Current Osteoporosis Reports (2019) 17:281–290
https://doi.org/10.1007/s11914-019-00525-x

EPIDEMIOLOGY AND PATHOPHYSIOLOGY (F COSMAN AND D SHOBACK, SECTION EDITORS)

The Role of Lower-Limb Geometry in the Pathophysiology of Atypical Femoral Fracture

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Published online: 13 August 2019

Abstract

Purposeof Review The etiology of atypical femoral fracture (AFF) is likely multifactorial. In this review, we examined the recent literature investigating the role of lower-limb geometry in the pathophysiology of AFF.

Recent Findings Increased femoral bowing was associated with prevalent AFF and a greater likelihood of a diaphyseal versus a subtrochanteric AFF location. Femoral neck geometry or hip alignment may also be related to AFF, but findings remain equivocal. Differences in femoral geometry may, in part, be responsible for the high rate of AFF in Asian compared with Caucasian populations. Finally, simulation studies suggest that lower-limb geometry influences AFF risk via its effects on mechanical strain of the lateral femoral cortex.

Summary Femoral geometry, and bowing in particular, is related to prevalent AFF, but more prospective investigation is needed to determine whether measurements of geometry can be used for clinical risk stratification.

Keywords Osteoporosis · Bisphophonates · Femoral bowing · Hip geometry · Femoral strain · Fracture risk

Introduction

Atypical femoral fracture (AFF) is categorized as a low-energy fracture of the femoral shaft or subtrochanteric region. As detailed in the second report of the American Society of Bone and Mineral Research (ASBMR) task force [1], AFF is defined by a complete or incomplete fracture with a characteristic transverse fracture line extending from the lateral cortex (Table 1). Complete AFF is further characterized by minimal comminution and a fracture line extending across both cortices that may become obliquely oriented towards the medial cortex, often displaying a medial spike (Fig. 1). Localized periosteal or endosteal thickening is also frequently observed along the lateral cortex of the fracture location [2–6]. The clinical presentation of AFF frequently includes prodromal thigh or groin pain with weight-bearing [2, 6, 7], and complete AFF often occurs with minimal trauma (i.e., a fall from standing height or lower). These detailed features of AFF suggest that they are coincident with a brittle-like failure as well as a mechanical fatigue phenomenon associated with cumulative loading.

The rate of femoral shaft and subtrochanteric fractures displaying radiographic features of atypia is reported to be 5 to 9 per 100,000 person-years [8, 9•]. In terms of absolute risk, this is considerably less than the 224 to 1050 per 100,000 person-years of osteoporotic hip fractures for women [10–12]. However, concerns have been raised surrounding growing evidence that prolonged use of antiresorptive agents without drug holiday increases the risk of AFF. Indeed, prolonged bisphosphonate (BP) use has been associated with relative AFF risks of 47.3 to 67 [10, 13] and odds ratios of 25.9 to 33.2 [10, 13, 14••]. It has been hypothesized that the

This article is part of the Topical Collection on *Epidemiology and Pathophysiology*

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Table 1 Major and minor features of AFF identified by the second report of the ASBMR task force [1]

Major features
The facture is associated with minimal or no trauma, as in a fall from standing height or less
The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
The fracture is noncomminuted or minimally comminuted
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")
Minor features
Generalized increase in cortical thickness of the femoral diaphyses
Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
Bilateral incomplete or complete diaphysis fractures
Delayed fracture healing

elevated risk of AFF amongst prolonged BP users is due to drug-related suppression of bone remodeling [3, 15, 16], which may lead to reduced collagen quality [17–19], greater mineral heterogeneity [19, 20], and microdamage accumulation [21, 22]—changes that may reduce the toughening and energy-absorption capacity of bone tissue [23, 24]. On the other hand, it is important to note that the exact mechanism underlying the association between AFF and BP use has yet to be determined and is likely multifactorial. Because antiresorptive agents represent an important mainstay in modern osteoporosis treatment, it is important that we identify the causal mechanisms of this phenomenon.

Additional factors associated with AFF, particularly those amongst BP users, include characteristic lower-limb geometry, specifically that of the hip and femoral shaft [9•, 14••, 25–29, 30••, 31–35, 36••, 37, 38••, 39, 40•, 41]. Assuming that the pathophysiology of AFF is related to a mechanical fatigue phenomenon, the increased risk associated with abnormal lower-limb geometry may be explained in part by elevated stress within the lateral cortex of the femoral shaft and subtrochanteric region during activities of daily living [35, 36••, 42•]. Since the identification of the potential role of lower-limb geometry in the pathophysiology of AFF by the ASBMR task force [1], a number of studies have verified this relationship through retrospective case-control observations [9•, 14••, 25–27, 34, 35, 36••, 37, 38••, 40•, 41] and various descriptive analyses [28, 29, 30••, 31, 32, 39]. Some recent studies have also explored the relationship between lower-limb geometry amongst individuals with AFF and the femoral

