REVIEW

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# Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research

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**ABSTRACT**

Bisphosphonates (BPs) and denosumab reduce the risk of spine and nonspine fractures. Atypical femur fractures (AFFs) located in the subtrochanteric region and diaphysis of the femur have been reported in patients taking BPs and in patients on denosumab, but they also occur in patients with no exposure to these drugs. In this report, we review studies on the epidemiology, pathogenesis, and medical management of AFFs, published since 2010. This newer evidence suggests that AFFs are stress or insufficiency fractures. The original case definition was revised to highlight radiographic features that distinguish AFFs from ordinary osteoporotic femoral diaphyseal fractures and to provide guidance on the importance of their transverse orientation. The requirement that fractures be noncomminuted was relaxed to include minimal comminution. The periosteal stress reaction at the fracture site was changed from a minor to a major feature. The association with specific diseases and drug exposures was removed from the minor features, because it was considered that these associations should be sought rather than be included in the case definition. Studies with radiographic review consistently report significant associations between AFFs and BP use, although the strength of associations and magnitude of effect vary. Although the relative risk of patients with AFFs taking BPs is high, the absolute risk of AFFs in patients on BPs is low, ranging from 3.2 to 50 cases per 100,000 person-years. However, long-term use may be associated with higher risk (~100 per 100,000 person-years). BPs localize in areas that are developing stress fractures; suppression of targeted intracortical remodeling at the site of an AFF could impair the processes by which stress fractures normally heal. When BPs are stopped, risk of an AFF may decline. Lower limb geometry and Asian ethnicity may contribute to the risk of AFFs. There is inconsistent evidence that teriparatide may advance healing of AFFs. © 2014 American Society for Bone and Mineral Research.

**KEY WORDS:** BISPHOSPHONATES; DENOSUMAB; SUPPRESSION OF REMODELING; FRACTURES; STRESS FRACTURE

## Introduction

Bisphosphonates (BPs) reduce bone loss and prevent fractures in postmenopausal women with osteoporosis, in men with osteoporosis, and in patients receiving glucocorticoid (GC) therapy. In the past decade, however, osteonecrosis of the jaw (ONJ)[1] and atypical femoral fractures (AFFs)[2] have emerged as potential complications of BP and, more recently, denosumab therapy (http://www.proliahcp.com/safety-profile). In contrast to ONJ, which came to attention in patients receiving high-dose BP therapy for malignancy, most though not all patients with AFFs were receiving the lower doses of BPs typically used to treat osteoporosis or osteopenia.[3] The initial publications were followed by many case reports and case series.[4–17] Recently, however, two case series were reported in patients with cancer.[18,19]

These fractures have led to substantial anxiety among patients and their physicians. In 2009, the American Society of Bone and Mineral Research (ASBMR) convened a multidisciplinary, international task force to develop a case definition so that subsequent studies reported on the same condition. The task force reviewed the English-language scientific literature on the epidemiology, risk factors, diagnostic imaging, and clinical management of AFFs and identified future areas for research. Based on its review of published and unpublished data and the widespread use of BPs in 2010, the task force concluded that the

Received in original form March 11, 2013; revised form May 11, 2013; accepted May 17, 2013. Accepted manuscript online May 27, 2013.

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Journal of Bone and Mineral Research, Vol. 29, No. 1, January 2014, pp 1–23
DOI: 10.1002/jbmr.1998

incidence of AFFs associated with BP therapy for osteoporosis was very low, particularly compared to the number of vertebral, hip, and other fractures that are prevented by BPs, and noted that a causal association between BPs and AFFs had not been established.[2] However, the task force also expressed concern that risk may rise with increasing duration of exposure and that underreporting may mask the true incidence of AFFs.

Since publication of the report in 2010, several studies have been published on the epidemiology of and risk factors for AFFs and their relationship to BP therapy. Certain studies have raised concerns about limitations of the ASBMR case definition and new data have emerged on the medical management of these fractures. Therefore, the ASBMR reconvened the task force at the 2012 Annual Meeting of the ASBMR. The first goal of the task force was to review the major reports that had been published since the original report in 2010, focusing on those that addressed three major aspects of atypical femur fractures: their epidemiology, pathogenesis, and medical management. The second goal was to assess whether the information in those reports provided data that could be used to refine the original case definition. The task force co-chairs (ES and DB) searched the medical literature for publications on atypical femur fractures that addressed epidemiology, pathogenesis, and medical management. The final document included reports published before March 10, 2013. In addition, they reviewed abstracts from the 2011 and 2012 Annual Meetings of the American Society for Bone and Mineral Research (ASBMR). Case reports were not included in the analysis, except for those related to medical management. Epidemiologic data were extracted from each report and summarized in tabular form. A subcommittee of the task force (DB, RD, TAE, HKG, JML, FM, and ES) held several conference calls on the case definition. Dr. Shane (epidemiology), Dr. Burr (pathogenesis), and Dr. Adler (medical management) wrote the first draft of the document, which was reviewed in detail by the task force members, and their revisions and concerns were addressed. The revised case definition was approved by formal vote, with 25 of 26 members voting to approve. The final report was also approved unanimously by formal vote.

Among the issues addressed by the task force was the case definition, which has been revised to more clearly delineate the features that distinguish AFFs from ordinary osteoporotic femur fractures. New epidemiologic studies, many of which incorporate radiographic review and provide new information on AFF incidence and association with BPs, and new data on the pathogenesis and management of AFFs were reviewed and summarized in this report. This document should be considered an update and companion to the first report, because much of the information in the first report has not been included here but is still valid and useful.

## AFFS: Original Case Definition and Clinical Characteristics

In the 2010 task force report, AFF were defined as atraumatic or low-trauma fractures located in the subtrochanteric region or femoral shaft. The diagnosis of AFF specifically excludes high-trauma fractures, fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors, and periprosthetic fractures. The fractures are usually not comminuted. Other characteristic radiographic features of AFFs (Fig. 1) include

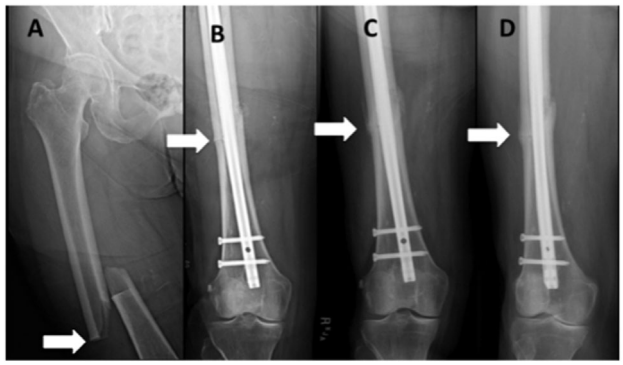


**Fig. 1.** An AFF of the femoral diaphysis (courtesy of Fergus McKiernan). (*A*) Note the transverse fracture line in the lateral cortex that becomes oblique as it progresses medially across the femur (white arrow). (*B*) On radiograph obtained immediately after intramedullary rod placement, a small area of periosteal thickening of the lateral cortex is visible (white arrow). (*C*) On radiograph obtained at 6 weeks, note callus formation at the fracture site (white arrow). (*D*) On radiograph obtained at 3 months, there is mature callus that has failed to bridge the cortical gap (white arrow). Note the localized periosteal and/or endosteal thickening of the lateral cortex at the fracture site (white arrow).

a transverse fracture line at the point of origination in the lateral cortex. As the fracture propagates across the diaphysis to the medial cortex, the orientation may become more oblique and when it becomes complete, a prominent medial "spike" may be present. There may be a focal or diffuse periosteal reaction of the lateral cortex surrounding the region where the fracture initiated. This reaction may appear as cortical "beaking" or "flaring" adjacent to a discrete transverse lucent fracture line,[6,20–22] or as focal thickening of the lateral cortex. Focal and diffuse endosteal reactions near the fracture site have been reported more recently (Fig. 2).[23] This focal cortical thickening represents cortical hypertrophy and may be unilateral or bilateral. There may also be generalized cortical thickening.

The original ASBMR case definition divided these characteristics into major and minor features and differentiated between complete and incomplete AFFs (Table 1).[2] Major features include their location in the subtrochanteric region and diaphysis of the femur, association with no or minimal trauma, transverse or short oblique configuration, and lack of comminution. Incomplete AFFs involve only the lateral cortex, whereas complete AFFs extend through both cortices and may have a medial spike. Minor features include: localized periosteal reaction or beaking of the lateral cortex; generalized cortical thickening of the femoral shaft; history of prodromal pain; bilateral fractures; delayed healing; and associations with certain drugs (BPs, GCs, proton pump inhibitors [PPIs]) and medical conditions (diabetes, rheumatoid arthritis, vitamin D deficiency). In addition, the case definition specified that all major features should be present to designate a fracture as atypical, and that minor features may or may not be present in individual cases. A precise definition of the terms "transverse" and "short oblique" was not included, nor was the localized periosteal reaction or beaking of the lateral cortex specified to occur at or near the site of fracture origination.

The first ASBMR task force reviewed the literature on 310 cases of AFFs, 286 in patients treated with BPs for osteoporosis, five in patients treated with BPs for malignancy, and 19 in patients who

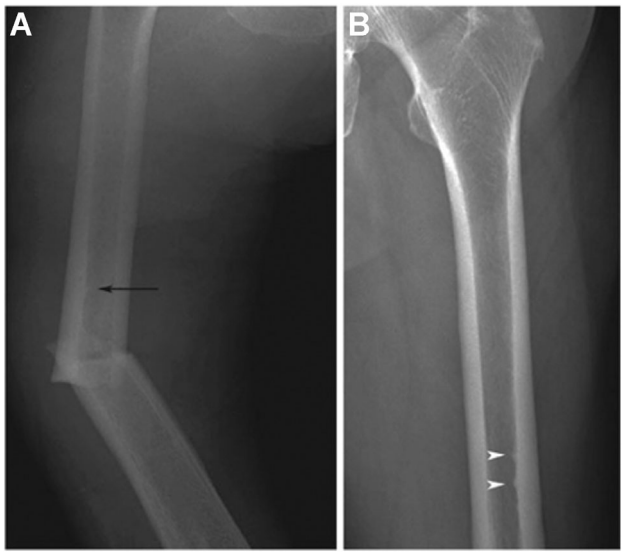


**Fig. 2.** A 76-year-old woman with osteoporosis who presented with an AFF. (*A*) Anteroposterior radiograph of the right femur shows a displaced AFF characterized by both periosteal and endosteal beaking with an endosteal lesion (black arrow) superior to it. (*B*) Anteroposterior radiograph of the left femur shows multifocal endosteal thickening (white arrowheads). Reprinted with permission from Mohan and colleagues.[23]

were not receiving BPs.[2] Most cases were women and had received oral alendronate monotherapy, although the specific BP was not provided in one-third of cases. The median duration of BP therapy was 7 years. Approximately 70% of patients had a history of prodromal groin or thigh pain, 28% had bilateral fractures and bilateral radiographic abnormalities, and 26% had delayed healing. Concomitant GC use was reported in 34% of cases and was associated with a fivefold increased risk of subtrochanteric fractures in one series.[10] Some patients were receiving other antiresorptive drugs in addition to BPs (estrogen, raloxifene, calcitonin).[24–26] PPI use was noted in 39% of cases that reported on this exposure.[26–29] Other systematic reviews were generally consistent with these findings.[27,30,31]

## Update on Epidemiology and Risk Factors

Studies of subtrochanteric and femoral shaft fracture incidence and their relationship to BP therapy fall into two general categories. In the first, subtrochanteric and femoral shaft (ST/FS) fractures are identified using large registry or database approaches with International Classification of Diseases, 9th edition (ICD-9) codes but there is no radiographic adjudication to ascertain whether the fractures have atypical features. Most,[32–38] though not all,[39] of these studies have found that rates of ST/FS fractures have not risen since BPs were approved for osteoporosis or among patients exposed to BPs. Such studies provide useful information on the prevalence and incidence of ST/FS fractures and the upper boundary of any potential harm associated with BPs. As a note of caution, however, diagnostic codes may misclassify fracture location.[40,41] For example, Spangler and colleagues[41] reported that ICD-9 codes had a specificity of only 36% for identifying ST/FS fractures, mainly because so many fractures were actually trochanteric. Narongroeknawin and colleagues[42] reviewed the records of 137 subtrochanteric fractures (11 were atypical) that occurred between 2004 and 2008 and compared the accuracy of claims-based ICD-9 codes to hospital discharge and physician codes. The positive predictive value (PPV) was high for location of fractures in the subtrochanteric region versus femoral neck or intertrochanteric regions, but was very low for identifying a fracture as atypical.[42] Thus, a stable total number of subtrochanteric fractures could potentially mask a shift from ordinary subtrochanteric fractures toward atypical fractures, as might be suggested by the analyses of Wang and

**Table 1.** 2010 ASBMR Task Force Case Definition of AFFs

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

Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.

