

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

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ABSTRACT

Reports linking long-term use of bisphosphonates (BPs) with atypical fractures of the femur led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address key questions related to this problem. A multidisciplinary expert group reviewed pertinent published reports concerning atypical femur fractures, as well as preclinical studies that could provide insight into their pathogenesis. A case definition was developed so that subsequent studies report on the same condition. The task force defined major and minor features of complete and incomplete atypical femoral fractures and recommends that all major features, including their location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete, and absence of comminution, be present to designate a femoral fracture as atypical. Minor features include their association with cortical thickening, a periosteal reaction of the lateral cortex, prodromal pain, bilaterality, delayed healing, comorbid conditions, and concomitant drug exposures, including BPs, other antiresorptive agents, glucocorticoids, and proton pump inhibitors. Preclinical data evaluating the effects of BPs on collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association with long-term BP use. Based on published and unpublished data and the widespread use of BPs, the incidence of atypical femoral fractures associated with BP therapy for osteoporosis appears to be very low, particularly compared with the number of vertebral, hip, and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been established. However, recent observations suggest that the risk rises with increasing duration of exposure, and there is concern that lack of awareness and underreporting may mask the true incidence of the problem. Given the relative rarity of atypical femoral fractures, the task force recommends that specific diagnostic and procedural codes be created and that an international registry be established to facilitate studies of the clinical and genetic risk factors and optimal surgical and medical management of these fractures. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Research directions should include development of animal models, increased surveillance, and additional epidemiologic and clinical data to establish the true incidence of and risk factors for this condition and to inform orthopedic and medical management. © 2010 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; BONE; PAIN; FRACTURE; ATYPICAL; SUBTROCHANTERIC; FEMORAL DIAPHYSIS; BISPHOSPHONATES

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Introduction

Reports of atypical femoral fractures, predominantly in patients receiving long-term bisphosphonates (BPs), led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address a number of key questions related to this disorder. Specifically, the task force was asked to

1. Make a recommendation for a provisional case definition of atypical femoral fractures so that subsequent studies report on the same condition.
2. Review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP usage.
3. Recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder.
4. Identify the key questions that the scientific community should address and recommend a research agenda to elucidate incidence, pathophysiology, and etiology of atypical femoral fractures and their potential relationship with BP usage.
5. Recommend clinical orthopedic and medical management of atypical femoral fractures based on available information.

This report summarizes the findings and recommendations of the task force.

Methods

The expert committee

The expert committee consisted of an international multidisciplinary group of 28 individuals with expertise in clinical and basic bone biology, endocrinology, epidemiology, radiology, biomechanics, and orthopedic surgery. The expert committee also included a basic scientist (TDB) working in the bone field but not in the areas of osteoporosis and BPs and a physician and bioethicist (RM) with expertise in conflict issues affecting biomedical researchers.

Review of the literature/data acquisition

A literature search using PubMed and OVID sought English-language articles with full text abstracts during the period January 1990 to April 30, 2010. The search terms specified included *atypical fracture, subtrochanteric fracture, femoral fracture, diaphyseal fracture, shaft fracture, cortical fracture, bilateral fracture, transverse fracture, low-energy fracture, spontaneous fracture, insufficiency fracture, stress fracture, bisphosphonates, antiresorptive, bone turnover, alendronate, pamidronate, etidronate, ibandronate, risedronate, zoledronate, zoledronic acid, Didronel, Actonel, Fosamax, Reclast, and Boniva*. The abstracts retrieved were reviewed by one coauthor (PRE) to assess their relevance to atypical fractures or long-term complications of BPs, and full text articles of each abstract selected were reviewed subsequently by four members of the

ASBMR task force in order to construct the relevant sections of this article. The numbers of subjects in each study; the age and sex of subjects; the specific BP(s) used (if any); the dose and duration of BP exposure; the clinical presentation; a prodrome of pain; the characteristics of the reported fracture(s); the level of trauma; the presence of either bilateral fractures or bilateral radiologic changes and comorbid conditions such as rheumatoid arthritis (RA) and diabetes (DM); the concomitant use of other antiresorptive drugs, glucocorticoids (GCs), or proton pump inhibitors (PPIs); the presence of vitamin D deficiency (<20 ng/mL); the presence of a bone mineral density (BMD) *T*-score greater than -2.5 (osteopenia or normal BMD); information on bone histology; management and outcome; and any other information were included, when available. Identification of case duplication between studies was achieved by cross-referencing studies whenever possible. The anatomic regions and locations of hip fractures are illustrated in Fig. 1.

Results and Discussion

Make a recommendation for a provisional case definition of atypical femoral fractures so that subsequent studies report on the same condition

Atypical femoral fractures are observed most commonly in the proximal one-third of the femoral shaft but may occur anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal femoral metaphysis. The fracture usually occurs as a result of no or minimal trauma, equivalent to a fall from a standing height or less. The fracture may be complete, extending across the entire femoral shaft, often with the formation of a medial spike (Fig. 2A). Complete atypical femoral fractures generally are transverse, although they may have a short oblique configuration, and are not comminuted. Alternatively, the fracture may be incomplete,

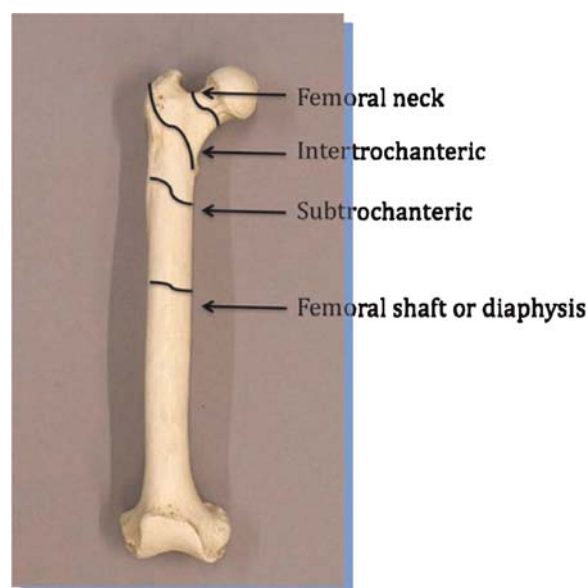


Fig. 1. Locations of common hip and femur fractures. (Courtesy of Thomas Einhorn, MD.)