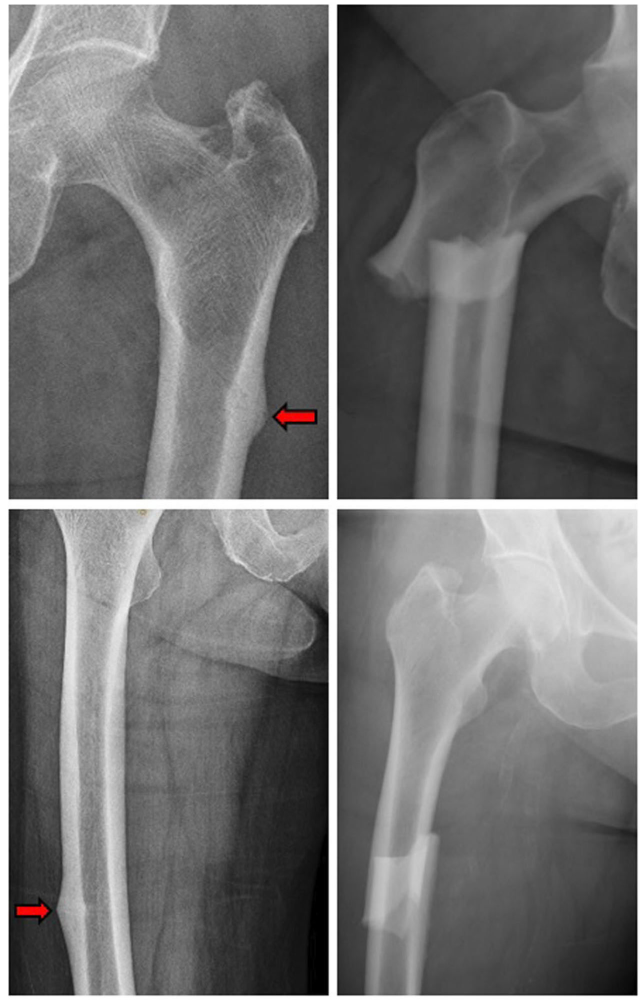

Fig. 1 Radiographs of AFF. Patients often present with localized periosteal thickening (red arrows; left) prior to fracture of the subtrochanteric or diaphyseal region (right)

stresses experienced during posture and locomotion [35, 36••].

The purpose of this review is to summarize the recent literature examining the role of lower-limb geometry in the pathophysiology of AFF. A thorough review of the work that has examined the relationship between lower-limb geometry and AFF will first be discussed. The strong relationship between lower-limb geometry and AFF location along with the increased risk of AFF in Asian populations, relative to other races, will then be addressed. Finally, mechanistic investigations looking to explain the relationship between lower-limb geometry and AFF risk via elevated stress in the lateral femoral cortex will be examined. A better understanding of the relationship between lower-limb geometry and the pathophysiology of AFF may ultimately help identify individuals at increased risk for AFF and provide vital information for optimizing surgical planning and management for patients with AFF.

Lower-Limb Geometry and AFF Risk

The association between lower extremity geometry and AFF risk has, to date, been limited to descriptive and case-control studies of relatively small sample sizes, presumably because of the rarity of this clinical problem. Lower extremity geometry has been studied using radiographic assessments, which include measurements such as femoral shaft curvature, femoral neck geometry, and lower extremity alignment.

Femoral Shaft Curvature

Femoral curvature, or bowing, is typically defined as the angle between two lines along the proximal and distal portions of the femoral shaft, or alternatively by the radius of curvature formed by a center path through the intramedullary canal (Fig. 2; top left). These measurements are traditionally performed on frontal and sagittal plane radiographs, allowing for the quantification of both lateral and anterior bowing angles or radius of curvature. Sasaki et al. [37] examined the femoral curvature of 12 femurs from nine Japanese women with AFF (all BP users, mean exposure 3.6 years) and compared them with age- and sex-matched, non-fractured controls (no BP exposure). The anterior and lateral bowing angles of individuals with AFF were approximately 8° greater than controls. Jang et al. [38••] recently reported similar findings in a study of 42 femurs from twenty-nine Korean women with AFF (all BP users, mean exposure 7.3 years) that illustrated greater anterior (~5°) and lateral (~8.5°) bowing angles relative to age- and sex-matched patients with typical femoral fracture (BP exposure not reported). A typical femoral fracture (TFF) was defined as a fracture of the femoral shaft or subtrochanteric region not meeting the revised case definition of AFF from the second report of the ASBMR task force. A descriptive study by Oh et al. [39] examined the femoral curvature of thirteen Japanese women with AFF (7 BP users, mean exposure 3.9 years) and defined excessive femoral curvature as an apparent mismatch between the fractured femur's radius of curvature in the frontal plane and the intramedullary rod used for fixation. The authors noted that 12 of 13 cases were characterized as having excessive femoral curvature according to this criterion. In the largest case-control study to date on the topic, Lim et al. [14••] reported that 196 Korean women with AFF (148 BP users, mean exposure 5.2 years) illustrated greater anterior (~2.5°)