AFF = atypical femur fracture; BP = bisphosphonate.

[a]All major features are required to satisfy the case definition of AFF. None of the minor features are required but have been sometimes associated with these fractures.

[b]Often referred to in the literature as "beaking" or "flaring."

Bhattacharyya.[43] In addition, because this type of study includes substantial numbers of ordinary subtrochanteric and femoral shaft fractures that are *not* atypical, they yield incidence rates for AFFs that are too high and associated odds ratios (ORs) with potential exposures that may be too low.[44] In the second category of studies, radiographs are reviewed and the fractures categorized according to whether or not they meet consensus criteria for AFFs. Most of these studies suggest that AFFs are strongly associated with BPs, although the absolute incidence of AFFs is very low.[7,10,11,21,45–50] However, such studies may be limited by smaller size, incomplete ascertainment of past drug exposure, and other biases.[44] In the following summary of epidemiological studies, some published before 2010 are included for completeness.

### Epidemiological studies of hip and femur fractures: no radiographic adjudication, person-level BP exposure information not available

Using the Nationwide Inpatient Sample (NIS), Wang and Bhattacharya[43] studied hospitalizations in the United States for femoral neck (FN), intertrochanteric (IT), and subtrochanteric (ST) fractures. Similar to an earlier study by Nieves and colleagues,[37] they found that FN/IT fractures declined significantly between 1996 and 2007. However, although Nieves and colleagues[37] found that age-adjusted ST/FS fracture rates remained stable during that period, Wang and Bhattacharya[43] found that the age-adjusted hospitalization rates of ST fractures increased 9.6% from 31.2 per 100,000 (95% confidence interval [CI], 30.4–32.0) in 1996 to 34.2 per 100,000 (95% CI, 33.4–34.9) in 2007. Analysis of a separate database indicated that the decline in FN/IT hip fractures and the rise in ST fractures coincided with an increase in BP prescriptions, indirect evidence for an association.[43] Ng and colleagues[51] compared the incidence of non-hip femur fractures in Olmsted Country, MN, USA, before and after 1995, when alendronate was first approved in the United States. The overall age- and sex-adjusted annual incidence of first non-hip femur fracture was low at 26.7 per 100,000. Similar to Wang and Bhattacharya,[43] between 1984 and 1995 and between 1996 and 2007, age-adjusted incidence rates for non-hip femur fractures increased significantly for women (from 20.4 to 28.7 per 100,000, $p = 0.002$) but not for men. This rise in incidence mainly occurred in women over age 60 years and was accounted for by minimal to moderate trauma fractures. An analysis of the French National Database found that age-adjusted FN/IT fracture incidence in women decreased significantly between 2002 and 2009, but incidence of ST/FS increased significantly.[52] Lee and colleagues[53] used national claims data to identify hip and femur fractures in South Korea, based on ICD-10 codes. In 2010, crude overall incidences of FN/IT and ST hip fractures among men and women 50 years old or older were 356.0 and 10.8 per 100,000 person-years, respectively. The annual change in age-adjusted incidence rates of FN/IT fractures between 2006 and 2010 was not significant for men and women during the study period. However, age-adjusted incidence rates of ST fractures increased for women by 4.1% per year (95% CI, 0.5–7.9). Over the 5-year study period, the number of prescriptions of BP increased significantly. In summary, most studies,[43,51–53] although not all,[37] have found the incidence of ST/FS fractures has increased and that the age-adjusted rate of these fractures in women is between 10 and 35 per 100,000.

### Epidemiological studies of association of hip and femur fractures with BPs: no radiographic adjudication

Two groups used the same Danish national data source to investigate associations between drugs for osteoporosis and femur fractures during largely the same time period, but approached the research question with different methods. Abrahamsen and colleagues[32] detected no difference in alendronate exposure between patients with FN/IT and ST/FS fractures; both were reduced with high adherence. In a separate study using the same data source,[33] they found that long-term alendronate users ($n = 39{,}567$) were more likely to suffer both FN/IT and ST/FS fractures than non-users ($n = 158{,}268$ untreated age- and gender-matched controls); the risk of ST/FS fracture did not differ by duration of therapy. The first study included only patients with prior fractures whereas the second study included all BP users. Vestergaard and colleagues[38] conducted a Danish nationwide cohort study to assess the association between several osteoporosis drugs and risk of ST/FS fractures. They compared each user of BPs and other osteoporosis drugs between 1996 and 2006 ($n = 103{,}562$) to three age- and gender-matched non-exposed control individuals from the general population ($n = 310{,}683$). The risk of ST/FS fractures was higher in BP users than controls both before and after initiation of alendronate, etidronate, and clodronate, likely representing confounding by indication. As in the study by Abrahamsen and colleagues,[32] ST/FS risk decreased with increasing duration of exposure.[38]

Kim and colleagues[36] used U.S. healthcare utilization data for Medicare in Pennsylvania and New Jersey to compare incidence and risk of ST/FS fractures and their association with duration of treatment in oral BP users and raloxifene or calcitonin users, using propensity score-matching to reduce potential confounding by indication. There were 104 ST/FS fractures among 33,815 patients. The estimated incidence of ST/FS fractures per 1000 person-years did not differ between BP and raloxifene/calcitonin users, nor was there a significant association between ST/FS fractures and BP versus raloxifene/calcitonin users. A twofold increase in risk in patients treated with BPs for longer than 5 years (hazard ratio [HR], 2.02; 95% CI, 0.41–10.00) was not significant, possibly because ST/FS fractures were so rare. Thus, they could not exclude the possibility that long-term BP use may increase risk of these fractures.[36]

Hsiao and colleagues[35] used Taiwan's National Health Insurance database to identify all women ($n = 11{,}278$; mean age, 77) with first hospitalizations for vertebral or hip fractures between 2001 and 2007, and compared rates of rehospitalization due to hip fracture or new hospitalizations for ST/FS fractures between users of alendronate and other osteoporosis drugs (raloxifene, calcitonin, teriparatide) after the index fracture hospitalization and untreated patients. They identified 2425 (21.5%) who received alendronate, 2694 (23.9%) who received other osteoporosis drugs, and 6159 (54.6%) untreated women. Compared with the untreated cohort, women prescribed alendronate were at lower risk of rehospitalization for hip fracture (HR, 0.67; 95% CI, 0.54–0.82). In women with a prior osteoporosis-related fracture, the risk of hospitalization for ST/FS fractures did not differ between untreated patients and those treated with alendronate (HR, 0.77; 95% CI, 0.40–1.47) or other drugs (HR, 0.49; 95% CI, 0.22–1.12), suggesting that alendronate treatment did not protect women from ST/FS fractures as it had protected them from hip fractures.

In contrast to the above studies,[32,33,35,36,38] a Canadian population-based, nested case-control study found a significantly higher relative risk of ST/FS fractures in women with prolonged exposure to oral BPs.[39] They analyzed 205,466 women aged 68 years or older who filled at least one prescription for an oral BP between 2002 and 2008 and were followed until 2009. Women hospitalized with an initial ST/FS fracture (excluding periprosthetic and high-trauma fractures) were matched to up to five controls without fracture. BP use was categorized as long-term (>5 years), intermediate (3–5 years), short-term (100 days to 3 years), and transient (<100 days). In 716 women who sustained a ST/FS fracture, BP exposure was transient in 5.9%, short-term in 48.7%, intermediate in 28.5%, and long-term in 16.9%. BP exposure was similar across these categories in the 3580 women who did not sustain fractures. However, compared with transient BP use, treatment for 5 years or longer was associated with an increased risk of ST/FS fracture (adjusted OR, 2.74; 95% CI, 1.25–6.02). The authors calculated that 1 in 10 ST/FS fractures could be avoided if no patient was treated for more than 5 years. On the other hand, risk of FN/IT fractures was lower among women in this category (adjusted OR, 0.76; 95% CI, 0.63–0.93). Moreover, the absolute risk of ST/FS fractures was low, even in long-term users; among 52,595 women with at least 5 years of BP therapy, a ST/FS fracture occurred in 71 (0.13% or 130 per 100,000 patient-years) during the subsequent year and 117 (0.22% or 220 per 100,000 patient-years) within 2 years. Limitations of this study noted in subsequent Letters to the Editor include concern for selection bias in that patients with extended BP use may have had more severe osteoporosis or poorer health, placing them at higher risk of fractures.[54] However, the investigators subsequently reported that 30% of both long-term and short-term BP users had a prior osteoporotic fracture, and that short-term users had poorer baseline health than long-term users, providing evidence for a "healthy adherer" effect in the long-term users that would bias against increased risk.[39]

## Epidemiological studies with radiographic adjudication

Studies of AFFs with radiograph adjudication are described in order of publication in Table 2, which includes the criteria used to designate atypia. All but two studies[40,55] specified that radiograph reviewers were blinded to medication exposures. The proportion of ST/FS fractures with AFF features varies from 1% to 48%.[10,11,21,45–49] The majority detected significant associations between BPs and AFFs, though the strength of the associations varied widely. Every study included AFF patients unexposed to BPs and every study used criteria consistent with ASBMR major criteria and one or more minor criteria.

In a retrospective case-control study using data from a single, level I trauma center in the United States, Lenart and colleagues[21] compared 41 postmenopausal women with low-energy ST/FS fractures between 2000 and 2007 to women matched by age, race, and body mass index (BMI) with one IT and one FN fracture occurring within the same time period. BPs were used by 37% of ST/FS and 11% of FN and IT cases (OR, 4.44; 95% CI, 1.77–11.35). ST/FS fracture cases were more likely to have used long-term BP, and duration of BP use was longer than in the FN and IT control groups ($p = 0.001$). Radiographic features of atypia were present in 10 of 15 (66.7%) ST/FS cases on a BP and in 3 of 26 (11.5%) cases not on a BP (OR, 15.3; 95% CI, 3.1–76.9).[21]

Girgis and colleagues[10] reported 152 patients (mean age 78, 132 women) with ST/FS fractures admitted to an Australian tertiary care center between 2003 and 2008. Radiographs were reviewed twice in random sequence by an orthopedic surgeon blinded to patient characteristics and medication use. Twenty patients (13%) had AFFs and 85% were current oral BP users. Of 132 patients with ordinary ST/FS fractures, three were taking BPs. The relative risk of an AFF patient being on a BP was 37.4 (95% CI, 12.9–113.3; $p < 0.001$). Additional risk factors included a prior low-energy fracture (OR, 3.2; 95% CI, 2.1–17.1; $p < 0.001$), GC therapy for more than 6 months (OR, 5.2; 95% CI, 1.3–31.0; $p = 0.01$), active rheumatoid arthritis (OR, 16.5; 95% CI, 1.4–142.3; $p < 0.001$), and serum 25-hydroxyvitamin D (25-OHD) concentration below 16 ng/mL (OR, 3.5; 95% CI, 1.7–18.7; $p < 0.001$).[10]

Giusti and colleagues[11] used ICD codes to identify 932 consecutive patients over 50 years old admitted for femoral fractures to a single hospital in the Netherlands between 1997 and 2007. Patients with unavailable radiographs, high-trauma or periprosthetic fractures, metastatic bone disease, and bone diseases other than osteoporosis were excluded, leaving 906 patients. Cortical thickness was measured just distal to the fracture site and/or 5 cm below the lesser trochanter and normalized to bone diameter at the measurement site. They compared 63 ST/FS fracture patients (cases) in a 1:2 ratio to 126 FN/IT fracture patients (controls). Cases and controls did not differ by cortical thickness, BP use (9.5% versus 8.7%) or duration (both 54 months), GC use or duration, but cases had a 3.6-fold higher prevalence of diabetes (95% CI, 1.45–9.07). Within the ST/FS group, those patients with AFFs ($n = 10$, 16%) had thicker cortices (as expected given the case definition used), were more likely to have had a clinical vertebral fracture and to be current BP users ($n = 4$; 40% versus 3.8%; OR, 17.00; 95% CI, 2.55–113.26; $p = 0.004$)[11]; one AFF patient was not currently on BPs but had substantial past exposure. One-half of the patients with AFFs had never taken BPs. AFFs in BP-treated patients accounted for 0.4% of all femur fractures and 10.6% of ST/FS fractures. The incidence of ST/FS fractures did not change over an 11-year period starting 1 year after alendronate approval in the Netherlands.