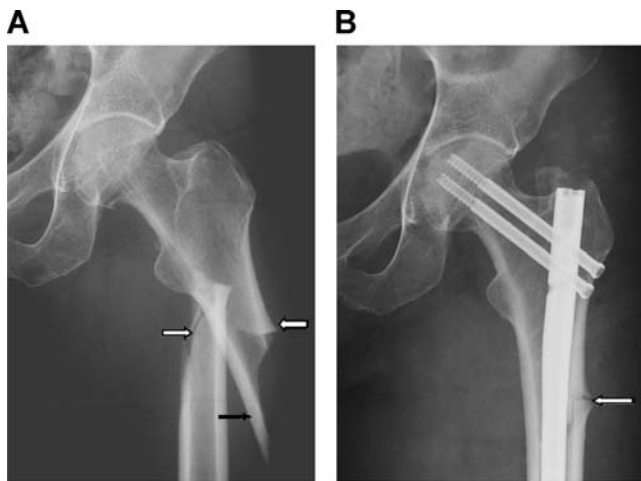


Fig. 2. Anteroposterior (AP) radiographs showing an atypical femoral shaft fracture (A) pre- and (B) postoperatively from the same individual. Note the oblique and transverse components (white arrows) and a medial “spike” (black arrow) on the preoperative view and the lateral, transverse, lucent fracture line and associated focal cortical thickening with a “beaked” appearance (arrow) on the postoperative view. (Courtesy of Thomas Einhorn, MD.)

manifested by a transverse radiolucent line in the lateral cortex. Both complete and incomplete fractures are commonly associated with a periosteal stress reaction and thickening of the lateral cortex at the fracture site (Fig. 2B), abnormalities indicative of a stress fracture. In addition, there may be generalized bilateral thickening of both the medial and lateral cortices. Either complete or incomplete atypical fractures may be bilateral. Healing of the fractures may be delayed. There are often prodromal symptoms such as a pain in the groin or thigh. Atypical fractures may be associated with a variety of comorbid conditions and the use of pharmaceutical agents. The diagnosis of atypical femoral fractures should specifically exclude fractures

of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with local primary or metastatic bone tumors, and periprosthetic fractures.

To assist in case finding and reporting, the task force defined major and minor features for complete and incomplete atypical fractures of the femur (Table 1). All major features should be present in order to designate a fracture as atypical and distinguish it from more common hip fractures (ie, femoral neck, intertrochanteric). Minor features commonly have been described in association with atypical fractures but may or may not be present in individual patients. Although atypical femoral fractures have been reported most prominently in individuals who have been treated with BPs, such fractures have been reported in individuals with no history of BP exposure. Therefore, to facilitate studies comparing the frequency of atypical femoral fractures in patients with and without BP therapy, association with BP therapy was included as a minor feature.

Review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP usage

The task force recognized that the incidence of atypical femoral fractures has come to medical attention principally in the setting of BP use and that the incidence in the general population not exposed to BPs is unknown. Although the association between BP use and atypical femoral fractures is consistent with a role for BPs, they have not been proven to be causal. To address this charge, the task force considered both preclinical and epidemiologic data, reviewed all case reports and series of atypical femoral fractures, and conducted interviews with physician and scientist representatives of pharmaceutical companies that market drugs for osteoporosis and the US Food and Drug Administration (USFDA).

Table 1. Atypical Femoral Fracture: Major and Minor Features^a

Major features^b

- 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^c
- 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, RA, hypophosphatasia)
- Use of pharmaceutical agents (eg, BPs, GCs, PPIs)

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

^bAll major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.

^cOften referred to in the literature as *beaking* or *flaring*.

Insights into the pathogenesis of atypical femoral fractures from basic studies

The radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures⁽¹⁾ and also may resemble that of pseudofractures.⁽²⁾ About 70% of patients with a confirmed stress fracture of the femur report prodromal pain for a period of weeks before the diagnosis. Radiographic features of stress fractures typically include a periosteal callus that appears hazy and indistinct initially and later solidifies. The periosteal callus is clear evidence of an attempt at repair prior to overt fracture and also occurs in atypical femoral fractures adjacent to the evolving fracture on the lateral cortex (Fig. 2B). Rats,^(3,4) rabbits,^(5,6) dogs,⁽⁷⁾ and horses^(8,9) all have been used to study stress fractures and, because of the similarities between stress fractures and atypical femoral fractures, could be useful models to study the pathogenesis of atypical femoral fractures.

Patients with atypical femoral fractures often also have a more generalized thickening of both the medial and lateral cortices bilaterally. This may be a normal genetically determined variant of femoral shape but has been observed often in those who have sustained an atypical femoral fracture. However, there is no evidence that BPs are associated with this more generalized cortical thickening because they are not known to stimulate periosteal apposition, nor do their antiremodeling effects lead to enhanced endosteal formation.

Atypical femoral fractures in patients on BPs have occurred in the setting of comorbid conditions with known adverse effects on bone quality (eg, DM).⁽¹⁰⁻¹³⁾ A relatively large proportion of patients also has taken GCs in addition to BPs. GCs reduce osteoblast activity, increase osteoblast apoptosis,⁽¹⁴⁻¹⁶⁾ and are also associated with osteonecrosis of the femoral head.^(14,17) In DM, high glucose levels cause the accumulation of advanced glycation end products (AGEs) that have been associated with an increased risk of fracture.⁽¹⁸⁾ In vitro⁽¹⁹⁾ and in vivo studies^(20,21) demonstrate that AGE accumulation increases the brittleness of bone.

BP effects on collagen. The organic matrix is the principal determinant of toughness, a measure of the intrinsic energy-absorption capacity of bone.⁽²²⁻²⁴⁾ Bone collagen contains both enzymatic and nonenzymatic collagen cross-links; both stabilize the matrix and have significant impact on the bone's mechanical properties. Enzymatic cross-links are first formed as immature divalent cross-links that are eventually converted to mature trivalent cross-links, pyridinoline (PYD), deoxypyridinoline (DPD), and pyrroles. Nonenzymatic cross-links are formed through the interaction of collagen and sugars via oxidation reactions. They are associated with the accumulation of AGEs in bone.