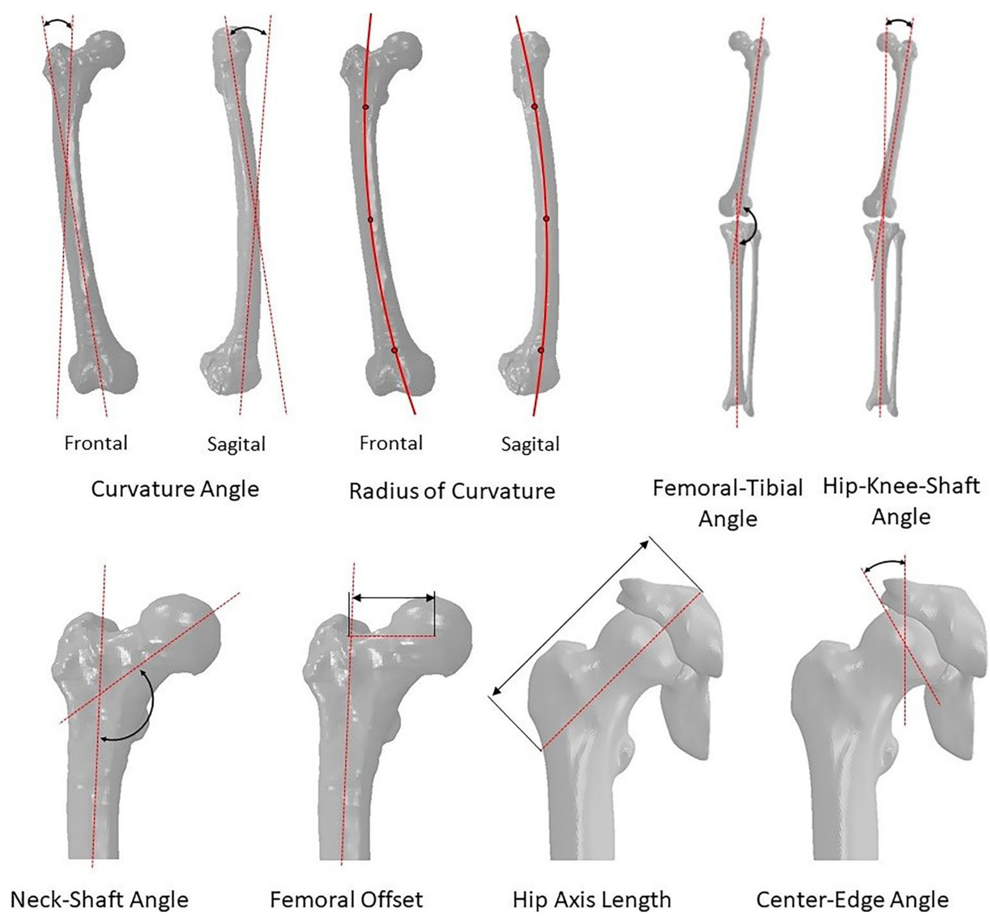

Fig. 2 Typical measurements of femoral geometry

and lateral (~ 1.8°) bowing angles than 94 women with TFF (10 BP users, exposure not reported). Morin et al. [40•] quantified femoral curvature using three-dimensional reconstructions from a low-dose bi-planar X-ray system (EOS™ imaging technology). The lateral bowing angles of 16 Caucasian women with AFF (all BP users, mean exposure 12.4 years) were approximately 2.4° greater than age-, sex-, and BP exposure-matched non-fractured controls. Univariate regression analysis indicated that each degree increase in lateral bowing from 0° increased the risk of AFF by 46%.

Femoral Neck Geometry

Femoral neck geometry measurements in patients with AFF have included the femoral neck-shaft angle, femoral offset, hip axis length, and center-edge angle in the frontal plane (Fig. 2; bottom). Taormina et al. [41] compared the femoral neck geometry from 53 radiographs of patients with AFF (51 females, all BP users, mean exposure 7.9 years) to 64 patients with typical subtrochanteric fractures (50 females, no BP exposure) and 43 non-fractured controls (39 females, all BP users, mean exposure 7.7 years). Patients with AFF illustrated a more acute, or varus, femoral neck-shaft angle, a shorter hip axis length, and a smaller center-edge angle. Similarly, Mahjoub et al. [9•] compared 56 patients with AFF (94% BP users, mean exposure 7.4 years) against 112 controls with traumatic or fragility hip fractures (32% BP users, mean exposure duration unknown), and found that AFF patients had more varus femoral neck-shaft angles and smaller femoral offset, as well as smaller femoral head and neck diameter. Hagen et al. [25] examined the femoral neck-shaft angle of 111 women with AFF (all BP users, mean exposure 7.4 years) and compared them with 33 sex-matched, non-fractured controls (all BP users, mean exposure 5 years). The mean neck-shaft angles of patients with AFF were approximately 4° less than the control group, equating to a more varus angulation. Chou et al. [26] reported no differences in femoral neck-shaft angle amongst Chinese women with AFF ($n = 31$; all BP users, mean exposure 4.8 years), TFF ($n = 49$; no BP users), and non-fractured controls ($n = 31$, all BP users, mean exposure 7 years). Buitendijk et al. [34] also reported no differences in femoral neck-shaft angle between 23 patients with AFF (all BP users, mean exposure 9.8 years) compared with 141 non-fractured controls (all BP users, mean exposure 6.0 years). Similarly, no differences in femoral neck-shaft angle were observed in the case-control studies of Lim et al. [14••] and Morin et al. [40•].

Lower Extremity Alignment

Two measures have been used to examine lower extremity alignment in AFF patients. The femoral-tibial angle has been defined as the angle between the anatomical axes of the tibia and femur. This was computed from landmarks identified on frontal plane radiographs, although somewhat different femoral landmarks may be used in different studies [43, 44]. Alternatively, the hip-knee-shaft angle has been defined as the angle between the mechanical and anatomical femoral axes (Fig. 2; top right). Saita et al. [27] examined the femoral-tibial angles of 14 femurs from ten Japanese women with AFF (9 BP users, mean exposure 4.9 years) and compared them with 14 patients with TFF (12 females, 4 BP users, mean exposure not reported). The femoral-tibial angles of those with diaphyseal AFF, but not subtrochanteric AFF, were greater than those with TFF. Those with diaphyseal AFF also displayed greater femoral-tibial angles than the 95% confidence interval of a Japanese population ($n = 5860$; older than 40 years) [45]. Interestingly, those with subtrochanteric AFF displayed smaller femoral-tibial angles than the 95% confidence interval of a Japanese population. It is worth noting that all patients with subtrochanteric AFF ($n = 5$) had long-term use of glucocorticoids (mean exposure 22 years) for autoimmune disorders such as lupus and myositis. Morin et al. [40•] observed no differences in the hip-knee-shaft angle between AFF patients and controls using EOS™ imaging technology.

Summary of Lower-Limb Geometry and AFF Risk

Numerous studies have reported that increased femoral bowing in the lateral and/or anterior direction is associated with increased AFF risk [14••, 37, 38••, 39, 40•]. While the effects of age, sex, and race have been typically well controlled, several studies compared cases and controls with different (or unknown) histories of BP exposure [37, 38••]. However, Morin et al. [40•] found that the association between femoral curvature and prevalent AFF was still present when comparing groups with similar BP exposure. Similarly, Lim et al. [14••] performed multivariate regression, and found that geometry was associated with increased AFF odds ratio, even after adjusting for BP use. Together, these studies suggest that elevated femoral bowing may increase the risk of AFF independent of BP exposure. Geometric parameters related to femoral neck geometry [9•, 14••, 25, 26, 40•, 41] and lower-limb alignment [27, 40•] have also been explored, but their relationship with AFF remains equivocal. It is possible that these parameters are not directly related to AFF but that they are weakly or moderately correlated with more impactful parameters like femoral bowing. Indeed, more data are needed to verify this assumption.