Schilcher and colleagues[48] reviewed radiographs of all women over 55 who sustained a ST/FS fracture in Sweden during 2008 ($n = 1234$). They identified 47 AFFs (transverse, fracture initiation on lateral cortex, noncomminuted, thickened lateral cortex at fracture site), 12 suspected AFFs (similar to cases, but without clear thickening of the lateral cortex or with a separate intermediate fracture fragment), and 263 controls with ST/FS fractures that were not transverse or on the lateral side. Data on drug use since 2005, and inpatient and outpatient care since 1987 were obtained from national databases. Of 1.5 million women 55 years old or older residing in Sweden in 2008, 83,311 received BPs during the 3 years preceding the fracture and 59 had AFFs; the age-adjusted risk of an AFF with any BP use was 47.3 (95% CI, 25.6–87.3). However, the increase in absolute risk was low: 50 cases per 100,000 patient-years (95% CI, 4–7). In the case-control analysis, 78% of cases and 10% of controls had received BPs (adjusted OR, 33.3; 95% CI, 14.3–77.8). The risk was similar for alendronate and risedronate, independent of coexisting conditions and concurrent use of GCs and PPIs. Longer use was associated with higher risk (1.3 per 100 daily doses; 95% CI, 1.1–1.6). After BPs were stopped, risk declined by 70%/year (OR, 0.28; 95% CI, 0.21–0.38). The lack of drug use data before 2005 raises the possibility of previous uncaptured exposure to BPs, other antiresorptives, and GCs.[48]

Thompson and colleagues[49] identified all patients admitted with femoral fractures ($n = 3515$) to two large teaching hospitals in the United Kingdom (UK) between 2008 and 2010 from prospective trauma databases. Information on mechanism of

**Table 2.** Studies of Atypical Subtrochanteric and Femoral Shaft Fractures With Radiographic Review

| First author/ reference/ date/country | Time | Design | Population | ST/FS, *n* | AFF criteria | AFFs, *n* (%) | AFFs on BPs, *n* (%) | Incidence rate | Relative risk for BP use, OR (95% CI) | Absolute risk for BP use, OR (95% CI) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenart,[21] 2009, USA | 2000–2007 | Retrospective case-control | PM women admitted to Level 1 trauma center in NY with ST/FS fx matched by age, race, BMI to 1 IT and 1 FN fx; excluded GCs and low D levels | 41 | Transverse or oblique orientation; cortical thickening; "beaking" of lateral cortex; no Kappa; all 3 had to agree | 10 (24) | Hard to calculate | NA | 15.33 (3.1–76.9) | NA | FN/IT fx decreased with longer duration of BP use; AFFs associated with longer duration of BP use; patients with AFFs on BPs were younger (70.4 versus 82.5) |
| Girgis,[10] 2010, Australia | 2003–2008 | Retrospective case-control | 152 M + W of any age admitted with ST/FS fx | 152 | Lateral transverse or <30-degree oblique; fx line in area of cortical thickening; medial unicortical beak; Kappa 0.8 | 20 (13) | 17 (85) | NA | 37.4 (12.9–113.3) | NA | Specificity of atypical pattern for BP use 96.7%; no clear association with duration of BP use; associated with GC exposure (OR, 5.2; 95% CI, 1.3–31) |
| Giusti,[11] 2011, Netherlands | 1997–2007 | Retrospective cohort case-control | 906 M + W ≥50 years old admitted with new femur fx; each ST/FS fx matched 1:2 to hip fx matched for age, gender | 63 (low energy) | Transverse or short oblique; noncomminuted in an area of thickened cortices; unicortical beaking Kappa 0.83 | 10 (16) | 5 (50) | NA | 17.0 (2.6–113.3) | NA | No change in frequency of IT/FN or ST/FS fx over 11 years; no difference in duration of BP between AFFs and ST/FS; AFFs associated with GC exposure, but not significant |
| Schilcher,[48] 2011, Sweden | 2008 | Retrospective cohort case-control | 12,777 women ≥55 years old of whom 3515 admitted with proximal femur fx in 2008; 59 women with AFFs matched to 263 women with fx at similar site representative of women vulnerable to fx | 1234 | Transverse; initiated on lateral side; noncomminuted; thickened lateral cortex at fx site; no Kappa | 59 (5) | 46 (78) | Ever use of BP 5.5/10,000 patient-year 1.9/10,000 for <1 to 1.9 years of use 8.4/10,000 for >2.0 years | Cohort: age-adjusted 47.3 (25.6, 87.3). case-control: multivariate-adjusted 33.3 (14.3–77.8) | 5 per 10,000 patient-years (4–7) | AFFs associated with longer duration of BP use; risk diminished by 70% per year after last use; no association with GC or PPI exposure; drug use only captured from 2005 onward; uncaptured prior BP exposure may have inflated rates |
| Thompson,[49] 2012, UK | 2008–2010 | Retrospective case series; no controls | 3515 M + W admitted with proximal femur fx | 407 | Simple transverse fx line in a region of cortical hypertrophy; no Kappa | 27 (7) | 22 (81) | NA | N/A | NA | 30% of patients with AFFs were on GCs; mean duration of BP use 4.6 years (0.4–12.1) |
| Feldstein,[45] 2012, USA | 1996–2009 | Retrospective cohort case-control | W ≥50 years old; M ≥65 years old; KPNW Members 5034 new femur fx; all qualifying fx matched to 300 FN and 300 IT fx | 197 femoral shaft fx (FSF) with X-rays | ASBMR Major: ST/FS location; low trauma; transverse or short oblique fx (see Comments); noncomminuted; Kappa 0.62 | AFFM 53 (27) AFF Major + Minor 22 (11) | Any BP dispenses past 6 months AFFM 6 (12) | AFFM: 5.9 per 100,000 person-years (4.6–7.4) | Unadjusted 2.29 (1.12–4.67); age-adjusted 2.11 (0.99–4.49) | AFFM: 5.9 per 100,000 person-years (4.6–7.4) | Incidence of AFFs with ASBMR Major + Minor criteria increased by 10.7% annually and was more strongly associated with BP use and with duration of BP and GC use than AFFs with only AFF Major criteria; these authors designated 35 fx with angles of <30 degrees as transverse, 43 fx with angles of 30–60 degrees as short oblique, and also included 3 fx >60 degrees; many would not agree that fx with angles >30 degrees are atypical |
| | | Incidence based on 1,271,575 person-years of observation with 98,580 people/year | | | ASBMR Minor: Localized periosteal reaction of the lateral cortex (beaking); thick cortices; unicortical stress fx; Kappa 0.84. | | AFF Major + Minor 11 (52) | | | NA | |

**Table 2.** (*Continued*)

| First author/ reference/ date/country | Time | Design | Population | ST/FS, *n* | AFF criteria | AFFs, *n* (%) | AFFs on BPs, *n* (%) | Incidence rate | Relative risk for BP use, OR (95% CI) | Absolute risk for BP use, OR (95% CI) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lo,[46] 2012, USA | 2007–2008 | Retrospective case-control | 3078 W ≥60 years old from KPNW with a hip/femur fx in 2007–2008 | 79 | Transverse or short-oblique pattern (with a medial spike); noncomminuted; lateral cortical thickening at fx site; no Kappa | 38 (48) | 37 (97) | NA | N/A | NA | No definition of short oblique; bisphosphonate duration longer in AFFs than controls (5.1 versus 2.3 years); no difference in GC exposure; patients with AFFs more likely to be Asian |
| Dell,[50] 2012, USA | 2007–2011 | Prospective cohort incidence | All femur fx over 5-year period in 1,835,116 M + W ≥45 years old enrolled in Healthy Bones Program in KPSW 11,466 fx reviewed | 4036 | ST/FS location; transverse or with short oblique extension; thickening of lateral cortex at fx site | 142 (4) | 128 (90); duration of use 1 month to 13 years; mean 5.5 ± 3.4 years | Age-adjusted IR of AFFs with BP use 1.78/100,000 (1.5–2.0) with 0.1–1.9 years 113.1/100,000 (69.3–156.8) with 8–8.9 years | N/A | NA | For comparison, IR of all hip fx in BP-exposed patients at KPSW was 463/100,000 patients/year in those on BPs for 0–1 years; IR of all hip fx decreased on BPs out to 5 years (384, 367–400), then stabilized, and was slightly increased after 8–9 years (544/100,000; 522–565); incidence of AFFs increased markedly with increasing duration of BP use; 49% of patients with AFFs were Asian; 12% of patients with AFFs were on GCs |
| Meier,[47] 2012, Switzerland | 1999–2010 | Retrospective case-control cases were 39 AFFs and 438 controls were patients with "classic" fx in same region | 477 M + W ≥50 years old, hospitalized with ST or FS fx; denominator for IR state population >50 years old | 477 | Transverse or short oblique; originating at lateral femoral cortex; Kappa 0.96 | 39 (8) | 32 (82) | Over 12 years, IR for classic fx was 357/1,000,000 person-years and was stable; for AFFs IR was 32/1,000,000 and increased by 10.7% (+1.2% to +20.3%; $p = 0.03$) | Crude OR 66.9 (627.1–165.1); adjusted OR (vitamin D, GCs, PPIs, sex, age) 69.1 (22.8–209.5) | For AFFs IR was 32/1,000,000 and increased by 10.7% (+1.2% to +20.3%; $p = 0.03$) | OR for recurrence in patients with AFF was 42.6 (12.8–142.4) compared to classic fx. OR for AFF versus classic fx increased with increasing BP duration from 35.1 (10.1–123.6) for <2 years, 46.9 (14.2–154.4) for 2–5 years, 117.1 (34.2–401.7) for 5–9 years, 175.7 (30.0–1027.6) for ≥9 years, compared with no BP use; mean duration of use 5.1 ± 3.1 years for AFF versus 3.3 ± 2.6 years for classic ($p = 0.02$) |
| Warren,[57] 2012, New Zealand | 2003–2008 | Retrospective case-control; cases were 6 AFFs and 65 controls were patients with fx in same region | 528 M + W ≥20 years old hospitalized with ST or FS fx; 319 excluded for coding errors, high trauma, tumors or other pathology, prostheses, minor comminution | 71 | Thickened cortices; transverse orientation; medial spike; single observer, no Kappa | 6 (1) | 3 (50) | NA | Crude OR 5.5 (0.97–31) | NA | AFFs and ordinary fx did not differ by age; 2/6 AFFS on GCs compared to 6/65 ordinary fx (OR, 4.9; 95% CI, 0.74–32.7); relationship to BPs and GCs was not significant |
| Shkolnikova,[55] 2012, Australia | 2007–2012 | Retrospective case-control; cases were 16 M + W with 20 AFFs and 46 patients with 46 ordinary fx in same region | 62 M + W with 66 ST/FS fx, no age exclusion, admitted to a single hospital | 66 | ST/FS location; cortical thickening; cortical beaking; lateral transverse fracture with or without medial oblique portion; two observers, Kappa 1.0, no information provided on blinding to clinical information | 20 (30) | 18 (90) | NA | Crude OR 128 (18–838) | NA | 7 patients had bilateral AFFs; patients with AFFs were younger (70.7 versus 79.9, $p = 0.01$) and more physically active before the fx than those with typical ST/FS fx |

(*Continued*)

**Table 2.** (*Continued*)

| First author/ reference/ date/country | Time | Design | Population | ST/FS, *n* | AFF criteria | AFFs, *n* (%) | AFFs on BPs, *n* (%) | Incidence rate | Relative risk for BP use, OR (95% CI) | Absolute risk for BP use, OR (95% CI) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Beaudouin, Bazire, 2012, France[40] | 2005–2010 | Retrospective frequency study | 4080 M + W ≥50 years old admitted for any femoral fx | 300 of 780 fx with ST/FS codes, 206 had unavailable data and 274 had erroneous codes; after exclusion of prostheses, pathological fx and high-trauma fx, 92 ST/FS fragility fx remained | ASBMR Major criteria: ST/FS location, no or minimal trauma; transverse or short oblique (fx line <30-degree) orientation; noncomminuted; complete +/− medial spike or incomplete; no Kappa | 12 (4% of all ST/FS fx and 13% of low-trauma ST/FS fx, not associated with prostheses or pathological fx) | 5 (41.6) | NA | NA | NA | Patients with AFFs were predominantly women (10/12) with a mean age of 71.5 years; information on BP therapy unknown in 2/12 AFF patients; 6/12 AFF patients also had "cortical hypertrophy"; 3 of these patients (50%) were on BPs and in 1, BP status was unknown; there was a very high rate of erroneous coding, but with respect to fx site and diagnosis of atypia, of 29 patients with radiographic features of atypia, 6 were excluded because of osteolytic lesions and 11 were excluded by chart review that revealed evidence of high trauma or pathologic fx |

All studies excluded periprosthetic and high trauma fractures and fractures associated with malignancy.