BPs are associated with both positive and negative effects on bone's organic matrix by altering both collagen maturity and cross-linking. Following 1 year of treatment with a wide range of BP doses, the PYD/DPD ratio was increased significantly in vertebral cancellous bone and tibial cortical bone from BP-treated dogs compared with untreated controls.^(20,21) An increased PYD/DPD ratio has been associated with increased strength and stiffness of bone,^(25,26) and subsequent mechanical analyses of vertebrae confirmed this in dogs. However, reducing bone turnover also increases pentosidine levels, a marker for

AGEs. AGEs are associated with tissue that is more brittle⁽²⁵⁾ and cause reductions in postyield deformation,^(19,26) energy to fracture,^(21,27) and toughness.⁽²⁰⁾ Indeed, tissue from both vertebral⁽²⁸⁾ and tibial⁽²¹⁾ bone from BP-treated animals was less tough than bone from animals not treated with BPs. Pentosidine levels also were increased in the ribs of dogs after 3 years of treatment with incadronate.⁽²⁹⁾ However, caution should be exercised when interpreting the results of these studies because they involved BP administration to normal rather than osteoporotic dogs.

There are limited data on collagen cross-links in humans treated with BPs. Using Fourier-transformed infrared spectroscopy (FTIR), Durchschlag and colleagues⁽³⁰⁾ showed that BP treatment prevented the maturation of collagen found in patients not treated with BPs and reduced collagen maturity in newly formed bone. Boskey and colleagues⁽³¹⁾ reported no change in collagen maturity in women treated with alendronate. Donnelly and colleagues⁽³²⁾ showed similar mean values but a narrowed distribution of collagen maturity and enzymatic cross-links in a small number of women with common proximal femoral fractures without features of atypia who had been treated with BPs for an average of 7 years.

BP effects on bone mineralization density distribution (BMDD). BMDD is a measure of the degree and heterogeneity of mineralization in bone tissue.⁽³³⁻³⁵⁾ In the healthy adult population, BMDD of cancellous bone shows only minor variations with age, gender, ethnicity, and skeletal site,⁽³⁶⁾ indicating that the normal BMDD corresponds to a biologic and mechanical optimum. Therefore, even small deviations from the normal BMDD may have biologic meaning. Because the effectiveness of bone in stopping cracks is directly proportional to the stiffness ratio across its internal interfaces, a homogeneous material will be less effective in slowing or stopping cracks initiated in the bone matrix, permitting cracks to grow more quickly to critical size and ultimately increase fracture risk.⁽³⁷⁾

BP treatment reduces bone turnover, increases overall mineralization, but leaves mineral particle shape, thickness, and orientation unaffected, narrows the BMDD, and increases bone strength and stiffness.^(33,34) BP effects on BMDD have been studied only in transiliac bone biopsies, so there is limited knowledge about their effects on cortical bone from other sites. However, Donnelly and colleagues^(38,39) have shown that the range of mineral distribution at the proximal femur is significantly narrower than that in the iliac crest and that postmenopausal women treated with BPs for an average of 8 years demonstrated substantially less tissue heterogeneity in terms of mineralization, crystal size, and crystal perfection than those who had not been treated. Cortical tissue seemed to be affected preferentially. Narrowing of the BMDD by BPs may be transient. After 5 to 10 years of BP treatment, BMDD was restored to within the normal premenopausal range.⁽⁴⁰⁻⁴³⁾

Effects of reducing remodeling on microdamage accumulation. Excessive bone remodeling results in microarchitectural deterioration and consequent loss of bone mass and strength and increased susceptibility to fragility fractures. BPs increase bone strength and decrease fracture risk by suppressing excessive bone remodeling. Reduction of remodeling, however,

is also associated with increased microdamage accumulation because cracks are not removed efficiently. Even in the absence of BP treatment, age-related reductions in bone turnover result in microdamage accumulation.⁽²⁸⁾ There is a threefold increase in damage accumulation in the vertebrae of dogs between 2 and 5 years of age that is associated with a 50% reduction in turnover.⁽²⁸⁾ Damage also accumulates significantly in humans with age, particularly after the age of 70 years,^(44,45) although there is broad interindividual variability in the amount. BPs may exacerbate damage accumulation because they impair targeted remodeling to a greater extent than remodeling not targeted to damage repair (ie, stochastic remodeling),^(46,47) thereby allowing microdamage to persist for longer compared with untreated bone. This accumulation of damage is nonlinear and increases more quickly the more that remodeling is suppressed.⁽⁴⁸⁾ However, marked reduction of turnover is not necessary to induce a significant accumulation of microdamage. Reducing trabecular bone activation frequency in the canine vertebra by approximately 40% with risedronate is associated with a threefold increase in microdamage compared with untreated controls,⁽⁴⁸⁾ and suppression by approximately 20% with raloxifene is associated with a doubling of microdamage.⁽⁴⁹⁾

Studies of iliac crest biopsies provide conflicting data about whether microdamage accumulates with BP treatment in humans. One study that evaluated women treated for an average of 5 years with alendronate showed significant microcrack accumulation in a subsample, but the study is inconclusive because the analyses of biopsies from the two different clinical sites associated with the study differed.⁽⁵⁰⁾ A second study did not find an association between BP treatment and damage accumulation in the iliac crest.⁽⁵¹⁾ Neither study evaluated samples from the femoral cortex, and because the accumulation of microdamage is site-specific, it is unknown whether damage accumulates in the cortex of the femoral diaphysis.

Effects of reducing remodeling on tissue mechanical properties. Not only is microdamage accumulation with BP treatment a function of reduced repair, but BP-treated bone also is more susceptible to increased crack initiation,⁽⁵²⁾ perhaps because AGE accumulation causes bone tissue to become more brittle. In one study, dogs were treated for 1 year with either risedronate or alendronate at doses equivalent to those used to treat postmenopausal osteoporosis.⁽⁵²⁾ Vertebrae then were removed and loaded cyclically in compression (5 Hz for 100,000 cycles at loads ranging from 100% to 300% of body weight); cracks were significantly more likely to initiate, but not necessarily to grow, in bone treated with alendronate than in those treated either with risedronate or with saline.⁽⁵²⁾

Preclinical studies show that treatment with BPs is associated with reduced bone toughness.^(48,53,54) Following 1 to 3 years of BP treatment at doses similar to or greater than those used in postmenopausal women, toughness was 20% to 30% lower than in control animals.^(48,53) It was thought initially that the decline in toughness was related to the well-documented accumulation of microdamage that was observed in lumbar vertebrae and other bones of dogs treated with BPs,^(48,54,55) although changes to both mineralization and collagen cross-linking also occur. More recent data show that toughness continues to decline in animals

with long-term BP treatment without an increase in microdamage accumulation or a further increase in secondary mineralization.⁽²⁸⁾ In a 1-year study using various doses of alendronate or risedronate, there was minimal correspondence between changes in microdamage accumulation and material-level toughness in vertebrae from several groups of BP-treated dogs.⁽⁴⁸⁾ Likewise, animals not treated with BPs have an age-related threefold increase in microdamage accumulation without a change in bone toughness.⁽²⁸⁾ These lines of evidence suggest that neither microdamage nor increased secondary mineralization is solely responsible for the change in bone material properties with BP therapy, leaving changes in collagen or interactions among all these properties as likely reasons for the progressive decline in toughness. However, the evidence also suggests that decreased remodeling is not solely responsible for reduced toughness, implicating a specific effect of BPs that is independent of reduced turnover.