Femoral Geometry and AFF Location

According to the criteria identified by the second report of the ASBMR task force, AFF can occur anywhere along the femoral shaft, i.e., just below the lesser trochanter to just proximal to the supracondylar flare [1]. However, the likelihood of AFF is not uniform across the femoral shaft but rather concentrated towards the subtrochanteric region or near the femoral midshaft [46]. Although reasons for this dichotomy are not fully understood, a number of recent case-control studies suggest that differences in femoral geometry may be related to AFF fracture location.

Comparisons of Subtrochanteric Versus Diaphyseal AFF

In the case-control study of Morin et al. [40•], women who sustained subtrochanteric AFF ($n = 5$) tended to illustrate lower femoral neck-shaft angles (5.7°; $p = 0.07$) and lateral bowing angles (3.3°; $p = 0.07$) than women with diaphyseal AFF ($n = 11$). Women with subtrochanteric AFF also tended to be heavier (7.4 kg; $p = 0.07$) than those with diaphyseal AFF. Hyodo et al. [28] examined 38 Japanese AFF patients (33 females, 31 BP users, mean exposure 5.1 years) and defined lateral bowing as a line from the tip of the greater trochanter through the center of the distal femoral condyles that fell outside of the medullary canal. Nineteen of 25 patients with AFF at the mid-diaphysis illustrated lateral bowing according to this definition, whereas no patients with AFF at the proximal third of the diaphysis illustrated lateral bowing. Those with mid-diaphyseal AFF were also older (9.9 years; $p = 0.014$), shorter (6.9 cm; $p = 0.012$), and lighter (12.9 kg; $p = 0.036$) than those with proximal diaphyseal AFF. Similar to Saita et al. [27], those with more proximal AFF were also more likely to have a history of glucocorticoid therapy when compared to those with mid-diaphyseal AFF. Yoo et al. [29] reported that 30 women with diaphyseal AFF (20 BP users, mean exposure 4.5 years) illustrated greater lateral bowing angles (6.8°) than 15 patients with subtrochanteric AFF (14 females, 9 BP users, mean exposure 4.7 years). Logistic regression suggested that diaphyseal AFF were more likely if the lateral bowing angle was greater than 5.3°. The diaphyseal AFF patients were also older (6.5 years; $p = 0.032$) and tended to weigh less (4.8 kg; $p = 0.07$) than subtrochanteric AFF patients. In a larger study, Kim et al. [30••] reported similar findings when comparing the femoral curvature of 52 Korean women with subtrochanteric AFF (38 BP users, mean duration 4.2 years) to 95 Korean women with diaphyseal AFF (73 BP users, mean duration 4.6 years). Patients with diaphyseal AFF illustrated greater anterior (2.9°) and lateral (6.2°) bowing angles than patients with subtrochanteric AFF. Again, diaphyseal AFF patients were also older (7.5 years; $p < 0.001$) and weighed less (4.6 kg; $p = 0.002$) than subtrochanteric AFF patients.

Correlations Between Lower-Limb Geometry and AFF Location

Chen et al. [31] examined the correlation between lateral bowing angle and the location of incomplete AFF in 17 femurs from eleven Chinese women (8 BP users, mean exposure 4.5 years). The lateral bowing angle explained 55% of the variance in AFF location ($r = 0.741$; $p < 0.001$) with a slope of 1.79, i.e., every degree increase in lateral bowing angle moved normalized AFF location 1.79% more proximal. After separating the patients into two groups according to the median lateral bowing angle (i.e., greater than and less than 7°), 100% of the patients with lateral bowing angle > 7° illustrated diaphyseal AFF, as opposed to only 36.4% of the patients with lateral bowing angle ≤ 7° (i.e., 63.6% subtrochanteric AFF). Patients with lateral bowing angles > 7° also tended to be older (4.5 years; $p = 0.08$) and weigh less (3 kg; $p = 0.07$) than patients with lateral bowing angles ≤ 7°. Soh et al. [32] examined the correlation between anterior and lateral bowing angles and the location of AFF in 21 Chinese women (All BP users, mean exposure 4.9 years). Anterior and lateral bowing angles explained 63% ($r = 0.794$; $p = 0.002$) and 68% ($r = 0.827$; $p < 0.001$) of the variance in AFF location, respectively. In addition to femoral curvature, Saita et al. [27] reported that the femoral-tibial angle explained 67% of the variance in AFF location ($r = 0.82$; $p < 0.001$) with greater angles being associated with a more distal AFF location. On the other hand, Saita et al. observed no relationship between the femoral-tibial angle and patients with TFF.

Summary of Femoral Geometry and AFF Location

A number of studies have identified an association between femoral curvature and fracture location. Whether looking at fracture location as a continuous variable (vertical distance from a datum) or as a categorical variable (midshaft vs. subtrochanteric), results consistently indicate that elevated femoral bowing is associated with a more distal fracture location. Interestingly, there is some evidence to suggest that individuals with diaphyseal AFF tend to be older and weigh less than those with subtrochanteric AFF [28, 29, 30••, 31, 46, 47].

Association Between AFF and Race

The majority of the research reviewed thus far, and therefore, much of what we know regarding the relationship between lower-limb geometry and AFF is based on participants of Asian descent. This research was likely prompted by the second report of the ASBMR task force [1], which noted that the

Asian race was associated with increased AFF risk. Indeed, an association between Asian race and AFF risk is well documented in the literature. A retrospective examination of 79 women with diaphyseal and subtrochanteric fractures from a large integrated healthcare delivery system in northern California reported that women with AFF were more likely to be on BP therapy (97% vs 42%), and more likely to be of Asian than Caucasian descent (50% vs 2.4%) when compared to women with TFF [2]. A more recent review of 68 women with AFF by the same group suggested that Asian women have an 8.5-fold increased risk of AFF when compared with Caucasian women, which remained 6.6-fold after controlling for BP exposure [48•]. In a review of 142 AFF cases from a large integrated healthcare delivery system in southern California, 49% were Asian and 42% were Caucasian [49]. This may appear as a small disparity, but given that the overall percentage of Asians in California at the time was 13 to 15% [50], this suggests an increased risk of AFF. Marcano et al. [51] investigated 54 patients with AFF (51 females, all BP users, mean exposure 8.7 years) and compared them with one-hundred nineteen non-fractured controls (112 females, all BP users, mean exposure 7.9 years). Patients with AFF were more likely to be Asian than those without AFF (17% vs 3%; $p = 0.004$).