ST/FS = subtrochanteric/femoral shaft; AFF = atypical femoral fracture; OR = odds ratio; BP = bisphosphonate; CI = confidence interval; PM = postmenopausal; fx = fracture; BMI = body mass index; IT = intertrochanteric; FN = femoral neck; GC = glucocorticoid; NA = not available; AFF = atypical femur fracture; M = men; W = women; PPI = proton pump inhibitor; KPNW = Kaiser Permanente Northwest; ASBMR = American Society for Bone and Mineral Research; AFFM = AFF with ASBMR Major Features; IR = incidence rate; KPSW = Kaiser Permanente Southwest.

injury, history of prodromal pain, BP use, and GC use were ascertained from the medical record, fracture database, and general practitioners. In a blinded radiograph review of all patients ($n = 407$) with ST/FS fractures, they identified 27 individuals with 29 AFFs (simple transverse fracture line in a region of cortical hypertrophy), representing 0.8% of all hip and FS fractures and 7% of ST/FS fractures. At admission, 22 of 27 (81%) patients were using BPs and five had never taken BPs. Fewer patients had prodromal pain (46%). Mean duration of BP use (4.6 years) was slightly shorter than other series.[49]

Feldstein and colleagues,[45] using electronic medical records and stored radiographs from Kaiser Permanente Northwest, studied the incidence of new femur fractures between 1996 and 2009 in women over 50 years old and men over 65 years old. Of 5034 new fractures, 864 radiographs (all ST and FS fractures, distal femur fractures, a random sample of 300 FN and 300 IT fractures) were reviewed. ST/FS ($n = 197$) fractures were categorized according to whether they fulfilled ASBMR major criteria or also had at least one of the ASBMR minor criteria (localized periosteal reaction of the lateral cortex, increased cortical thickness, unicortical stress fracture); 75 (38%) met at least the major criteria. Over 1,271,575 person-years of observation, ST/FS fracture incidence was stable, as was incidence of AFFs with ASBMR major criteria (5.9 per 100,000 person years; 95% CI, 4.6–7.4). AFFs with ASBMR minor criteria were not seen before 1999, after which the incidence increased to 5 per 100,000 person-years by 2009. BP exposure was highest in the AFF group; 24% had BPs dispensed during the year before the fracture, with a mean dispensing of 4.4 years and 33% had more than 5 years of use. Compared to patients with only ASBMR major criteria, those individuals with fractures satisfying both major and minor criteria were younger (70.5 versus 79.8 years old), more likely to be women (90.5% versus 75.5%), had a longer duration of GC use (4.8 versus 2.6 years), and more prodromal pain (27% versus 0%). In addition, those with both major and minor criteria were more likely to have had BPs dispensed prior to the index fracture (62% versus 16%), had longer duration of BP use (5.6 versus 2.5 years), and were more likely to have more than 5 years of BP exposure (29% versus 2%) than those patients whose fractures met only ASBMR major criteria. The OR of ever having a BP dispensed in AFF versus an ordinary fracture was 2.11 (adjusted for age, gender, GC dispensing, number of medications; 95% CI, 0.99–4.49). These data suggest that AFFs are very rare (5 per 100,000 patient-years), particularly when compared to classical hip fractures, which decreased from 400 to 300 per 100,000 patient-years. The data also suggest that BPs are a risk factor for AFFs, particularly those meeting ASBMR minor criteria, and that minor criteria are more indicative of AFFs than the major criteria.[45] A major limitation of this study, however, is that the majority of fractures included were not within the 30-degree angle typically considered "short oblique."

In another study from Kaiser Permanente Northwest, Lo and colleagues[46] evaluated 3078 women over 60 years old hospitalized with a hip or femur fracture between 2007 and 2008; 79 (2.8%) had a low-trauma ST or FS fracture and 38 (1.2%) met criteria for atypia (noncomminuted transverse or short-oblique pattern with a medial spike and lateral cortical thickening at the fracture site). Compared to those with ordinary ST/FS fractures, women with AFFs were significantly younger (74 versus 81 years old), less likely to have diabetes or chronic kidney disease, and more likely to have received BP therapy (97% versus 42%). They were also more likely to be Asian (50% versus 2%), which is noteworthy because Asian women over 60 years old

comprised only 12% of health plan members. A stress fracture of the contralateral femur was present in 40% of AFFs versus 2% of ordinary fractures, and an additional 21% of AFF cases had focal cortical hypertrophy of the contralateral femur. One-third of women with AFFs had prodromal pain and one-third had focal cortical periosteal reaction on prefracture radiographs. Although no incidence data were reported, the predilection for Asian women is of interest.

Dell and colleagues[50] prospectively reviewed all femur fractures that occurred between 2007 and 2011 in 1,835,116 patients over 45 years old enrolled in the Healthy Bones Program of Kaiser Permanente Southwest, and reviewed radiographs when a ST or FS fracture was mentioned anywhere in the medical record. They collected data on age, sex, race, and BP use and duration between 1996 and 2011. A total of 11,466 patients had hip fractures during this period, but the number of radiographs reviewed of patients with ST and FS fractures was not provided. AFFs (transverse or short oblique pattern, thickening of lateral cortex at fracture site) were documented in 142 (1.2%) patients, of whom 90% used BPs. The average age was 69, 96% were women, 49% were Asian, and 17 (12%) were taking GCs. Bilateral fractures occurred in 22.5%, usually at the same location of the contralateral side and prodromal pain occurred in 69%. Age-adjusted AFF incidence in patients receiving BPs increased from 1.8 per 100,000 cases per year for 0.1 to 1.9 years of use to 113.1 per 100,000 cases per year for 8.0 to 9.0 years of use. These data suggest that AFFs are rare in BP-treated patients, but their incidence increases with increasing duration of exposure.[50] In a separate study, the age-adjusted incidence of common hip fractures was much higher among those exposed to BPs for 1 to 2 years (463 per 100,000 patient-years), decreased by 17% to 384 per 100,000 patient-years after 4 to 5 years of BPs, and was back to baseline at 8 to 9 years (544/100,000 patient-years),[56]

Meier and colleagues[47] reviewed computerized medical records and digitized radiographs to identify 477 patients over 50 years of age admitted to a Swiss trauma center university hospital with ST/FS fractures between 1999 and 2010. Patients were classified by whether the fracture was atypical (transverse or short-oblique fracture line, originating at the lateral femoral cortex) or classic (wedge, segmental, complex irregular). Contralateral fractures were recorded. The AFF and classic fracture patients were compared to 200 age-matched patients without a femoral fracture. Thirty-nine AFFs were identified (8% of all ST/FS fractures). BP use, assessed by the computerized medications list in the hospital medical records, and confirmed by contacting the patient or their physician, was documented in 82% of the AFF group, 6% of the classic fracture group (adjusted OR, 66.9; 95% CI, 22.8–209.5), and 12% of the group without fractures. Furthermore, longer BP exposure (5–9 years) was associated with greater risk of AFFs (OR, 117.1; 95% CI, 34.2–401.7) than shorter exposure, although risk was higher even with less than 2 years of use (OR, 35.1; 95% CI, 10.0–123.6). More patients with AFFs used GCs (18% versus 6%, $p = 0.004$), vitamin D supplements (49% versus 21%, $p < 0.001$), and PPIs (56% versus 40%, $p = 0.06$). A contralateral fracture occurred in 28% of AFFs and only 0.9% of classic cases (OR, 42.6; 95% CI, 12.8–142.4). The incidence of AFFs was low (3.2 cases per 100,00 person-years) and increased by 10.7% annually over the decade. In contrast, the incidence of classic fractures was much higher (35.7 per 100,000 person-years) and remained stable, and BPs were associated with a 47% reduction in fracture risk.[47]

In New Zealand, Warren and colleagues[57] reviewed 528 patients admitted for fractures coded as ST/FS fractures between 2003 and 2008. They excluded patients under age 20 years old, fractures associated with significant trauma or underlying bone tumors, or coding errors. A single radiologist who was blinded to the patients' clinical information reviewed the remaining 195 radiographs and an additional 124 patients were excluded because of trauma, malignancy, other bone pathology, peri-prosthetic associations, or coding errors. The miscoding rate was 20%. Of the 71 patients meeting entry criteria, six had AFFs (thickened cortices, transverse orientation, medial cortical spike) and six had AFF features but were excluded for minor degrees of comminution. Three of six (50%) AFF patients were on alendronate compared to 10 of 65 (15%) with ordinary fractures (OR, 5.5; 95% CI, 0.97–31). Three patients were on "any BP," but it is unclear whether this is in addition to those on alendronate. Two of six (33%) were on GCs compared to 6 of 65 (9%) with ordinary fractures (OR, 4.9; 95% CI, 0.74–32.7).

In Australia, Shkolnikova and colleagues[55] conducted a retrospective chart and radiograph review of 62 patients who presented with ST/FS fractures between 2007 and 2012. Twenty AFFs (cortical thickening, cortical beaking, and lateral transverse fracture pattern with or without a medial oblique portion) in 16 patients (13 women) and 46 typical fractures in 46 patients were identified. AFFs represented 30% of ST/FS fractures. Patients with AFFs were younger ($73 \pm 10$ versus $80 \pm 12$, $p = 0.01$) and 90% used BPs, with a median duration of 6 years; seven patients had bilateral AFFs and seven had prodromal pain (both 44%). Patients with AFFs reported a higher prefracture level of physical function with more walking for exercise.[55]

Beaudouin-Bazire and colleagues[40] used ICD-10 codes to evaluate the incidence of all femoral fractures in patients admitted to three large French university hospitals between 2005 and 2010. All patients over 50 with ST and FS codes and available radiographs ($n = 574$) were reviewed by two observers; 274 fractures (48%) were excluded for miscoding and 208 were excluded for previously unrecognized pathological, periprosthetic, or traumatic fractures. Of the 92 remaining ST/FS fragility fractures, 80 were ordinary and 12 met ASBMR major radiologic criteria. Those patients with AFFs were predominantly women ($n = 10$), with a mean age of 71.5 years; five of 12 (41.6%) had a history of BP use and in two BP treatment was unknown. Six AFFs also had cortical hypertrophy, of whom three patients (50%) were on BPs and one was unknown. Notably, almost one-half of the cases were miscoded; with corrected coding, AFFs accounted for only 0.3% of all femoral fractures.

La Rocca Vieira and colleagues[58] prospectively reviewed 200 femoral radiographs in 100 asymptomatic patients with at least 3 years of highly compliant BP therapy from a single osteoporosis specialty practice. Two patients (2%), both relatively young women (50 and 57 years old) with 8 years of BP therapy had three insufficiency fractures, all with atypical features. This rate is higher than suggested in the literature, but is the only study to image asymptomatic BP users prospectively.