The mechanical effect of BPs to decrease tissue toughness is countered by their capacity to increase bone mass and mineralization, promote collagen matrix maturation, and prevent microarchitectural deterioration of bone. These factors lead to increases in bone strength and stiffness that offset reduced toughness and make bone stronger at the structural level.

Affinity and retention of BPs in bone. The high affinity of BPs for bone mineral⁽⁵⁶⁾ and their long-term retention in bone⁽⁵⁷⁾ are of some concern because continued accumulation of BPs or persistent reduction of remodeling for prolonged treatment periods eventually could increase the risk of fracture, even in the face of increased bone mass. However, the toughness of the femoral diaphysis in nonosteoporotic dogs treated for as long as 3 years was not reduced, even with high doses of alendronate.⁽⁵⁸⁾ Moreover, cortical thickening, a feature of atypical femoral fractures, was not detected. In the absence of estrogen deficiency, the turnover rate in cortical bone has been estimated at approximately 3% per year,⁽⁵⁹⁾ based on biopsies from the rib, which is known to have a relatively high rate of turnover compared with other cortical bone sites. This is about one-tenth the rate of turnover in cancellous bone.⁽⁵⁹⁾ The turnover rate of the femoral diaphysis is undoubtedly even slower than cortical bone from the rib. In 5-year-old beagle dogs, which have cortical bone that is structurally very similar to human bone, the rate of turnover in the femoral cortex is about 1% per year,⁽⁵⁸⁾ very much like that found in cortical bone from the femoral neck.⁽⁶⁰⁾ While this slow turnover makes the possibility of oversuppression of cortical bone remodeling in the femur unlikely, it is possible that prolonged reduction of remodeling could have an additive effect over time, especially if BPs continue to accumulate in the tissue. This may be relevant to atypical femoral fractures, where case series suggest a potentially significant effect of duration of treatment and a median treatment period of 5 years, according to Giusti and colleagues,⁽¹¹⁾ and 7 years, according to the current review.

Effects of BPs on fracture healing. Stress fractures and acute fractures of long bones heal by different mechanisms. Complete fractures heal via endochondral ossification, with an initial inflammatory response and the formation of a cartilage callus. BPs do not impair the initial phases of fracture healing or the

development of a proliferative callus.^(61–63) They only slow the remodeling phase, delaying the remodeling of the calcified cartilage callus to mature bone. In contrast, stress fractures heal by normal bone remodeling, which is reduced by BP treatment. BPs in the form of technetium-99m are used for bone scintigraphy and localize at sites of high bone turnover, microdamage, and fractures.^(1,64) The localization of BPs at sites of stress injury would not affect periosteal callus formation but could compromise intracortical bone repair of the damage itself by lowering the activation of new remodeling even further. Consistent with this hypothesis, treatment with BPs during military training did not lower the risk for stress fractures.⁽⁶⁵⁾ Animal studies using repetitive ulnar loading in combination with BP treatment also show that prior alendronate treatment does not protect against a fatigue-related reduction in mechanical properties.⁽⁶⁶⁾ However, prior alendronate treatment did eliminate the adaptive remodeling response, suggesting that BP treatment could impair the healing response to a stress fracture. Therefore, it is possible that in the case of a developing stress fracture, reduction of bone remodeling would prevent or delay the repair of the stress reaction without suppressing the appearance of a periosteal callus and that this may result eventually in consolidation of the damage and a complete fracture of the stressed site.

Effects of BPs on angiogenesis. The effects of BPs on stress fracture repair could be exacerbated if BPs are also antiangiogenic. The periosteum of the femoral shaft is thick and highly vascularized.⁽⁶⁷⁾ An effective stress fracture healing response requires an increase in periosteal vascularity. Although some observations identify a direct suppression of vasculogenesis by BPs,⁽⁶⁸⁾ it can be difficult in bone to distinguish between inhibition of new vessel growth and suppression of osteoclastic activity because both are coupled. However, dissociation between the two is possible during skeletal development in animal models, and studies of growing animals showed no antiangiogenic effect of clodronate.⁽⁶⁹⁾ Still, primary studies in nonskeletal tissues suggest that angiogenesis indeed may be reduced by BPs over and above the normal reduction that would occur because of the absence of effective osteoclastic tunneling.⁽⁷⁰⁾ Interestingly, in a rat model of stress fracture, there is upregulation of vascular endothelial growth factor (VEGF) mRNA within 1 to 4 hours of initiation of the stress fracture^(71,72) and upregulation of osteogenic genes in the cambium layer of the periosteum within 3 days. Early upregulation of interleukin 6 (IL-6) and IL-11 suggest the importance of remodeling in stress fracture healing.⁽⁷²⁾ These responses may well be coordinated, and any agent that suppresses angiogenesis could inhibit the repair of an impending stress fracture.

Summary of preclinical studies. The preclinical data provide a mixed picture of the effects of BPs on bone's matrix composition and mechanical properties. BPs reduce bone remodeling, preventing the loss of bone and deterioration of cancellous microarchitecture that accompany it. By reducing the number of new remodeling sites, BPs increase bone density, mineralization, and strength. Increases in fully mature collagen cross-links further contribute to the increased strength and stiffness

associated with these other changes. However, at the same time, lowering of remodeling by BPs allows the accumulation of microdamage and increases the formation of AGEs, both of which reduce tissue toughness or the energy-absorbing capacity of bone tissue. Reduced remodeling also increases the homogeneity of the bone tissue, which could permit further damage accumulation, although this effect may be transient and not associated with long-term BP use. However, changes that reduce energy-absorbing capacity may be particularly significant if a person sustains a low-energy impact such as a fall. Reduced remodeling may impair the healing of a stress fracture without altering the callus bridging that is the adaptation to and accompanies the stress fracture itself. Reduced angiogenesis would contribute to this delay in healing. While the preclinical studies reviewed here provide some insights regarding the possible pathogenesis of atypical femoral fractures, additional studies are required to identify potential pathogenic mechanisms that involve pathologic changes to bone matrix (Table 2), and animal models that more accurately mimic atypical fractures need to be developed.