It remains unclear if the increased risk of AFF in Asians reported in the previous studies was due to race-related differences in femoral geometry, as studies did not, or were unable to, provide comparisons of lower-limb geometry. However, it is known that variations in hip and femoral geometry do exist between Asians and different races and that these specific differences are likely associated with AFF risk. For example, Japanese women tend to have shorter femoral necks and a more varus femoral neck-shaft angle, which has been argued to explain their lower incidence of osteoporotic hip fracture [52]. Of course, this may expose them to an increased risk of subtrochanteric and diaphyseal fractures [41]. In a large report of 3922 femurs from individuals of difference races, femurs from Asians demonstrated a smaller lateral and anterior radius of curvature, i.e., greater femoral bowing, than femurs from Caucasian and African Americans [53]. A similar conclusion was reached after assessing the femoral curvature of 132 femurs from Japanese individuals and comparing these measurements with those reported in the literature [54].

It should be noted, however, that the relationship between AFF risk and race is not unequivocally supported in the literature. Specifically, Schilcher et al. [47] recently compared AFF patients in Singapore (89% BP users, duration of use not reported) with those in Sweden (81% BP users, duration of use not reported). Given the relationships amongst femoral curvature, race, and AFF location, the authors anticipated more diaphyseal AFFs in patients from Singapore and more subtrochanteric AFFs in patients from Sweden. In contrast, patients from Singapore had a much larger proportion of subtrochanteric fractures than those from Sweden, with 48% and 17% of all AFFs reported as subtrochanteric in the two populations, respectively. The reason for this discrepancy is not entirely clear, but an earlier study of AFF in a Swedish population [46] reported that patients with subtrochanteric AFF were approximately 10 years younger than those with diaphyseal AFF. This same interesting discrepancy in age existed between the Swedish and Singapore patients within the Schilcher et al. [47] study. That is, patients from Singapore were approximately 10 years younger than patients from Sweden, and previous research in Asian populations suggested that patients with diaphyseal AFF tended to be older than those with subtrochanteric AFF [28, 29, 30••]. Importantly, Schilcher et al. [47] reported that patients with diaphyseal AFF in both populations (i.e., Singapore and Sweden) illustrated increased femoral bowing, thereby further supporting the relationship between femoral geometry and AFF risk.

Summary of Association Between AFF and Race

A number of studies have found that individuals of Asian descent are at greater risk of AFF [2, 48•, 49, 51]. However, the reasons for this association are not fully understood. It is likely that some of the increased risk of AFF in Asians is due to race-related differences in femoral geometry, as studies have found that Asian descent is associated with elevated femoral bowing [53, 54] and more varus femoral neck geometry [52]. As noted in previous sections, both of these factors may be related to AFF risk. However, it is noteworthy that a commensurate increase in TFF risk has not been reported in the Asian population, suggesting that the increase in risk is due to the unique etiology of AFF rather than race-related differences in overall bone fragility.

Mechanistic Studies of Lateral Femoral Stress and Strain

The body of work described above suggests a relationship between femoral geometry and AFF risk, as well as AFF location. However, these studies do not elucidate a causal mechanism linking femoral geometry to AFF. In this section, we discuss recent findings suggesting that geometry influences AFF risk via its effects on femoral stress and strain during activities of daily living.

The major and minor features of AFF, such as the absence of significant trauma, focal periosteal thickening resembling a stress fracture callus, and prodromal pain before fracture [1], suggest that AFFs are the result of a mechanical fatigue phenomenon. This phenomenon has been well studied through ex vivo material-level testing, illustrating that the mechanical response of bone (i.e., stress or strain) is strongly related to fatigue life, or the number of cycles to failure [55, 56].

Patterns in the location of AFF further suggest the importance of mechanical strain in this clinical problem. If failure was due to systemic biological changes alone, we would expect AFF to be equally likely throughout all cortical bones in the femoral shaft, or all long bones for that matter. This is not the case, as AFFs are known to initiate at the lateral femoral cortex only [1, 4]. Analytical models [57, 58], experimental studies [59], and modern finite element (FE) simulation studies [42•, 60, 61] all demonstrate that this region is under tensile loading, in contrast to the medial shaft which is loaded in compression. Bone is more susceptible to tensile rather than compressive failure [62], and this suggests that a sufficient tensile loading environment is necessary for the development of AFF. It is also noteworthy that up to 50% of individuals with AFF experience bilateral femoral focal periosteal thickening or fracture [4, 27, 30••, 63, 64]. Given likely symmetries between the loadings of contralateral limbs, this further suggests that the mechanical environment plays an important role in this injury.

A number of recent FE simulation studies suggest that AFF risk is associated with the stress/strain environment of the femur and that this environment is more deleterious for high-risk geometries. Oh et al. [35] compared four patients with bowing deformity and AFF against 14 individuals with thigh pain but no radiographic evidence of AFF, and found that AFF patients had elevated femoral strains compared with controls. A more recent study [36••] compared 12 patients with diaphyseal AFF, 10 with subtrochanteric AFF, and 11 with thigh pain but radiographic evidence of AFF. The study demonstrated statistically significant differences in peak strains amongst the three groups, with fracture location corresponding to the location of peak stress. This study also reported a linear relationship between femoral bowing and the magnitude of peak strain. Inspired by these findings, our group recently used FE simulation and parametric mesh morphing to further quantify the relationship between geometry and femoral strain [65]. We observed that bowing angles had the greatest influence on peak femoral shaft strain. The study also revealed that the increased bowing angle caused a distal shift in the location of peak strain, which agrees with clinical observations that elevated femoral curvature is related to a more distal fracture location [27–29, 30••, 31, 32, 40•] and supports the notion that femoral geometry is linked to AFF risk via its influence on femoral stress and strain. An important limitation to this body of work, however, is that none of these simulation studies applied subject-specific gait or postural loading scenarios. Differences in patient characteristics can influence gait mechanics and forces during walking [66] which would, in turn, influence FE predictions of strain. To our knowledge, no previous studies have explored this phenomenon in the context of AFF. Although it is challenging to measure gait mechanics in individuals after AFF, it may be possible to do so in individuals illustrating early risk factors, i.e., Asian race, focal periosteal thickening of the shaft, or prodromal pain.