Over a 3-month period in 2010 to 2011, Powell and colleagues[59] prospectively evaluated 201 patients (149 women), aged 28 to 94 years, receiving intravenous zoledronic acid ($n = 102$) or pamidronate ($n = 97$) for benign indications, predominantly osteoporosis or Paget's disease, because of oral BP intolerance. All completed a questionnaire that included questions on dental health, thigh pain, and information on BP indication, dose, and duration (median duration 7 years). One patient had ONJ and 27 (13.4%) reported thigh pain during the 3-month audit. Bilateral femoral radiographs obtained for those with thigh pain, revealed four patients (2%) with six AFFs;

all were on pamidronate (duration 8 to 22 years) and none were being treated for osteoporosis or Paget's disease. The incidence of AFFs in the audit population was 36.6 per 10,000 patient years of intravenous BP or 50.7 per 10,000 patient years of pamidronate. No control population was available. These two studies are of concern, because they suggest the incidence of AFFs may be higher than previously reported.

Prior to publication of the ASBMR task force report in 2010, only one case of a lower-energy subtrochanteric femoral fracture associated with high-dose BP treatment for cancer had been reported.[6] Since then, two studies examined patients receiving high-dose intravenous BP treatment for cancer[18,19] and a case report was published.[60] One study was a retrospective review of 327 patients with skeletal malignancy who had received a minimum of 24 doses of intravenous BPs (pamidronate or zoledronic acid) between 2004 and 2007 (median 43, interquartile range, 33–57 doses) with a median duration of 66 months (interquartile range, 49–81 months).[19] Four women (1.2%) had ST ($n = 3$) or impending ($n = 1$) AFFs (transverse or short oblique, low trauma, diffuse cortical thickening, focal cortical thickening at the fracture site). BP exposure did not differ between those who did and did not develop AFFs. Notably, one patient also developed ONJ after the fracture was repaired. Chang and colleagues[18] identified all patients at Kaiser Permanente Northwest with known intravenous BP therapy for multiple myeloma or breast cancer and any femoral fracture between 2005 and 2010. Of 62 patients identified, six (~10%) had AFFs (transverse or oblique orientation, focal cortical thickening of the lateral cortex, without malignancy or radiation of the fracture site), five had bilateral findings, and two had ONJ. Patients with AFFs received significantly ($p < 0.001$) more BP infusions (115 versus 55) and had longer treatment duration (5.9 versus 1.6 years). Data on the total number of BP-exposed cancer patients was not available.[18]

In summary, an increasing number of published high-quality epidemiological studies with radiographic adjudication (albeit of varying designs and with somewhat variable definitions of atypia), indicate that AFFs are more frequent in patients on BP therapy[10,11,21,45–50] and that longer treatment is associated with higher risk. These points are supported by a recent systematic review and meta-analysis of the risk of AFFs associated with BP use.[61] In addition, most,[10,45,47,49,50] though not all,[46,48] studies with radiographic review have reported significant association between GC use and AFFs, and two additional studies found an increased association that was not significant.[11,57] However, although these studies indicate that the relative risks of a patient with an AFF being on BPs are very high, ranging from 2.11[45] to 66.9[47] or as high as 128 in an unadjusted analysis,[55] the absolute risk is uniformly very low. Although radiographic review was not conducted, Park-Wyllie and colleagues[39] reported that in 52,595 women with at least 5 years of BP therapy, a ST or FS fracture occurred in 71 (0.13% or 130 per 100,000 patient-years) during the subsequent year (year 6 of BP use) and 117 (0.22% or 220 per 100,000 patient-years) during the subsequent 2 years. However, the proportion of these fractures that were atypical is unknown. Schilcher and colleagues[48] reported what is thus far the highest absolute risk of AFFs in a study with radiographic adjudication, 50 cases (with ASBMR major and minor criteria) per 100,000 patient-years (95% CI, 40–70) attributable to BP use (although many years of BP exposure may not have been captured), that decreased 70%/year after stopping BPs. Meier and colleagues[47] reported an absolute risk of 3.2 cases (with ASBMR major and minor criteria) per 100,000 person-years and Feldstein and colleagues[45] reported an absolute risk of 5.9 cases (with only ASBMR major criteria) per 100,000 person-years. With regard to long-term use, however, Dell and colleagues[50] reported a much higher incidence of 113.1 per 100,000 cases per year for 8.0 to 9.0 years of use, similar to that reported in the study by Meier and colleagues,[47] in which longer BP exposure (5–9 years) was also associated with greater risk of AFFs (OR, 117.1; 95% CI, 34.2–401.7). Although the task force still holds the opinion that a causal relationship between BPs and AFFs has not been established, evidence for an association has continued to accumulate in the 2 years since the first report was published and is quite robust. Moreover, the fairly consistent magnitude of the association between BPs and AFFs is unlikely to be accounted for by unknown or unmeasured confounders.

## Update on Pathogenesis

The pathogenesis of AFFs remains unclear, although several mechanisms have been proposed.[2,62,63] Some authors have suggested that AFFs represent another form of osteoporotic fracture.[32,33] However, several radiological and clinical features differ fundamentally from ordinary osteoporotic femur fractures and strongly suggest a distinct pathogenesis. The distinguishing radiologic features include the transverse orientation and general lack of comminution, which is unusual for a femoral fracture and is characteristic of brittle failure, as well as localized cortical thickening at the fracture site, which is characteristic of stress fractures. The distinguishing clinical features include their bilaterality and prodromal pain. Fractures with features similar to AFFs have been reported in patients with other bone diseases, including hypophosphatasia,[64,65] pycnodysostosis caused by mutations of the cathepsin K gene,[66] and osteopetrosis.[67–69] This information largely falls into four categories of investigation:

- Commonalities between lower limb stress fractures and AFFs;
- The effects of suppression of bone remodeling on bone's material properties;
- The effects of suppression of remodeling on healing of stress fractures; and
- The relationship of hip and lower limb geometry to AFFs.

### AFFs as stress or insufficiency fractures

Bones subjected to repetitive loading that overwhelms the body's capacity for repair are at risk for developing a stress fracture. In this discussion, the term "stress fracture" is used in its broadest sense, but more accurately a "stress fracture" implies abnormal, or excessive, loading of a normal bone, whereas "insufficiency fracture" implies normal loading of an abnormal or deficient bone. Stress or insufficiency fractures develop most commonly in the lower extremities, which are more routinely subjected to higher loading than other skeletal sites. Over time, fatigue damage in the form of microcracks develops within the bone cortex and accumulates. The microcracks coalesce and without repair will eventually grow to a critical-sized defect that precipitates a fracture.[70] Stress fractures heal by targeted remodeling of the injured site through a process of osteocyte apoptosis, which signals for repair through elevated production of receptor activator of NF-κB ligand (RANKL),[71,72] osteoclastic resorption to remove the damage, and then osteoblastic formation to replace resorbed bone.

At least two publications have provided glimpses into the natural history of the evolution of AFF prior to fracture.[73,74] In 2010, an evolving atypical femoral diaphyseal fracture was captured on serial dual-energy X-ray absorptiometry (DXA) scans obtained before, during, and after therapy with alendronate.[74] Another case report demonstrates the initial development of periosteal callus, and the eventual appearance of a transverse cortical fracture (often termed the "dreaded black line"[15,23]) in the region of periosteal thickening. Another study shows a similar sequence of events.[59] This pattern is typical of the development of a stress fracture. Based on evidence of periosteal and endosteal callus, and on the appearance of a transverse cortical fracture prior to overt fracture, the current consensus of the task force is that AFFs are stress or insufficiency fractures that develop over time.[75] AFFs do differ in some respects from exercise-induced femoral stress fractures, which usually initiate on the medial cortex of the femur, are located in the proximal one-third of the femoral diaphysis, and result in a more oblique fracture surface than do AFFs.[76–79] In contrast, AFFs initiate on the lateral cortex, are located between the lesser trochanter and the femoral condyles, and result in a smooth transverse surface, more characteristic of a brittle material. The lateral cortex of the femur is known to sustain high levels of tensile stress due to bending,[80,81] which may precipitate the damage in this location especially in those people with lower limb geometry that could exacerbate that effect (eg, a bowed femur, Asian race).

## Effects of remodeling suppression on bone material properties

Several recent studies have examined differences in bone tissue properties in subjects with femoral fractures of all types, in subjects taking BPs and those who are BP naïve. These studies are inconclusive about whether bone tissue in those with AFF is significantly different either physically or mechanically from bone tissue in subjects on long-term BP therapy, or in those with typical femoral fractures.

Donnelly and colleagues[80] used Fourier transform infrared spectroscopy (FTIR) to compare the physical properties of cortical and cancellous bone of the proximal hip in subjects with hip or femoral fractures who were BP-naïve (–BP; 19 IT fractures, 1 typical femoral fracture) with those who had taken BPs for a mean of 7 years (+BP; 13 IT fractures, 1 typical femoral fracture, 6 AFFs). Mean values were not different for parameters describing mineralization, crystallinity, or collagen maturity, but those individuals on BPs had significantly more homogeneous crystallinity and collagen maturity (although not in overall matrix mineralization), suggesting greater uniformity of tissue composition in those individuals treated with BPs. The small sample size precluded separate analysis of AFFs.

Guerri-Fernandez and colleagues[82] used a new in vivo microindentation technique that permits the measurement of bone properties thought to be related to material stiffness and toughness. Their study included 20 subjects who were BP-naïve and without a fracture, six subjects without a fracture who had been treated for an average of 5.4 years with BPs, 38 BP-naïve patients with typical osteoporotic fractures, and 6 patients with AFFs treated with BPs for an average of 5.5 years. Although bone material properties were worse for the fracture groups, both compared to controls and to nonfractured long-term BP users, subjects with AFFs were not significantly worse than those with typical fractures. Moreover, long-term BP users who did not fracture did not have significantly deteriorated properties compared to nontreated controls.

Neither of these studies leads to the conclusion that the mechanical and physical properties of bone are negatively affected by either long-term BP use. Nor do they suggest any difference between patients who eventually present with AFFs and those with common hip fractures or ordinary femoral shaft fractures.

## Effects of remodeling suppression on healing of stress fractures

Approximately 19 studies have included attempts to measure bone turnover from biopsies. These studies, summarized in the first ASBMR task force report,[2] are about evenly divided between iliac crest biopsies and biopsies taken at the fracture site at various intervals following an incident AFF. Nearly all studies observe reduced or absent populations of osteoclasts and osteoblasts, with few or no double labels. Two studies[26,83] found increased resorption and reduced formation. A recent transiliac crest bone biopsy study[84] reports no evidence of decreased bone formation or mineralization, and the appearance of fully normal lamellar bone. Therefore, the evidence from both the iliac crest and the femoral fracture site predominantly supports the conclusion that bone turnover is suppressed, perhaps leading to "insufficiency" under normal loading. This is not especially surprising because all biopsies were from patients being treated with BPs, which suppress turnover. However, there is no evidence that periosteal bridging is affected in any way, suggesting that normal osteoblastic bone formation is not suppressed when it is not coupled to prior resorption. This is consistent with several other studies that show that BPs do not affect the formation of initial fracture callus[85] nor do they affect formation of woven bone, which can also be a part of the fracture healing process.[86–88]

Initial stabilization of a developing stress fracture occurs by endosteal or periosteal bridging of the crack, followed by repair by normal bone remodeling. This allows intracortical remodeling to repair the crack, ideally before a full fracture occurs. Periosteal and endosteal surface calluses develop in AFFs and do not seem to be impaired by BP treatment.[23,73,75] Complete repair of the fracture itself, however, occurs by normal coupled bone remodeling processes. BPs localize at sites of high bone turnover, including those sites at which stress fractures are forming, because of the increased blood flow associated with attempted remodeling and repair in these areas.[89] Indeed, this phenomenon is the basis for scintigraphy, which is used diagnostically to identify the stress fracture site.[89] As BPs suppress remodeling, they are also likely to affect adversely intracortical repair of a developing stress fracture in AFFs, allowing the crack to grow to critical size. Localization of an agent known to suppress coupled bone remodeling to a site that requires repair may be a precipitating event that allows the damage to progress to full fracture. Clinical data support this mechanism. In the Swedish 2008 study, Schilcher and colleagues[48] found that the risk of AFF declined by 70% in the following year if BP treatment is withdrawn. Data from the Kaiser database suggests that only 20% of contralateral limbs will fracture following an AFF on one limb if the BP is stopped soon after the first fracture has occurred, compared to a rate of 50% if the BP is continued for 3 years.[90]

## Lower limb geometry

The geometry of the hip and proximal femur determines in part the stresses that are experienced on the lateral aspect of the femoral cortex.[91] The bilateral incidence of AFFs and similar fracture location on the contralateral femur in cases with bilateral fractures suggest a relationship between the axis of the lower

extremity and risk for AFF. At the 2012 ASBMR meeting, Saita and colleagues[92] reported that the site of the AFF along the femoral diaphysis was highly correlated ($r^2 = 0.64$, $p = 0.008$) to the deviation between the anatomical axis of the femur and tibia and the mechanical axis of the lower limb along which weight bearing occurs. Those with a more diaphyseal AFF had a larger tibiofemoral angle than those who fractured closer to the lesser trochanter (183 versus 171 degrees). In a Japanese population, those patients who developed AFFs had significantly greater curvature of the femoral diaphysis than age- and gender-matched controls.[93] Although these studies do not provide a reason for the fracture, they suggest that the location of AFFs is related to mechanical forces on the lower limb. The geometry of the entire lower extremity could be considered as a potential contributor to altered stress on the lateral cortex of the femur that may, in conjunction with other detrimental changes in the bone itself, predispose to development of an AFF. The relative absence of studies of lower limb geometry on femoral stresses and risk for fracture argues for more work in this area.