Epidemiology of Subtrochanteric and Femoral Shaft Fractures

General epidemiology of subtrochanteric and femoral shaft fractures. Fractures located in the subtrochanteric region or femoral shaft (diaphysis) account for 7% to 10% of all hip/femoral diaphyseal fractures.^(73,74) Approximately 75% of complete subtrochanteric and femoral shaft fractures are associated with major trauma such as motor vehicle accidents,⁽⁷³⁾ in which the energy transmitted to the bone results in the propagation of multiple fracture lines, thus producing comminution. Especially in older patients, femoral shaft fractures may occur below the stem of the prosthesis after total hip replacement.⁽⁷⁵⁾ In adults of all ages, more than half of femoral shaft fractures are spiral fractures, with the remainder presenting with a transverse or oblique configuration.^(73,76)

Subtrochanteric fractures have important effects on mortality and morbidity. A study of 87 patients with subtrochanteric fractures showed a mortality rate of 14% at 12 months and 25% at 24 months. Moreover, by 24 months, almost half had not achieved their prefracture functioning in terms of walking and performing other activities of daily living. In addition, many (71%) were unable to live in conditions similar to those before the

Table 2. Possible Pathogenetic Mechanisms Associated With Atypical Subtrochanteric Femoral Fractures

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- Alterations to the normal pattern of collagen cross-linking
 - Changes to maturity of cross-links formed by enzymatic processes
 - Advanced glycation end-product accumulation
 - Microdamage accumulation
 - Increased mineralization
 - Reduced heterogeneity of mineralization
 - Variations in rates of bone turnover
 - Reduced vascularity and antiangiogenic effects
-

fracture.⁽⁷⁷⁾ These outcomes are similar to long-term outcomes for people with femoral neck fractures.^(78–81)

A comprehensive review of 6409 femoral shaft fractures in Swedish inpatients showed a bimodal age distribution of incidence in both males and females,⁽⁸²⁾ similar to that reported by Singer and colleagues.⁽⁸³⁾ The age-specific incidence rates (per 100,000) for subtrochanteric fractures increased between the 65- and 85-year categories in both males and females in Iran,⁽⁸⁴⁾ in the United States,⁽⁸⁵⁾ and in the United Kingdom.⁽⁸⁶⁾ Although femoral shaft fractures were more common among males than among females up to age 49, this gender difference was reversed in the 60- to 69-year age group.⁽⁸²⁾ Thus subtrochanteric fractures share features of typical osteoporosis-related fractures, including (1) higher incidence among women than among men, (2) a steep increase in incidence with age, and (3) more common occurrence in the elderly after low-energy trauma.^(82,87–89) The number of admissions for femoral shaft fractures was unchanged from 1998 to 2004 in Sweden⁽⁸²⁾ and from 1996 to 2006 in the United States.⁽⁷⁴⁾

The epidemiology of femoral neck and trochanteric and intertrochanteric hip fractures was compared with that of subtrochanteric and femoral shaft fractures in the United States among people 50 years of age and older using both the National Hospital Discharge Survey from 1996 to 2006 and MarketScan, a large medical claims database, from 2002 to 2006.⁽⁷⁴⁾ In women, hospital discharge rates of hip fracture (femoral neck and trochanteric and intertrochanteric regions) decreased from about 600 per 100,000 to 400 per 100,000 person-years in the decade after 1996. In contrast, subtrochanteric and femoral shaft fracture rates did not change, with an annual incidence of less than 30 per 100,000 person-years.⁽⁷⁴⁾ These findings confirmed that hip fracture incidence has declined since BPs were approved for use, whereas subtrochanteric and femoral shaft fractures have remained stable. Another US study of hospitalizations between 1996 and 2007 for hip (ie, femoral neck, intertrochanteric) and subtrochanteric fractures confirmed that femoral neck/intertrochanteric fractures declined by 12.8% (263,623 in 1996 to 229,942 in 2007).⁽⁹⁰⁾ However, in contrast to the study by Nieves and colleagues,⁽⁷⁴⁾ subtrochanteric fractures increased from 8273 to 10,853 over the same period.⁽⁹⁰⁾ Neither study could ascertain specific radiologic features of atypia discussed in the case series.^(74,90)

Recent data from the Study of Osteoporotic Fractures (SOF), a prospective population-based US study of 9704 white women 65 years of age and older followed for as long as 24 years indicate that the incidence of subtrochanteric fractures is very low (3 per 10,000 person-years) compared with the overall incidence of hip fracture (103 per 10,000 person-years).⁽⁹¹⁾ After excluding high-energy, pathologic, and periprosthetic fractures, 48 subtrochanteric fractures occurred in 45 women (3.4% of hip fractures), 9 of whom received BPs. Predictors of subtrochanteric hip fracture were older age, lower total hip BMD, and a history of falls. In multivariate models, only increasing age remained significant. Predictors of femoral neck fracture were similar in this largely BP-naive group. Since fracture radiographs were not available, features of atypia were not ascertained. However, in 33 of the 45 women from the SOF with subtrochanteric fractures, baseline pelvis radiographs were available. When compared with 388 randomly selected controls, women with the thickest medial femoral shaft cortices were at lower risk of subtrochanteric and

femoral neck fracture than those with the thinnest cortices.⁽⁹²⁾ Although lateral cortical thickening is described commonly in patients with atypical fractures, thickness of the lateral cortex was not related to fracture risk. Since only 6 women in the subset with pelvic radiographs had taken BPs, more data are required on the role of cortical thickness in atypical femoral fractures in BP users.

Subtrochanteric and femoral shaft fractures and BP use. In a retrospective case-control study of postmenopausal women,⁽⁹³⁾ 41 cases of low-trauma subtrochanteric and femoral shaft fractures were identified and matched by age, race, and body mass index (BMI) to one intertrochanteric and one femoral neck fracture patient who presented during the same time period (2000–2007). BP use was documented in 15 of the 41 (37%) subtrochanteric and femoral shaft fracture patients compared with 9 of the 82 (11%) intertrochanteric and femoral neck fracture patients, resulting in an odds ratio (OR) of 4.44 [95% confidence interval (CI) 1.77–11.35]. Long-term BP use was more likely and duration of BP use was longer in subtrochanteric and femoral shaft fracture patients than in both hip fracture control groups ($p = .001$). Radiographs showed fractures with a transverse or oblique orientation, cortical thickening, and localized diffuse bone formation on the lateral cortex in 10 of the 15 fracture patients on a BP and in 3 of 26 fracture patients who were not taking a BP (OR = 15.33, 95% CI 3.06–76.90, $p < .001$).