Summary of Mechanistic Studies of Lateral Femoral Stress and Strain

FE simulation suggests that elevated bowing is associated with greater magnitudes of stress/strain [35, 42•] and peak strain locations closer to the midshaft [36••, 42•]. These findings are consistent with the cross-sectional observations discussed in previous sections, which observed that elevated bowing was associated with increased AFF prevalence and a greater likelihood of midshaft fracture. Together, the current body of literature suggests that femoral geometry influences AFF prevalence via its effect on mechanical strain. It is unclear, however, whether current simulation techniques are sufficient to distinguish between AFF and non-AFF individuals. Although one study identified differences in stress measures between patients with midshaft AFF and controls, differences in stress measures between patients with subtrochanteric AFF and controls were not reported [36••]. It may be that more subject-specific information is needed within FE simulations, as previous models did not account for differences in activity volume, or subject-specific gait or postural loading scenarios.

Conclusions

While the etiology of AFF is not fully understood, there is a preponderance of evidence that suggests femoral geometry, and increased femoral bowing in particular is associated with increased AFF risk. Studies in the literature have been either retrospective case-control or descriptive in their design. Therefore, more prospective investigation including gait analysis, weight-bearing imaging, and a better understanding of the progression of femoral bowing over time is required to determine whether measurements of femoral geometry can help assess individual risk of AFF. More data is also needed to determine if and how femoral geometry interacts with BP exposure to influence AFF risk. A better understanding of how femoral geometry is linked to AFF may allow for clinical risk stratification for patients with osteoporosis, who would benefit from BP use for fragility fracture prevention, but may have an increased risk for AFF given their abnormal femoral geometry. Lastly, femoral geometry quantification in this population may also assist with intramedullary nail implant development for patients with increased femoral bowing.

Compliance with Ethical Standards

Conflict of Interest Ifaz Haider and Brent Edwards reports grants from Amgen outside the submitted work. Prism Schneider declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American society for bone and mineral research. J Bone Miner Res. 2014;29:1–23.
2. Lo JC, Huang SY, Lee GA, Khandewal S, Provus J, Ettinger B, et al. Clinical correlates of atypical femoral fracture. Bone. 2012;51:181–4.
3. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010;25:2267–94.
4. Kwek EBK, Goh SK, Koh JSB, Png MA. Howe T Sen. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury. 2008;39:224–31.
5. Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma. 2008;22:346–50.
6. Goh S-K, Yang KY, Koh JSB, Wong MK, Chua SY, Chua DTC. Subtrochanteric insufficiency fractures in patients on alendronate therapy. J Bone Joint Surg (Br). 2007;89:349–53.
7. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the american society for bone and mineral research. J Bone Miner Res. 2010;25:2267–94.
8. Feldstein AC, Black D, Perrin N, Rosales AG, Friess D, Boardman D, et al. Incidence and demography of femoral fractures with and without atypical features. J Bone Miner Res. 2012;27:977–86.
9.• Mahjoub Z, Jean S, Leclerc JT, Brown JP, Boulet D, Pelet S, et al. Incidence and characteristics of atypical femoral fractures: clinical and geometrical data. J Bone Miner Res. 2016;31:767–76 **This study examined femoral neck geometry in AFF patients compared with controls who experienced a traumatic or fragility fracture. AFF patients had more varus femoral neck-shaft angle, greater femoral neck offset, and smaller femoral head and neck diameter.**
10. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med. 2011;364:1728–37.
11. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. J Am Med Assoc. 2009;302:1573–9.
12. Adams AL, Shi J, Takayanagi M, Dell RM. Ten-year hip fracture incidence rate trends in a large California population, 1997–2006. Osteoporosis Int. 2013;24:373–376.
13. Schilcher J, Koeppen V, Aspenberg P, Michaëlsson K. Risk of atypical femoral fracture during and after bisphosphonate use. Acta Orthop. 2015;86:100–7.
14.•• Lim S-J, Yeo I, Yoon P-W, Yoo JJ, Rhyu K-H, Han S-B, et al. Incidence, risk factors, and fracture healing of atypical femoral fractures: a multicenter case-control study. Osteoporos Int. 2018; **One of the largest studies to explore AFF and femoral geometry, comparing 196 women with AFF against 94 women with TFF. AFF was associated with greater lateral and anterior bowing compared with controls, but no differences in femoral neck-shaft angle were reported.**;29:2427–35.
15. Ettinger B, Burr DB, Ritchie RO. Proposed pathogenesis for atypical femoral fractures: lessons from materials research. Bone. 2013;55:495–500.
16. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CYC. Severely suppressed bone turnover : a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294–301.
17. Allen MR, Gineyts E, Leeming DJ. Bisphosphonates alter trabecular bone collagen cross-linking and isomerization in beagle dog vertebra. Osteoporos Int. 2008;19:329–37.
18. Acevedo C, Bale H, Gludovatz B, Wat A, Tang SY, Wang M, et al. Alendronate treatment alters bone tissues at multiple structural levels in healthy canine cortical bone. Bone. 2015;81:352–63.
19. Gourion-arsiquaud S, Allen MR, Burr DB, Vashishth D, Tang SY, Boskey AL. Bisphosphonate treatment modifies canine bone mineral and matrix properties and their heterogeneity. Bone. 2010;46:666–72.
20. Donnelly E, Meredith DS, Nguyen JT, Gladnick BP, Rebolledo BJ, Shaffer AD, et al. Reduced cortical bone compositional heterogeneity with bisphosphonate treatment in postmenopausal women with intertrochanteric and subtrochanteric fractures. J Bone Miner Res. 2015;27:672–8.
21. Allen MR, Iwata K, Phipps R, Burr DB. Alterations in canine vertebral bone turnover , microdamage accumulation , and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. Bone. 2006;39:872–9.
22. Yamagami Y, Mashiba T, Iwata K, Tanaka M, Nozaki K, Yamamoto T. Effects of minodronic acid and alendronate on bone remodeling, microdamage accumulation, degree of mineralization and bone mechanical properties in ovariectomized cynomolgus monkeys. Bone. 2013;54:1–7.
23. Allen MR, Reinwald S, Burr DB. Alendronate reduces bone toughness of ribs without significantly increasing microdamage accumulation in dogs following 3 years of daily treatment. Calcif Tissue Int. 2008;82:354–60.
24. Burr DB, Liu Z, Allen MR. Duration-dependent effects of clinically relevant oral alendronate doses on cortical bone toughness in beagle dogs. Bone. 2015;71:58–62.
25. Hagen JE, Miller AN, Ott SM, Gardner M, Morshed S, Jeray K, et al. Association of atypical femoral fractures varus hip geometry. J Bone Jt Surg. 2014;96:1905–9.
26. Chou ACC, Ng ACM, Png MA, Chua DTC, Ng DCE, Howe TS, et al. Bone cross-sectional geometry is not associated with atypical femoral fractures in Asian female chronic bisphosphonate users. Bone. 2015;79:170–5.
27. Saita Y, Ishijima M, Mogami A, Kubota M, Baba T, Kaketa T, et al. The fracture sites of atypical femoral fractures are associated with the weight-bearing lower limb alignment. Bone. 2014;66:105–10.
28. Hyodo K, Nishino T, Kamada H, Nozawa D, Mishima H, Yamazaki M. Location of fractures and the characteristics of patients with atypical femoral fractures: analyses of 38 Japanese cases. J Bone Miner Metab. 2017;35:209–14.
29. Yoo H, Cho Y, Park Y, Ha S. Lateral femoral bowing and the location of atypical femoral fractures. Hip Pelvis. 2017;29:127–32.
30.•• Kim JW, Kim JJ, Byun YS, Shon OJ, Oh HK, Park KC, et al. Factors affecting fracture location in atypical femoral fractures: a cross-sectional study with 147 patients. Injury. 2017;48:1570–4 **One of the largest studies to look at factors influencing AFF fracture location. A total of 147 patients with AFF were separated into diaphyseal and subtrochanteric fracture groups. Age, BMD, and lateral and anterior bowing angles were**