### Summary

At this time, the evidence suggests that AFFs are stress fractures. There is generalized suppression of remodeling as the result of BP treatment, but this remodeling suppression does not negatively impact the formation of periosteal or endosteal bridging callus. However, because BPs localize in areas that are developing stress fractures, suppression of targeted intracortical remodeling at the site of an AFF is likely to impair the processes by which stress fractures normally heal; when BPs are stopped, the risk of an AFF may decline.[75] It is possible, and indirectly supported by the reported difference in risk between ethnic groups, that lower limb geometry contributes to the risk for developing an AFF.

## Revised Case Definition

Based on several studies published since the first task force report and summarized below, the task force has revised the case definition of AFFs to be more specific for features that distinguish these fractures as stress fractures and differentiate them from ordinary low-trauma osteoporotic ST and FS fractures in the elderly. Although this revision may assist in developing a clearer understanding of the pathophysiology of AFFs, it may select for radiological features that distinguish BP users from nonusers.

Koeppen and colleagues[94] and Schilcher and colleagues,[95] using the original Sweden 2008 cohort database,[48] addressed the specificity of several minor criteria for AFFs. They pointed out that AFFs resemble stress, or fatigue, fractures, which have a distinctive radiographic appearance: a transverse fracture line in the cortical diaphysis and localized cortical hypertrophy that represents fracture callus.[95] A different physician blinded to patient characteristics and drug treatments reanalyzed all radiographs and measured fracture angles. One line was drawn parallel to the lateral cortex of the femoral diaphysis, ignoring any periosteal callus formation. The second line was drawn parallel to the fracture line, extending medially from the lateral cortex across approximately one-third of the shaft.[95] Frequency distribution analysis of the fracture angles detected a trimodal distribution, with one peak between 75 and 105 degrees (mean angle, $89 \pm 10$ degrees) and two broader peaks between 15 to 45 degrees and 125 to 165 degrees. Medial spike, periosteal callus reaction, and BP use overlapped with this subgroup. Approximately 74% of patients with fracture angles between 75 and 105 degrees used BPs versus 13% of those with other fracture angles. Specificity was high for BP use for fracture angles between 75 and 105 degrees and presence of a callus reaction, and low for number of fragments. Fractures were reclassified and considered atypical only when all ASBMR major features were present, with minor features not required. Transverse or short oblique was interpreted as an angle of less than 30 degrees from a line drawn perpendicular to the lateral femoral cortex. ASBMR major criteria had lower specificity for BP use; 61% of patients with atypical fractures used BPs, compared to 78% in the original study,[48] resulting in a decrease in the age-adjusted relative risk associated with BP use from 47 (95% CI, 26–87)[48] to 19 (95% CI, 12–19).

Koeppen and colleagues[94] also addressed whether patients with AFFs have thicker cortices than those with ordinary ST/FS fractures. Cortical thickness, the difference between the width of the femoral shaft and the medullary cavity, was measured 5 and 10 cm below the lesser trochanter, and a unitless cortical thickness index (ratio between cortical thickness and outer shaft diameter)[96] was calculated to account for differences in radiographic magnification and femoral size. A high index reflects greater cortical thickness. The contralateral femur was measured when the fractured femur could not be measured. At the 5-cm level, the cortical thickness index of the fractured femur decreased with age ($r^2 = 0.17$; $p < 0.0001$). Patients with AFFs had a higher cortical thickness index ($0.41 \pm 0.09$ versus $0.37 \pm 0.08$; $p = 0.003$), but were almost a decade younger ($75 \pm 10$ versus $84 \pm 9$ years old). After adjusting for their younger age, the higher cortical thickness index was no longer significant (95% CI, $-0.01$ to $+0.04$). Results were similar at the 10-cm level. Patients using BPs had a higher cortical thickness index at 5 cm, before but not after age correction (95% CI, $-0.02$ to $+0.03$). The evidence suggested that substitution with contralateral measurements did not cause bias. In summary, they found no association between AFFs and generalized cortical thickening, after adjusting for the younger age of AFF patients.[94] Aspenberg and colleagues[95] favor more stringent criteria for diagnosis of AFFs to differentiate them from ordinary osteoporosis-related fractures.

Feldstein and colleagues[45] found that patients with AFFs with both ASBMR major and minor radiographic criteria were significantly younger, were more likely to have reported prodromal pain, to have taken BPs and to have taken them for longer, and had more GC exposure. Moreover, only AFFs with both major and minor radiographic criteria appeared to be increasing over time. One problem with this study, however, lies in their definition of transverse as $<30$ degrees and short oblique as 30 to 60 degrees. Although a precise definition of "short oblique" was not part of the original ASBMR case definition, the orthopedists on the task force consider transverse to mean essentially perpendicular to the lateral cortex and short oblique to be an angle of $<30$ degrees. Of the 75 FS fractures designated atypical by Feldstein and colleagues,[45] only 35 (46.7%) had an angle of $<30$ degrees and met the ASBMR definition of "transverse, although they may have a short oblique configuration."[2] The majority of fractures designated as atypical by the investigators had angles between 30 and 60 degrees and three fractures had angles $>60$ degrees. Notably, their study has the lowest association of AFFs with BP use, possibly because fewer than one-half of the fractures included as AFFs are transverse or short oblique. In contrast, Schilcher and colleagues[95] defined "transverse or short oblique" as an angle of less than 30 degrees from a line drawn perpendicular

**Table 3.** ASBMR Task Force 2013 Revised Case Definition of AFFs

| |
|---|
| **To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.** |
| **In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.** |
| Major features[a] |
| The fracture is associated with minimal or no trauma, as in a fall from a standing height or less |
| **The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur** |
| Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex |
| The fracture is noncomminuted **or minimally comminuted** |
| **Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")** |
| Minor features |
| Generalized increase in cortical thickness of the **femoral diaphyses** |
| Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh |
| Bilateral **incomplete or complete femoral diaphysis fractures** |
| Delayed **fracture** healing |

Changes are in bold.

ASBMR = American Society for Bone and Mineral Research; AFF = atypical femur fracture.

[a]**Excludes** fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia).

(90 degrees) to the lateral femoral cortex. The category of fractures with angles of $89 \pm 10$ degrees overlapped with findings of periosteal callus reaction and medial spike. Specificity for BP use was greater than 0.9 for fracture angle between 75 and 105 degrees and presence of a callus reaction. The number of fragments had the lowest specificity of all features (0.48; 95% CI, 0.41–0.55). Reclassification of fractures according to the ASBMR criteria yielded a lower specificity for BP use and led to a decrease in the age-adjusted relative risk associated with BP use from 47 (95% CI, 26–87)[48] to 19 (95% CI, 12–19), albeit still highly significant. Notably, the generalized cortical thickening in patients with AFFs was no longer significant after adjusting for their younger age.[94]

Based on these studies by Feldstein and colleagues,[45] Schilcher and colleagues,[48,95] Schilcher and Aspenberg,[75] and Koeppen and colleagues,[94] the task force agreed that both a transverse fracture line originating in the lateral cortex and a periosteal or endosteal callus reaction at the fracture site were central to the diagnosis of AFFs. Moreover, all 12 studies with radiographic review published since the original task force report included one or both of these features in their definition (Table 2).

The revised AFF case definition is presented in Table 3. It is now preceded by the following statement: "To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five Major Features must be present. None of the Minor Features is required but have been sometimes associated with these fractures. Requiring four out of five, rather than all, Major Features leaves some latitude for clinical judgment when most but not all features are present or there is missing information."

The term "transverse or short oblique configuration" from the original case definition has been revised for greater precision to read: "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." As before, the precise definition of angle was not provided because it can be very difficult to measure angle in all cases, depending on the alignment of fracture fragments and projection of the X-rays. However, the transverse nature of the fracture line is emphasized. Because many orthopedists on the task force have seen AFF cases with minimal comminution, that criterion has been amended from "noncomminuted" to "the fracture is noncomminuted or minimally comminuted." "Localized periosteal reaction of the lateral cortex" has been moved from the minor to the major features and the language has been revised for greater precision to allow for, but not require, inclusion of endosteal reactions based on the study by Mohan and colleagues,[23] who observed multifocal endosteal thickening in patients with AFFs. The criterion now reads: "Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ('beaking' or 'flaring')." Among the minor features, cortical thickening was retained because the data on this are still inconclusive, and there are some differences in phrasing to improve clarity. Finally, the features linking AFFs to comorbid conditions and medication exposures, including BPs and GCs, were removed, because it was deemed more appropriate for studies to seek these associations rather than to include them in the case definition. The majority (25/26) task force members approved the revised case definition.

## Update on Medical Management

The natural history of AFFs suggests that they evolve over time, with initial development of a cortical "bump" that likely represents early periosteal thickening, and the eventual appearance of a transverse cortical lucency (fracture) in the region of periosteal thickening, which may or may not progress to a complete fracture.[59,73,74] Until more evidence becomes available regarding the clinical significance of such areas of cortical thickening, the opinion of the task force is that such lesions, whether they are detected on DXA scans or plain radiographs, should be further evaluated with higher-order imaging to determine whether a cortical lucency is associated with the

periosteal thickening. Options for imaging include magnetic resonance imaging (MRI), which could detect a cortical fracture line and associated bone and marrow edema or hyperemia, indicative of a stress fracture. If MRI cannot be performed, computed tomography (CT) could detect the cortical fracture or lucency and associated new-bone formation. Radionuclide bone scan could detect focal bone and marrow hyperemia but with less specificity than MRI or CT. If higher-order imaging detects a cortical lucency, such a lesion could be considered an incomplete AFF. If no cortical lucency is present but marrow edema is present, then such lesions could be considered a stress reaction.

Suggested management of an incomplete AFF is summarized in the 2010 original task force report.[2] For patients with a stress reaction, stress fracture, or incomplete or complete subtrochanteric or femoral shaft fracture, potent antiresorptive agents should be discontinued. Dietary calcium and vitamin D status should be assessed, and adequate supplementation prescribed. Prophylactic reconstruction nail fixation is recommended for incomplete fractures (with cortical lucency) accompanied by pain. If the patient has minimal pain, a trial of conservative therapy, in which weight-bearing is limited through the use of crutches or a walker, may be considered. However, if there is no symptomatic and radiographic improvement after 2 to 3 months of conservative therapy, prophylactic nail fixation should be strongly considered, because these patients may progress to a complete fracture. For patients with incomplete fractures and no pain, or those with periosteal thickening but no cortical lucency, limited weight-bearing may be continued and vigorous activity avoided. Reduced activity should be continued until there is no bone edema detected on MRI or no increased activity detected on bone scan.

