and radiographic feature.

Management of Patients After Atypical Femur Fractures

The literature suggests that surgical treatment of AFF is more complex than that of typical femoral fractures, healing time is prolonged, and reduction and surgical technique is more demanding, leaving little room for error. Surgically, cephalomedullary nailing is the preferred method for surgical fixation of complete and incomplete AFF [111]. However, plate fixation and other methods may come into consideration depending on fracture location. For patients with bowed femurs, an alternative nail entry site may be necessary [112], and for these patients, lateral fixation has been suggested as an alternative [113]. It should be kept in mind that a greater percentage of fractures treated with plate fixation (31.3%) require revision surgery than fractures treated with intramedullary nailing (12.9%) [114]. In any event, surgery should be followed by a rehabilitation program.

Several studies show increased healing time for AFF. Lee et al. 48 showed that only 63% of 46 fractures healed within 6 months, but 95.7% subsequently healed without any further surgery. Egol et al. [115] reported 98% healing within 12 months of surgical treatment, almost two-thirds returned to self-reported baseline function. The same study also found that malreduction was associated with delayed healing. Other studies have not been able to achieve the same high healing rate. A review by Koh et al. [114] including 733 patients with 834 fractures showed an overall healing rate of 85% and a revision rate of 12.6%.

Lim et al. [116] tested 46 variables for association with healing time longer than 6 months or nonunion. High BMI and subtrochanteric fracture location were significantly associated with delayed healing time, but these factors are not controllable. More interesting was that delayed union or nonunion was significantly associated with postoperative gaps at the fracture site, primarily at the lateral or anterior cortex. Failing to restore the anatomical neck-shaft angle, when reducing and fixing AFF, has also been shown to cause significant longer healing time [117]. In cases of excessive bowing, anatomical reduction might require special techniques or implants [118]. Iatrogenic intraoperative fractures and implant failures are also more frequent compared with typical femur fractures [119].

Medical Management of AFF

For patients with AFF in either form, a stress reaction, stress fracture, incomplete or complete subtrochanteric or femoral shaft fracture, bisphosphate, or other potent antiresorptive agents should be discontinued. Dietary calcium and vitamin D status should be assessed, and adequate supplementation prescribed [6]. Simple fixation without optimizing bone metabolic profile and stopping any possible influencing factors may prevent healing [120] and even cause failure in these cases [121]. Whether the antiresorptive agents should be discontinued permanently or could be resumed after a "drug holiday" of 3–5 years is unknown [122].

Teriparatide (TPTD), a recombinant parathyroid hormone (PTH), has been suggested as a possible option of treatment of AFF, particularly for patients with incomplete AFF who have not undergone surgery. It has also the potential to

enhance bone healing in patients with delayed healing or nonunion and is, in theory, a good option for supplement treatment in patients with bisphosphonate-associated AFF since bone turnover is suppressed in these cases. However, the response to teriparatide has been variable (24), and while anecdotal evidence of the beneficial effect exists, there are also anecdotal case reports of teriparatide failure to prevent AFF [121]. In an open-label study, Watts and co-workers [122] performed iliac crest bone biopsies and clinical assessment in 14 patients treated with teriparatide for 2 years. Five had incomplete fractures (two bilateral), six had unilateral complete fractures, one had bilateral complete fracture, and two 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. Therefore, teriparatide's role in the treatment of AFF is still unknown and should not be used routinely.

The use of low-intensity pulsed ultrasound (LIPUS) [123] and bone marrow aspirate concentrate [124] has been reported in small retrospective series and case–control series, but evidence is still too limited to conclude any beneficial effect.

Time for a New Treatment Paradigm

Over the past two decades, bisphosphonates have booked their place as the first option for osteoporosis treatment. With the introduction of the inexpensive generic oral bisphosphonate therapy, it has become the standard of care. Gaining more experience with the safety profile of bisphosphonates and link between AFF and long duration of bisphosphonates therapy, there were suggestions for a new approach of osteoporosis management. In the DATA-SWITCH study [125], 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. Suggestions to use teriparatide (as well as abaloparatide) as first-line therapy have faced two main hurdles: (1) they are administered as subcutaneous injections on a daily basis and (2) they are much more expensive than oral bisphosphonates. Even in glucocorticoid-induced osteoporosis, for which a study [126] showed fewer fractures in patients treated with teriparatide than with alendronate, the American College of Rheumatology still recommends oral bisphosphonates as the first treatment option. However, with the introduction of generic less expensive form of teriparatide, and the introduction of the recently licensed dual-action romosozumab, further changes in the treatment paradigm are expected.

The inclusion of the absolute fracture risk in the treatment pathways paved the way for new approaches to identify high-risk patients who most likely would require relatively longer-term therapy. For these patients starting with an anabolic agent first, would be the best option. Increasing bone mass and improving microarchitecture with an anabolic medication before starting a bisphosphonate might change the risk for fracture when the patient is reassessed 5 years after antiresorptive therapy. With this paradigm, it is likely that more patients will be eligible for a drug holiday. In the 2-year VERO study [127], 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 the duration of bisphosphonate exposure, as has been shown by some [128] but not all [129] 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 1 year) could then be followed by reinstitution of bisphosphonate treatment. While a plan such as this has some theoretical appeal, there may be a potential to implement it among the treatment recommendations in the coming few years.

In conclusion, though AFF remains a rare complication in comparison to the osteoporotic fractures prevented by antiresorptive therapy, AFF represents a challenge to health-care profes-

sionals treating osteoporosis. The ASBMR has been defined as "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." Though linked to long-term bisphosphonate therapy, it occurred also in association with other medications. Greater understanding of the biological and genetic pathogenesis of AFF may permit a more precise approach to assessing individual risk before starting antiresorptive therapy. Recent development of single-energy DXA scan technology that can detect incipient cortical "beaking" may permit monitoring of patients on long-term antiresorptive therapy for incomplete AFFs prior to fracture. Until newer methods to treat osteoporosis are developed, creative management strategies, avoidance of treatment for those at low risk, as well as careful monitoring of treated patients are the only tools currently available to minimize the incidence of AFF.

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