significantly related to AFF fracture location, with greater bowing associated with more diaphyseal fractures.
31. Chen LP, Chang TK, Huang TY, Kwok TG, Lu YC. The correlation between lateral bowing angle of the femur and the location of atypical femur fractures. Calcif Tissue Int. 2014;95:240–7.
32. Soh HH, Chua ITH, Kwek EBK. Atypical fractures of the femur: effect of anterolateral bowing of the femur on fracture location. Arch Orthop Trauma Surg. 2015;135:1485–90.
33. Haider IT, Schneider P, Michalski A, Edwards WB. Influence of geometry on proximal femoral shaft strains: implications for atypical femoral fracture. Bone. 2018;110:295–303.
34. Buitendijk SKC, van de Laarschot DM, Smits AAA, Koromani F, Rivadeneira F, Beck TJ, et al. Trabecular bone score and hip structural analysis in patients with atypical femur fractures. J Clin Densitom. 2018;In Press:1–9.
35. Oh Y, Wakabayashi Y, Kurosa Y, Fujita K, Okawa A. Potential pathogenic mechanism for stress fractures of the bowed femoral shaft in the elderly: mechanical analysis by the CT-based finite element method. Injury. 2014;45:1764–71.
36.•• Oh Y, Fujita K, Wakabayashi Y, Kurosa Y, Okawa A. Location of atypical femoral fracture can be determined by tensile stress distribution influenced by femoral bowing and neck-shaft angle: a CT-based nonlinear finite element analysis model for the assessment of femoral shaft loading stress. Injury. 2017;48:2736–43 **This is a simulation study looking at femoral strains, and to our knowledge, the only study to compare strain predictions from AFF patients against controls. Comparing 12 patients with midshaft AFF, 10 with subtrochanteric AFF, and 10 individuals with thigh pain but not radiographic evidence of fracture, the study found that AFF site corresponded to location of peak strain, and that bowing angle was related to magnitude of peak strain. A Kruskal-Wallis test revealed statically significant differences in peak strain amongst the 3 groups, but more detailed post-hoc comparisons were not reported.**
37. Sasaki S, Miyakoshi N, Hongo M, Kasukawa Y, Shimada Y. Low-energy diaphyseal femoral fractures associated with bisphosphonate use and severe curved femur: a case series. J Bone Miner Metab. 2012;30:561–7.
38.•• Jang SP, Yeo I, So SY, Kim K, Moon YW, Park YS, et al. Atypical femoral shaft fractures in female bisphosphonate users were associated with an increased anterolateral femoral bow and a thicker lateral cortex: a case-control study. Biomed Res Int. 2017;2017. **A recent study reporting that both lateral and anterior bowing angles were greater in AFF patients vs. controls with typical osteoporotic fracture.**:1–10.
39. Oh Y, Wakabayashi Y, Kurosa Y, Ishizuki M, Okawa A. Stress fracture of the bowed femoral shaft is another cause of atypical femoral fracture in elderly Japanese: a case series. J Orthop Sci. 2014;19:579–86.
40.• Morin SN, Wall M, Belzile EL, Godbout B, Moser TP, Michou L, et al. Assessment of femur geometrical parameters using EOS (TM) imaging technology in patients with atypical femur fractures; preliminary results. Bone. 2016;83:184–9 **In this well-controlled study, 16 women with AFF were compared against age-, sex-, height-, and BP exposure–matched controls. Patients with AFF had greater lateral bowing angles compared with controls. Femoral bowing was also more prominent in patients with a midshaft fracture vs. a subtrochanteric fracture. Differences in femoral neck geometry or lower extremity alignment were not significant.**
41. Taormina DP, Marcano AI, Karia R, Egol KA, Tejwani NC. Symptomatic atypical femoral fractures are related to underlying hip geometry. Bone. 2014;63:1–6.
42.• Haider IT, Schneider P, Michalski A, Edwards WB. Influence of geometry on proximal femoral shaft strains: Implications for atypical femoral fracture. Bone. 2018;110. **A simulation study used parametric mesh morphing to quantify the relationship between femoral geometry and strain. These simulations confirm a direct causal link between femoral geometry and strain, with shaft diameter and bowing angles reported having the greatest effect on peak strain. Increased bowing angle caused a distal shift in the location of peak strain, consistent with clinical observations that elevated femoral curvature is related to more distal AFF locations.**:295–303.
43. Petersen TL, Engh GA. Radiographic assessment of knee alignment after total knee arthroplast. J Arthroplast. 1988;3:67–72.
44. Matsumoto T, Hashimura M, Takayama K, Ishida K, Kawakami Y, Matsuzaki T, et al. A radiographic analysis of alignment of the lower extremities - initiation and progression of varus-type knee osteoarthritis. Osteoarthr Cartil. 2015;23:217–23.
45. Oka H, Muraki S, Akune T, Nakamura K, Kawaguchi H, Yoshimura N. Normal and threshold values of radiographic parameters for knee osteoarthritis using a computer-assisted measuring system (KOACAD): the ROAD study. J Orthop Sci. 2010;15:781–9.
46. Koeppen VA, Schilcher J, Aspenberg P. Dichotomous location of 160 atypical femoral fractures. Acta Orthop. 2013;84:561–4.
47. Schilcher J, Howe TS, Png MA, Aspenberg P, Koh JSB. Atypical fractures are mainly subtrochanteric in Singapore and Diaphyseal in Sweden: a cross-sectional study. J Bone Miner Res. 2015;30:2127–32.
48.• Lo JC, Hui RL, Grimsrud CD, Chandra M, Neugebauer RS, Gonzalez JR, et al. The association of race/ethnicity and risk of atypical femur fracture among older women receiving oral bisphosphonate therapy. Bone. 2016;85:142–7 **This was a retrospective epidemiological survey from a large integrated healthcare delivery system in northern California, looking at 48 000 BP users. Controlling for age and BP exposure, Asian women were 6.6 times more likely to experience AFF compared with Caucasian women.**
49. Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012;27:2544–50.
50. U.S. Census Bureau. Modified Race Data 2010 [Internet]. Available from: https://www.census.gov/data/datasets/2010/demo/popest/modified-race-data-2010.html. Accessed 10 Mar 2019.
51. Marcano A, Taormina D, Egol KA, Peck V, Tejwani NC. Are race and sex associated with the occurrence of atypical femoral fractures? Clin Orthop Relat Res. 2014;472:1020–7.
52. Nakamura T, Turner CH, Yoshikawa T, Slemenda CW, Peacock M, Burr DB, et al. Do variations in hip geometry explain differences in hip fracture risk between japanese and white americans? J Bone Miner Res. 1994;9:1071–6.
53. Maratt J, Schilling PL, Holcombe S, Dougherty R, Murphy R, Wang SC, et al. Variation in the femoral bow: a novel high-throughput analysis of 3922 femurs on cross-sectional imaging. J Orthop Trauma. 2014;28:6–9.
54. Abdelaal AHK, Yamamoto N, Hayashi K, Takeuchi A, Morsy AF, Miwa S, et al. Radiological assessment of the femoral bowing in Japanese population. Sicot-J. 2016;2:2.
55. Carter DR, Caler WE, Spengler DM, Frankel VH. Fatigue behavior of adult cortical bone: the influence of mean strain and strain range. Acta Orthop. 1981;52:481–90.
56. Pattin CA, Caler WE, Carter DR. Cyclic mechanical property degradation during fatigue loading of cortical bone. J Biomech. 1996;29:69–79.
57. Koch JC. The laws of bone architecture. Am J Anat. 1917;21:177–298.
58. Edwards WB, Gillette JC, Thomas JM, Derrick TR. Internal femoral forces and moments during running: implications for stress fracture development. Clin Biomech (Bristol, Avon). Elsevier Ltd. 2008;23:1269–78.