Since the first task force report,[2] there have been numerous anecdotal reports of medical therapy. Most reports extend early descriptions of using teriparatide (TPTD) in patients with AFFs.[83,97] Gomberg and colleagues[98] treated a 63-year-old woman with thigh pain and bilateral AFFs who taken BPs for 13 years. After 6 months of daily TPTD, her pain diminished, MRI revealed less edema around the fracture, and after 16 months, there was complete healing and relief of pain. Similarly, Carvalho and colleagues[99] described a 77-year-old woman whose AFF closed after only 1 month of TPTD. Interestingly, Carvalho and colleagues[99] treated two other patients (women 63 and 77 years old) with strontium ranelate, with fracture closure after 2 and 3 months, respectively, of treatment. More recently, Huang and colleagues[100] described a 63-year-old woman treated with BPs for only 3 years who presented with thigh pain and a stress fracture. After 10 months of TPTD followed by 5 months of raloxifene, the fracture healed completely.

Another report provides information on a somewhat different case. A 70-year-old man with prostate cancer[101] was treated with androgen deprivation therapy and 4 mg intravenous zoledronic acid monthly for 2 years. He complained of thigh pain and was found to have a transverse femoral shaft fracture. An orthopedic nailing procedure produced a further fracture. After 2 months of TPTD therapy, there was full healing.

Thus, discontinuation of BP therapy and TPTD treatment (and strontium ranelate in two cases) has been associated with fracture healing. Nonetheless, in a randomized, placebo-controlled study of women with distal radius fractures, the efficacy of TPTD was questioned because although 20 μg daily appeared to hasten fracture healing, 40 μg daily dosing did not.[102] Moreover, the unpublished clinical experience of bone experts is that only some patients appear to respond to TPTD. Variable response to TPTD was reflected in several reports of medical treatment of AFFs presented at the ASBMR Annual Meeting in 2012. Mastgalia and colleagues[103] described a 57-year-old Argentine woman who had been treated with alendronate for 7 years and sustained a non-healing FS fracture. Her pain improved after 10 days of TPTD and healing was complete after 3 months. However, Bock and Felsenberg[104] reported that only one of three German patients with AFF responded to 2 years of TPTD. Similarly, Cheung and colleagues[105] reported 13 Canadian women with BP-associated AFFs treated with TPTD. Three required surgery, five improved with TPTD, and the others did not improve or even worsened. Miller and McCarthy[106] performed bone biopsies before and after TPTD treatment in 15 women with surgically-treated AFFs. TPTD increased mineral apposition rate and bone formation rate, as expected. All patients appeared to improve clinically.

Finally, a study of 14 consecutive patients with AFFs was reported from Australia.[107] Nine patients chose surgical or nonoperative management, and five opted for TPTD. High-resolution peripheral CT of the radius and tibia were performed before and 6 months after starting TPTD. Only one of the non-TPTD group had fracture healing (after 1 year). In the TPTD group, union occurred in two patients with the fracture line no longer visible. Two patients became pain-free and the remaining three patients had improvement in pain scores. Images, assessed by a novel software analysis, revealed less densely mineralized bone with TPTD treatment. In addition, bone turnover markers increased in the TPTD group.

In the absence of a randomized, placebo-controlled trial, no definite conclusion can be reached regarding the efficacy of TPTD treatment of patients with AFF. From the low-quality evidence available, the recommendations of the ASBMR task force for medical management[2] remain reasonable: discontinuation of BPs, adequate calcium and vitamin D, and consideration of TPTD for those who appear not to heal on conservative therapy.

## Summary and Conclusions

AFFs are characterized by unique radiographic (transverse fracture line, periosteal callus formation at the fracture site, little or no comminution) and clinical features (prodromal pain, bilaterality) that resemble stress fractures or reactions. Based upon new information, the task force revised the original case definition to highlight the unusual radiographic features that distinguish AFFs from ordinary osteoporotic femoral diaphyseal fractures and to provide more precise guidance on what is meant by transverse orientation. In addition, the requirement that fractures be noncomminuted was relaxed to include those with minimal comminution, the periosteal and/or endosteal stress reaction at the fracture site was moved from the minor to the major features, and the association with specific diseases and drug exposures was removed from the minor criteria, in the spirit that these associations should be sought rather than part of the case definition.

The epidemiological evidence for a relationship between BP use and atypical subtrochanteric and femoral shaft fractures has become more compelling. AFFs appear to be more common in patients who have been exposed to long-term BPs, usually for more than 3 years (median treatment 7 years), but every series includes patients who have not been treated with BPs, suggesting that the "background rate" of AFF in osteoporosis patients is not zero. Moreover, the risk for AFFs may decline after BPs are stopped. The majority of studies have found a significant

association with GC use or duration. Although the relative risks of AFFs are very high in patients on BPs, ranging from 2.1 to 128, their absolute risk is extremely low, ranging from 3.2 to 50 cases per 100,000 person-years. Thus, these fractures are rare, particularly when considered against the incidence of common osteoporotic fractures of all types and of ordinary FN and IT fractures, all of which have been proven to decrease with BP therapy. However, long-term use may be associated with higher risk (>100 per 100,000 person-years). In conclusion, AFFs remain of concern and more information is urgently needed, both to assist in identifying patients at particular risk and to guide decision-making about duration of BP therapy.

## Disclosures

The American Society for Bone and Mineral Research (ASBMR) is well served by the fact that many of those responsible for policy development and implementation have diverse interests and are involved in a variety of activities outside of the Society. Accordingly, the ASBMR requires all ASBMR Officers, Councilors, Committee Chairs, Editors-in-Chief, Associate Editors, and certain other appointed representatives to disclose any real or apparent conflicts of interest (including investments or positions in companies involved in the bone and mineral metabolism field), as well as any duality of interests (including affiliations, organizational interests, and/or positions held in entities relevant to the bone and mineral metabolism field and/or the American Society for Bone and Mineral Research).

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| Name | Affiliation | Corporation/ organization | Role | Institution/ individual | Amount | Current or past 3 years | Comments |
|---|---|---|---|---|---|---|---|
| Elizabeth Shane | Columbia University | Amgen | Honoraria or royalties | Individual | <$10,000 | Current | Prepared an educational presentation on atypical femur fractures |
| | | Eli Lilly | Research grants | Institution | <$10,000 | Current | PI of an FDA grant and Lilly is providing drug and placebo for the study |
| | | *JBMR* | Other | Institution | $0 | Current | Associate editor |
| | | Novartis | Research grants | Institution | $10,000–$100,000 | Current | PI of a grant that Novartis has supported |
| David Burr | Indiana University School of Medicine | AbbieVie | Consulting fees (other than advisory board or board of directors) | Individual | $0 | Current | Have not received anything yet |
| | | Amgen | Research grants | Institution | $10,000–$100,000 | Current | PI on grant |
| | | Merck | Advisory board or board of directors | Individual | <$10,000 | Current | Payment for being on Global Experts Panel |
| | | Eli Lilly | Research grants | Institution | $10,000–$100,000 | Current | PI on grant |
| | | Elsevier | Other | Individual | $10,000–$100,000 | Current | Payment for being Associate Editor for *Bone* |
| | | Japan Implant Practice Society | Honoraria or royalties | Individual | $10,000–$100,000 | Current | For presentation of an anatomy course to Japanese dentists |
| | | Agnovos | Consulting fees (other than advisory board or board of directors) | Individual | <$10,000 | Current | Consulting on research project |
| | | PharmaLegacy | Consulting fees (other than advisory board or board of directors) | Individual | $0 | Past | No activity |
| Bo Abrahamsen | Copenhagen University Hospital Gentofte | Merck | Other | Individual | <$10,000 | Current | Speakers fees |
| | | Novartis | Research grants | Institution | >$100,000 | Current | PI on epidemiology study |
| | | Eli Lilly | Other | Individual | <$10,000 | Current | Speakers fees |
| | | Amgen | Advisory board or board of directors | Individual | <$10,000 | Current | Member of advisory board for Denmark |
| | | Nycomed | Other | Individual | <$10,000 | Current | Speakers fees |
| | | Merck | Advisory board or board of directors | Individual | <$10,000 | Current | Advisory board for Denmark |

*(Continued)*

(*Continued*)

| Name | Affiliation | Corporation/ organization | Role | Institution/ individual | Amount | Current or past 3 years | Comments |
|---|---|---|---|---|---|---|---|
| | | Amgen | Research grants | Institution | $10,000–$100,000 | Current | PI on clinical trials, epidemiology, and health economics analyses |
| | | Nycomed | Advisory board or board of directors | Individual | <$10,000 | Current | Danish advisory board |
| | | Amgen | Other | Individual | <$10,000 | Current | Speakers fees |
| | | NPS Pharmaceuticals | Research grants | Institution | >$100,000 | Past | National PI on clinical trial |
| Robert Adler | McGuire Veteran's Administration Medical Center | Genentech | Research grants | Institution | <$10,000 | Current | Investigator-initiated study; amount may change. |
| | | Amgen | Consulting fees (other than advisory board or board of directors) | Individual | $10,000–$100,000 | Current | Webinar on male osteoporosis; spent 1 day at Amgen teaching and discussing male osteoporosis and glucocorticoid-induced osteoporosis; also consulting on some studies with academic investigators, supported by Amgen. |
| | | Novartis | Research grants | Institution | <$10,000 | Current | Site PI for extension of registration trial of zoledronic acid |
| | | Eli Lilly | Research grants | Institution | <$10,000 | Current | Site PI for surveillance study of growth hormone in adults |
| | | Merck | Research grants | Institution | <$10,000 | Current | Site PI for study of odanacatib in men |
| | | Amgen | Research grants | Institution | <$10,000 | Current | Investigator on a Veterans Affairs Study sponsored by Amgen |
| Thomas D Brown | University of Iowa | Smith & Nephew Orthopaedics | Consulting Fees (other than advisory board or board of directors) | Individual | $10,000–$100,000 | Current | Scientific Advisory Board member |
| | | Musculoskeletal Transplant Foundation | Research grants | Institution | $10,000–$100,000 | Current | Research grant PI |
| | | *Journal of Bone and Joint Surgery* | Honoraria or royalties | Individual | $10,000–$100,000 | Current | Deputy Editor for Research |
| Angela M Cheung | University Health Network | Eli Lilly | Advisory board or board of directors | Institution | <$10,000 | Current | Participated at the national advisory board meeting |
| | | Eli Lilly | Honoraria or royalties | Institution | $10,000–$100,000 | Current | Spoke at a few international meetings in China (in June and in December) and a few other CME events |
| | | Amgen | Advisory board or board of directors | Institution | <$10,000 | Current | Participated at the international and national advisory board |
| | | Eli Lilly | Research grants | Institution | $10,000–$100,000 | Current | Site-PI for a couple of teriparatide studies |
| | | Novartis | Honoraria or royalties | Institution | <$10,000 | Current | Spoke at one Novartis-sponsored CME event |
| | | Merck | Honoraria or royalties | Institution | <$10,000 | Current | Spoke on bone strength at Merck-sponsored symposium at ECTS this past year |
| | | Amgen | Honoraria or royalties | Institution | <$10,000 | Current | Spoke at a few Amgen-sponsored CME events |
| | | Warner Chilcott | Honoraria or royalties | Institution | <$10,000 | Current | Spoke at one Warner Chilcott–sponsored CME event |
| | | Merck | Advisory board or board of directors | Institution | <$10,000 | Current | Served on national advisory board once this past year |
| | | Merck | Research grants | Institution | $10,000–$100,000 | Current | Site-PI for odanacatib QCT and HRpQCT study |