In a cross-sectional study of 11,944 Danish people over age 60, Abrahamsen and colleagues⁽⁹⁴⁾ compared age-specific fracture rates and BP exposure in various kinds of proximal femur fractures identified by International Classification of Diseases (ICD)-10 codes. Alendronate exposure was the same in patients with subtrochanteric fractures (ICD-10, S72.2; 6.7%), femoral diaphyseal fractures (S72.3; 7.1%), and the more common femoral neck (S72.0) and intertrochanteric fractures (S72.1; both 6.7%). They tested the hypothesis that increased risk of subtrochanteric and femoral shaft fractures in patients treated with alendronate exceeded the increased risk of femoral neck and intertrochanteric fractures. Each patient who received alendronate for at least 6 months ($n = 5187$) was matched with two controls ($n = 10,374$). In this register-based matched-cohort study, the hazard ratio (HR) for subtrochanteric or diaphyseal fracture with alendronate was 1.46 (95% CI 0.91–2.35, $p = .12$), similar to the hazard ratio of 1.45 (95% CI 1.21–1.74, $p < .001$) for femoral neck and intertrochanteric fractures; both estimates were adjusted for comorbidity and concurrent medications. Patients with subtrochanteric and diaphyseal fractures were no more likely to be on alendronate but were more likely to use oral GCs than those with typical hip fractures.

In another national register-based Danish cohort study, 4854 patients without prior hip fracture were followed for a mean of 6.6 years after starting alendronate; data also were obtained from a large matched-cohort analysis of 31,834 alendronate users and 63,668 comorbidity-matched controls over a mean follow-up period of 3.5 years.⁽⁹⁵⁾ The overall incidence of subtrochanteric and diaphyseal fractures did not differ between patients in the lowest quartile of cumulative alendronate use (mean 0.2 dose-years) and those in the highest quartile of use (mean 8.7 dose-years), 4.7 per 1000 versus 3.1 per 1000, respectively. In contrast,

there was a decline in femoral neck/intertrochanteric hip fracture incidence with increasing dose-years of alendronate from lowest (22.8 of 1000) to highest quartile (10.9 of 1000). The hazard ratio for subtrochanteric/diaphyseal fracture with alendronate was 1.50 (95% CI 1.31–1.72) compared with 1.29 (95% CI 1.21–1.37) for femoral neck/intertrochanteric hip fracture. Although rates of all fractures were higher in alendronate users than in nonusers, highly compliant patients had significantly lower risk of femoral neck/intertrochanteric fractures (HR = 0.47, 95% CI 0.34–0.65) and subtrochanteric/diaphyseal fractures (HR = 0.28, 95% CI 0.12–0.63).⁽⁹⁴⁾ Furthermore, in a small subset of persons who remained highly compliant long term (>6 years), subtrochanteric/diaphyseal fractures comprised 10% of fractures compared with 12.5% in the control cohort. Consistent with these results, data from another Danish cohort suggest that the risk of subtrochanteric/diaphyseal fractures and all fractures is present before BP initiation.⁽⁹⁶⁾

In summary, the Danish data indicate no greater risk for a subtrochanteric or diaphyseal femoral fracture in alendronate-treated patients than for an osteoporosis-related fracture of any part of the femur (including the hip).^(94,95) Studies of this type provide important broad and contextual data on the epidemiologic characteristics and incidence of subtrochanteric and diaphyseal femoral fractures. However, there is no adjudication of radiographs, and thus they cannot provide specific information on the clinical and radiographic features of the atypical fractures described in case reports and series versus the more typical fractures seen at the same sites.

No cases of subtrochanteric fractures were reported in preclinical studies or placebo-controlled registration trials of oral BPs involving more than 17,000 patients. However, the maximum duration of BP exposure for most subjects in these trials was less than 4 years. Recently, however, Black and colleagues⁽⁹⁷⁾ reported a secondary analysis of three large randomized clinical trials of BPs, two of oral alendronate, the Fracture Intervention Trial (FIT) and its long-term extension (FLEX), and one of zoledronate (HORIZON-PFT). FIT randomized women to alendronate or placebo for 3 to 4.5 years. In FLEX, 1099 women originally randomized to alendronate were rerandomized to alendronate 5 or 10 mg/day or placebo. The total duration of alendronate was 10 years for those randomized to alendronate and 5 years for those randomized to placebo. In the HORIZON trial, 7736 women were randomized to zoledronate 5 mg or placebo and followed for 3 years. All 284 hip and femur fractures were reevaluated to identify femoral shaft fractures and assess features of atypia. However, the reevaluation was based on the radiographic report because radiographs were available for only one subject. Twelve subtrochanteric/diaphyseal fractures (4%) were found in 10 subjects, 3 of whom had not received BPs. The relative hazard ratios of alendronate versus placebo were 1.03 (95% CI 0.06–16.5) in FIT and 1.33 (95% CI 0.12–14.7) in FLEX. The relative hazard ratio of zoledronate versus placebo was 1.5 (95% CI 0.25–9.0). The authors concluded that the risk of subtrochanteric/diaphyseal fracture was not significantly increased, even among women treated for as long as 10 years. Although the FLEX data that compare 5 and 10 years of alendronate treatment provide some reassurance regarding reported associations of subtrochanteric/diaphyseal fracture with long-term BP treatment, this study had a number of very important limitations.⁽⁹⁸⁾ Radiographs were not available to evaluate features of atypia.

Only a minority received more than 4 years of BP, and some received a lower dose of alendronate (5 mg) than commonly prescribed. Most important, because of the rarity of these fractures, statistical power was extremely low.