59. Aamodt A, Lund-Larsen J, Eine J, Andersen E, Benum P, Husby OS. In vivo measurements show tensile axial strain in the proximal lateral aspect of the human femur. J Orthop Res. 1997;15:927–31.
60. Martelli S, Pivonka P, Ebeling PR. Femoral shaft strains during daily activities: implications for atypical femoral fractures. Clin Biomech Elsevier Ltd. 2014;29:869–76.
61. Duda GN, Heller M, Albinger J, Schulz O, Schneider E, Claes L. Influence of muscle forces on femoral strain distribution. J Biomech. 1998;31:841–6.
62. Mirzaali MJ, Schwiedrzik JJ, Thaiwichai S, Best JP, Michler J, Zysset PK, et al. Mechanical properties of cortical bone and their relationships with age, gender, composition and microindentation properties in the elderly. Bone. 2016;93:196–211.
63. Kumar N, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. J Bone Jt Surg. 2009;91:2556–61.
64. Schilcher J, Aspenberg P. Incidence of stress fractures of the femoral shaft in women treated with bisphosphonate. Acta Orthop. 2009;80:413–5.
65. Haider IT, Goldak J, Frei H. Femoral fracture load and fracture pattern is accurately predicted using a gradient-enhanced quasi-brittle finite element model. Med Eng Phys. 2018;55:1–8.
66. De Pieri E, Lunn DE, Chapman GJ, Rasmussen KP, Ferguson SJ, Redmond AC. Patient characteristics affect hip contact forces during gait. Osteoarthr Cartil. 2019;In Press.