(*Continued*)

| Name | Affiliation | Corporation/ organization | Role | Institution/ individual | Amount | Current or past 3 years | Comments |
|---|---|---|---|---|---|---|---|
| | | Amgen | Research grants | Institution | $10,000–$100,000 | Current | Site-PI for the denosumab and alendronate HRpQCT study |
| | | Osteoporosis Canada | Chair of the Scientific Advisory Council | Individual | $0 | Current | |
| | | Canadian Bone Strength Working Group | Chair | Individual | $0 | Current | |
| | | ASBMR Bone Strength Working Group | Organizer | Individual | $0 | Current | |
| Felicia Cosman | Helen Hayes Hospital | Eli Lilly | Advisory board | Individual | <$10,000 | Current | |
| | | Eli Lilly | Consultant for new drug development | Individual | <$10,000 | Current | |
| | | Eli Lilly | Honoraria or royalties | Individual | $10,000–$100,000 | Current | Promotional speaking on behalf of Eli Lilly |
| | | Eli Lilly | Research grants | Institution | | Current | Supply of medication for NIH and Investigator-Initiated Research |
| | | Novartis | Honoraria or royalties | Individual | $10,000–$100,000 | Current | Promotional speaking |
| | | Amgen | Advisory board | Individual | <$10,000 | Current | |
| | | Amgen | Honoraria or royalties | Individual | $10,000–$100,000 | Current | Promotional speaking fees |
| | | Amgen | Research grants | Institution | $10,000–$100,000 | Current | Fees for participation in pharmaceutical Phase 2 Study |
| | | Merck | Advisory board | Individual | <$10,000 | Current | |
| | | Merck | Research grants | Institution | $10,000–$100,000 | Current | Fees for participation in Phase 2 Research Study |
| | | Novartis | Advisory board | Individual | <$10,000 | Past | |
| | | Novartis | Consulting | | <$10,000 | Past | |
| | | Unigene | Consulting | | <$10,000 | Past | |
| | | Tarsa | Consulting | | <$10,000 | Past | |
| | | Novartis | Research grant | Institution | $10,000–$100,000 | Past | |
| | | Lilly Medication Supply for Research | Research grant | Institution | $10,000–$100,000 | Past | |
| Jeffrey Curtis | University of Alabama at Birmingham | Merck, Lilly | Honoraria or royalties | Individual | <$10,000 | Current | Honoraria and consulting services |
| | | Amgen | Honoraria or royalties | Individual | $10,000–$100,000 | Current | Consultant/Honoraria |
| Richard Dell | Kaiser Permanente Bellflower | | | | | | No past/current disclosures reported |
| David W Dempster | Columbia University | Amgen Inc. | Consulting fees (other than advisory board or board of directors) | Individual | $10,000–$100,000 | Current | Consulting on bone biology |
| | | Eli Lilly | Consulting fees (other than advisory board or board of directors) | Individual | >$100,000 | Current | Consulting on bone biology |
| | | Merck and Co. | Advisory board or board of directors | Individual | $10,000–$100,000 | Current | Advising on clinical trial |
| | | Eli Lilly and Co. | Other | Individual | $10,000–$100,000 | Current | Speakers' bureau |
| | | Eli Lilly and Co. | Research grants | Institution | >$100,000 | Current | To study drug mechanism of action |
| | | Merck and Co. | Consultant in litigation for commercial entities | Individual | $10,000–$100,000 | Current | Expert testimony |
| | | Amgen Inc. | Advisory board or board of directors | Individual | $10,000–$100,000 | Current | Advising on drug development |
| | | Eli Lilly | Advisory board or board of directors | Individual | $10,000–$100,000 | Current | Advising on drug actions |

*(Continued)*

(*Continued*)

| Name | Affiliation | Corporation/ organization | Role | Institution/ individual | Amount | Current or past 3 years | Comments |
|---|---|---|---|---|---|---|---|
| Peter R Ebeling | University of Melbourne | Novartis | Honoraria or royalties | Institution | <$10,000 | Current | Honoraria for lectures |
| | | *Osteoporosis International* | Other | Individual | $0 | Current | Editorial board membership |
| | | Merck | Other | Institution | <$10,000 | Current | Honoraria |
| | | Novartis | Research grants | Institution | <$10,000 | Current | Advisory board and honoraria |
| | | Novartis | Other | Individual | <$10,000 | Current | Advisory board |
| Thomas A Einhorn | Boston Medical Center | Anika | Consulting fees (other than advisory board or board of directors) | Individual | $10,000–$100,000 | Current | Consult |
| | | Medtronic | Honoraria or royalties | Individual | <$10,000 | Current | Consult and receive royalties |
| | | NeoStem | Stock options or bond holdings | Individual | <$10,000 | Current | Consult and own stock options |
| | | Bioventus | Consulting fees (other than advisory board or board of directors) | Individual | <$10,000 | Current | Consult and give lectures |
| | | Lilly | Research grants | Institution | >$100,000 | Past | Received research grants (through institution) |
| | | Lilly | Consulting fees (other than advisory board or board of directors) | Individual | <$10,000 | Past | Consulting |
| | | Merck | Honoraria or royalties | Individual | $10,000–$100,000 | Past | Honoraria for lectures and webinars |
| Harry K Genant | University of California at San Francisco | Synarc | Ownership or partnership | Individual | >$100,000 | Current | Founder |
| | | Amgen, Lilly, Merck, Pfizer, GSK, Roche, Novartis, BMS, ONO, Janssen, Servier | Advisory board or board of directors | Individual | <$10,000 | Current | SAB member |
| Tet Sen Howe | Singapore General Hospital | GSK | Consulting fees (other than advisory board or board of directors) | Institution | $0 | Past | Consultant for Denosumab/GSK |
| Piet Geusens | University Hasselt, Belgium | | | | | | No past/current disclosures reported |
| Klaus Klaushofer | Hanusch Hospital, Ludwig Boltzmann Institute of Osteology | Eli Lilly | Other | Institution | >$100,000 | Current | Research cooperation with Ludwig Boltzmann Institute of Osteology based on institutional agreement |
| | | Roche | Other | Institution | <$10,000 | Current | Research cooperation with Ludwig Boltzmann Institute of Osteology based on institutional agreement |
| | | Amgen | Other | Institution | $10,000–$100,000 | Past | Research cooperation with Ludwig Boltzmann Institute of Osteology based on institutional agreement |
| | | MSD | Other | Institution | >$100,000 | Past | Research cooperation with Ludwig Boltzmann Institute of Osteology based on institutional agreement |
| Joseph M Lane | Hospital for Special Surgery | Zimmer | Advisory board or board of directors | Individual | $10,000–$100,000 | Current | Scientific Advisory Board |
| | | Graftys | Advisory board or board of directors | Individual | <$10,000 | Current | Scientific Advisory Board |
| | | CollPlant | Consulting fees (other than advisory board or board of directors) | Individual | <$10,000 | Current | Research and development |
| | | Bone Therapeutics, Inc. | Consulting fees (other than advisory board or board of directors) | Individual | <$10,000 | Current | Research and development |
| | | Eli Lilly | Honoraria | Individual | $10,000–$100,000 | Current | Speakers' bureau |
| | | Amgen | Honoraria | Individual | <$10,000 | Current | Speakers' bureau |

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| Name | Affiliation | Corporation/ organization | Role | Institution/ individual | Amount | Current or past 3 years | Comments |
|---|---|---|---|---|---|---|---|
| | | BioMimetics | Consulting fee | Individual | $10,000–$100,000 | Current | Research and development |
| | | Novartis | Honoraria or royalties | Individual | <$10,000 | Past | Speakers' bureau |
| Fergus McKiernan | Marshfield Clinic | Alexion | Research grants | Institution | $10,000–$100,000 | Current | Principal investigator |
| | | Amgen | Consulting fees (other than advisory board or board of directors) | Institution | <$10,000 | Past | Consultant |
| Ross McKinney | Duke University School of Medicine | Gilead Sciences | Other | Individual | <$10,000 | Current | Member of two data safety monitoring boards for Gilead Sciences studies. (DSMB member) |
| | | *American Journal of Bioethics* | Other | Individual | $0 | Current | Member of the editorial board of the *American Journal of Bioethics*, as well as its Conflict of Interest Committee |
| Alvin Ng | Singapore General Hospital | Servier | Honoraria or royalties | Individual | <$10,000 | Current | Speaker's honoraria and scientific meetings sponsorships |
| | | GSK | Honoraria or royalties | Individual | <$10,000 | Current | Speaker's honoraria and scientific meetings sponsorships |
| Jeri Nieves | Helen Hayes Hospital | Merck | Honoraria or royalties | Individual | <$10,000 | Past | One lecture given in Fall 2010; attended one advisory meeting in 2011 |
| | | Eli Lilly | Other | Individual | <$10,000 | Past | Attended women scientist dinner at ASBMR in 2010 and 2011 |
| Regis O'Keefe | University of Rochester | Amgen | Research grants | Institution | $10,000–$100,000 | Current | PI of research project |
| | | Roche Pharmaceuticals | Consultant in litigation for commercial entities | Individual | <$10,000 | Current | Consultant |
| Socrates Papapoulos | Leiden University Medical Center | Amgen/GSK | Advisory board | Individual | <$10,000 | Current | Advice on clinical studies |
| | | Amgen/GSK | Consulting | Individual | <$10,000 | Current | Consulting on clinical studies |
| | | Amgen/GSK | Honoraria or royalties | Individual | $10,000–$100,000 | Current | Speaking fees |
| | | Merck and Co. | Advisory board | Individual | <$10,000 | Current | Advice on clinical trials |
| | | Merck and Co. | Consulting | Individual | $10,000–$100,000 | Current | Consulting on clinical studies |
| | | Merck and Co. | Expert witness or consultant in litigation | Individual | $10,000–$100,000 | Current | Consulting in litigation |
| | | Novartis | Expert witness or consultant in litigation | Individual | $10,000–$100,000 | Current | Consulting in litigation |
| | | International Osteoporosis Foundation | Any other situation or in which you have a formal role | Individual | $0 | Current | Member Board of Trustees |
| | | International Osteoporosis Foundation | Any other situation or in which you have a formal role | Individual | $0 | Current | Committee scientific advisors |
| | | Eli Lilly | Honoraria or royalties | Individual | $10,000–$100,000 | Past | |
| | | Novartis | Honoraria or royalties | Individual | $10,000–$100,000 | Past | |
| | | Roche/GSK | Honoraria or royalties | Individual | $10,000–$100,000 | Past | |
| | | Warren Chilcott | Honoraria or royalties | Individual | $10,000–$100,000 | Past | |
| | | Wyeth | Honoraria or royalties | Individual | $10,000–$100,000 | Past | |
| Marjolein CH van der Meulen | Cornell University | *Journal of Orthopaedic Research* | Deputy editor | Individual | $0 | Current | |
| | | Johnson & Johnson | Stock holdings | Individual | $10,000–$100,000 | Current | |
| | | Novartis | Stock holdings | Individual | $10,000–$100,000 | Current | |
| | | Procter & Gamble | Stock holdings | Individual | $10,000–$100,000 | Current | |
| | | Orthopaedic Research Society | Secretary, board of directors | Individual | $0 | Current | |
| Robert S Weinstein | University of Arkansas for Medical Sciences | | | | | | No past/current disclosures reported |

*(Continued)*

(*Continued*)

| Name | Affiliation | Corporation/ organization | Role | Institution/ individual | Amount | Current or past 3 years | Comments |
|---|---|---|---|---|---|---|---|
| Michael P Whyte | Shriners Hospital for Children | Alexion Pharmaceuticals | Consulting | | <$10,000 | Current | |
| | | Alexion Pharmaceuticals | Research grants | Institution | >$100,000 | Current | |
| | | Amgen, Inc. | Research grants | Institution | $10,000–$100,000 | Current | |
| | | Merck | Stock holdings | Individual | $10,000–$100,000 | Current | |
| | | *Clinical Cases in Bone and Mineral Metabolism* | Other | Individual | $0 | Current | |
| | | *Journal of Clinical Densitometry* | Other | Individual | $0 | Current | |

## ASBMR Disclosures

The American Society for Bone and Mineral Research (ASBMR) is the premier professional, scientific and medical society established to promote excellence in bone and mineral research and to facilitate the translation of that research into clinical practice. The ASBMR has a hard-earned reputation for scientific integrity.

Most of the Society's revenue comes from membership dues, fees paid to attend the Society's annual meeting, and subscriptions to ASBMR publications. Like many scientific, professional, and medical organizations, ASBMR also accepts grants from pharmaceutical companies, the federal government, and other entities to support its mission. ASBMR receives corporate support in the form of unrestricted educational grants from pharmaceutical companies, rental of exhibit space at its annual meeting, and paid advertisements in its journal. To ensure that the Society adheres to the highest ethical practices, ASBMR has an ethics committee, consults with experts in health care ethics, and periodically reviews its practices with regard to managing potential conflict of interest.

Although task force members were required to disclose their potential conflicts of interest and their disclosures are published with this document, ASBMR recognizes that this might not go far enough to demonstrate to some that the final output of the task force is free of all bias. In an effort to address this concern, an ethicist knowledgeable about the musculoskeletal system who does not work directly on bone or BPs or with pharmaceutical companies who make or market BPs is a member of the task force and provided ethical oversight to the work of the task force. The ethicist has verified and attested to witness no commercial bias.

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