Preliminary data are now available on the incidence of atypical femoral fractures from a large US health maintenance organization (HMO) that serves 2.6 million people over age 45.⁽⁹⁹⁾ Using electronic data sources, 15,000 total hip and femur fractures were identified by both ICD-9 and Current Procedural Terminology (CPT) coding in patients older than 45 years over a 3-year period between 2007 and 2009. After excluding fractures above the subtrochanteric region and below the distal femoral flair and periprosthetic, pathologic, and high-trauma fractures, 600 radiographs were reviewed, of which 102 (~17%) had features of atypia (ie, transverse fracture with short oblique extension medially, cortical thickening, periosteal callus on the lateral cortex). Most (97 of 102) patients had taken a BP. Based on the number of patients receiving BPs in the HMO, preliminary estimates of atypical femoral fracture incidence increased progressively from 2 per 100,000 cases per year for 2 years of BP use to 78 per 100,000 cases per year for 8 years of BP use. These data suggest that atypical femoral fractures are rare in both the general population and BP-treated patients, but their incidence may increase with increasing duration of BP exposure. However, there was no age-matched control group of patients who did not use BPs, and it is possible that the incidence of all fractures in women at this age would increase over 6 years. Important strengths of this study include the expert adjudication of all 600 radiographs of the region of interest and availability of data on filled prescriptions for oral BPs.

Summary of epidemiologic studies. It is important not to equate the anatomic entity of subtrochanteric/diaphyseal femoral fracture with that of atypical femoral fractures. In addition to location, the latter diagnosis should include all other major features outlined in the case definition (Table 1). The interest in subtrochanteric and diaphyseal fractures in an epidemiologic context is that the total number of these fractures marks the upper boundary of any potential harm owing to atypical femoral fractures. Notably, subtrochanteric and diaphyseal fractures together account for only about 5% to 10% of all hip/femoral fractures; of these, only a subset is atypical (17% to 29%). The proportion of subtrochanteric and diaphyseal fractures that have features of atypia depends on whether fractures owing to high-impact trauma or periprosthetic fractures are excluded and varies in the different patient series from 17%⁽⁹⁹⁾ to 29%.⁽¹⁰⁰⁾ It is this subset of fractures that has been associated with the use of BPs, an association that may or may not be causal. It is also important to note that atypical fractures have been reported in patients who have not been exposed to BPs. This occurred in 3 of the 8 patients with atypical fragility fractures of the femur reported by Schilcher and colleagues,⁽¹⁰¹⁾ in 1 of 20 patients in the Neviasser case series,⁽¹⁰⁰⁾ in 5 of 102 patients reported by Dell and colleagues,⁽⁹⁹⁾ in 1 of 4 patients reported by Bunning and colleagues,⁽¹⁰²⁾ and in 3 of 26 patients in the Lenart study,⁽⁹³⁾ as well as in patients with hypophosphatasia.^(2,103)

Epidemiologic studies show that fractures of the subtrochanteric region of the femur and the femoral shaft follow an age and

sex distribution similar to osteoporotic fractures. However, decreases in age-specific hip fracture rates in the community have not been accompanied by decreases in the rates of subtrochanteric or diaphyseal femoral fractures despite similarities in epidemiology and an association with BMD. While register-based studies provide useful information on the prevalence and incidence of subtrochanteric/diaphyseal fractures, it is important to recognize that these studies rely on diagnostic codes for case finding that may misclassify fracture location⁽¹⁰⁴⁾ and do not assess the radiologic hallmarks of atypia. Thus a stable total number of subtrochanteric fractures potentially could mask a shift from typical osteoporotic subtrochanteric fractures toward more atypical fractures, as might be suggested by Dell's results⁽⁹⁹⁾ and those reported by Wang and Bhattacharyya.⁽⁹⁰⁾

If BPs are targeted to patients with a fracture risk similar to that in FIT,⁽¹⁰⁵⁾ using alendronate in women without baseline vertebral fractures, about 700 nonvertebral and 1000 clinical vertebral fractures would be avoided per 100,000 person-years on treatment. In women with prior vertebral fractures, the corresponding numbers are 1000 and 2300.⁽¹⁰⁶⁾ Based on the assumption that up to one in three subtrochanteric fractures is atypical, these numbers are 13 and 29 times higher, respectively, than the 78 per 100,000 incidence figure reported by Dell and colleagues⁽⁹⁹⁾ and 10 and 23 times higher, respectively, than the highest estimate of the rate of atypical subtrochanteric/diaphyseal fractures of 100 per 100,000 in long-term users of alendronate from the Danish study.⁽⁹⁵⁾ Thus the risk-benefit ratio clearly favors BP treatment in women at high risk of fracture.

Atypical subtrochanteric and femoral shaft fractures:

Clinical data

In its review of published case reports and series as described in "Methods," the task force recognized that the quality of the evidence reported in a substantial proportion was poor, with missing important historical or clinical information. The task force recommends that a hierarchy of data quality should be established for all future studies reporting cases of atypical femoral fractures. The data quality for a case would be based on the quality in seven areas, as indicated in Tables 3 and 4.

Case series and case reports. The total number of reported cases was 310 after overlapping case reports had been excluded (Table 5); 286 cases occurred in association with BP treatment for osteoporosis and 5 in patients with BP treatment for malignancy (ie, myeloma or metastatic renal cell carcinoma). In 19 cases, BP use was not identified. The subjects ranged in age from 36 to 92 years. Only nine fractures were in men, but gender was not identified in three large case series.^(100,107,108) The majority (160 of 189) occurred after oral alendronate monotherapy: 12 patients were treated with oral risedronate (of these, 1 was followed by oral alendronate, whereas 2 were treated previously with alendronate and another was treated previously with pamidronate), 4 with a combination of intravenous pamidronate followed by intravenous zoledronic acid (myeloma), 4 with either oral or intravenous pamidronate (osteoporosis), 2 with intravenous zoledronic acid (renal cell carcinoma and osteoporosis), 2

Table 3. Hierarchy of Data Quality for Atypical Femoral Fractures

The quality of evidence should be assessed for the following key areas:

1. Patient characteristics
 - a. Age
 - b. Gender
2. Description of atypical subtrochanteric and femoral shaft fracture
 - a. Location in femoral shaft from just distal to the lesser trochanter to just proximal to the supracondylar flare of the distal femoral metaphysis
 - b. Presence of transverse or short oblique configuration of fracture
 - c. Low level of trauma
 - d. Noncomminuted
 - e. Presence of thickened cortices with or without a periosteal callus
3. Bisphosphonate exposure history
 - a. Specific drug(s)
 - b. Specific dose history
 - c. Duration of and adherence to therapy before diagnosis of fracture
4. Bisphosphonate therapy indication
 - a. Disease (osteoporosis, osteopenia, myeloma, etc.)
 - b. History of prior low-trauma fracture
5. Comorbid conditions
 - a. Presence of vitamin D deficiency (<20 ng/mL)
 - b. Presence of other comorbid conditions
 - RA
 - Other diseases requiring corticosteroids
 - Diabetes
 - Cancer
 - Hypophosphatasia
6. Concomitant medication history
 - a. Identity of concomitant medications, including
 - Glucocorticoids
 - Proton pump inhibitors
 - Other antiresorptive drugs (eg, estrogen, raloxifene, calcitonin, denosumab)
 - b. Doses of concomitant medications and duration of therapy prior to subtrochanteric fracture
7. Investigations
 - a. Bone densitometry
 - b. Bone turnover markers
 - c. Bone histomorphometry, including an assessment of bone turnover

with oral alendronate followed by oral ibandronate, and 102 with an unspecified oral BP.

The duration of BP therapy ranged from 1.3 to 17 years, although duration was not identified in 1 patient. The median duration was 7 years. The presence or absence of prodromal pain was assessed in 227 of 310 patients; it was present in 70% (158 of 227). Concomitant GC use was assessed in 76 of 310 patients; it was present in 34% (26 of 76) and increased the risk of subtrochanteric fractures in one large series (OR = 5.2).⁽¹⁰⁷⁾

Table 4. Classification of Data Quality

The overall hierarchy of evidence quality for a case would be based on the quality of these seven areas:

Best evidence:

Information complete for all seven categories

Good evidence:

Information complete for categories 1–5, 6a, and 7a

Acceptable evidence:

Information complete for categories 1–4, but 5, 6a, and 7a not all complete

Marginal evidence:

Information complete only for categories 2a and 3a

Insufficient evidence:

Information unavailable for categories 2a, 3a, and 4a regardless of other information provided

Bilateral fractures were assessed in 215 of the 310 patients and were present in 28% (60 of 215). Bilateral radiologic changes were assessed in 224 of the 310 patients and were present in 28% (63 of 224). Healing was assessed in 112 of the 310 patients and was reported to be delayed in 26% (29 of 112).^(13,102,109–119) In one large series, other historical risk factors associated with subtrochanteric fractures were a prior low-trauma fracture (OR = 3.2), age younger than 65 years (OR = 3.6), and active RA (OR = 16.5).⁽¹⁰⁷⁾ PPI use was assessed in 36 of the 310 patients and was noted in 14 (39%).^(112,119–121)

Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured in 84 patients, and 5 (6%) had vitamin D deficiency [25(OH)D < 20 ng/mL]. In one large series, serum 25(OH)D concentrations of less than 16 ng/mL increased the risk of subtrochanteric fractures (OR = 3.2).⁽¹⁰⁷⁾ Of the 67 patients who had bone densitometry recorded, 45 (67%) had osteopenia or normal BMD.

Relatively few reports included bone turnover markers (BTMs).^(13,109,113–116,122,123) When measured, however, bone resorption markers are usually within the normal premenopausal range^(109,114–116,123,124) and occasionally are elevated.^(114,115,122) In only a minority of cases have BTMs been suppressed.^(13,109,116) Thus BTMs, at least when measured after atypical femoral fractures have occurred, do not suggest oversuppression of bone turnover in the majority of patients. However, since fractures per se are associated with increased BTMs, measurements obtained after a fracture may reflect fracture healing rather than the rate of bone remodeling throughout the skeleton. BTM determination prior to the fracture would be more informative.

Summary of case series and case reports. Several case series and multiple individual case reports suggest that subtrochanteric and femoral shaft fractures occur in patients who have been treated with long-term BPs. However, these fractures also may occur in BP-naïve patients. Several unique radiographic and clinical features have emerged from these case reports and series. All the individual case reports of atypical femoral fractures^(118,119,122,125–129) illustrate one or more radiographic features suggestive of a fracture distinct from the common osteoporosis-, prosthesis-, or major trauma-related fractures.

These include lack of precipitating trauma,^(118,122,127) bilaterality (either simultaneous or sequential),^(118,119,122,129) transverse fractures,⁽¹²⁷⁾ cortical hypertrophy or thickness,⁽¹¹⁸⁾ stress reaction on the affected and/or unaffected side,^(118,122,125,127,129) and poor fracture healing.^(118,128) Other features include prodromal pain in the thigh or groin for weeks or months prior to the fracture,^(118,122,127) use of an additional antiresorptive agent (eg, estrogen, raloxifene, or calcitonin), use of GCs or PPIs in addition to the BP,^(118,119,125) presence of RA or DM, serum 25(OH)D concentrations less than 20 ng/mL, and normal or low BMD but not osteoporosis in the hip region.^(13,115,119) Several reports describe iliac crest biopsies with very low bone turnover rates (Table 6); however, this is not a distinguishing feature of patients with atypical fractures on BPs because even short-term use of a BP results in dramatic reductions in rates of bone turnover.^(119,130) BTMs have not shown any consistent pattern but are often not suppressed. In sharp contrast to prior experience with osteonecrosis of the jaw,⁽¹³¹⁾ the number of cases of atypical fracture reported in cancer patients receiving high-dose intravenous BPs is substantially lower than those in patients being treated for osteoporosis. Whether this is a reporting bias remains to be seen. However, if true, this would argue against a simple causal relationship with the amount of BP received and perhaps suggests that duration may be more important than amount.

Guisti and colleagues conducted a systematic review of 141 women with postmenopausal osteoporosis treated with BPs who sustained subtrochanteric/diaphyseal fractures.⁽¹¹⁾ Their results are generally comparable with this task force report with regard to age, mean duration of BP use, proportions with bilateral fractures, prodromal pain, comorbid conditions (ie, DM or RA), and concomitant use of estrogen, raloxifene, tamoxifen, and GCs. They also reported that patients with subtrochanteric versus femoral shaft fractures had a higher number of comorbid conditions, were more likely to have bilateral fractures, and were more often using PPIs. Patients who had used BPs for less than 5 years were more likely to be Asian and to have had a femoral shaft fracture prior to initiating BP therapy.⁽¹¹⁾

It is highly likely that case reports and case series of atypical femur fractures will continue to accumulate. In this regard, abstracts submitted to the 2010 Annual Meeting of the ASBMR^(132–136) reported another 47 cases not included in this analysis. Many physicians who treat substantial numbers of patients with osteoporosis have described additional cases anecdotally, the majority of which are unlikely to be published. Similarly, cases may not be reported owing to lack of recognition by clinicians. Thus there is concern that the reported cases represent a minority of the actual number of cases that exist.

Bone histology and histomorphometry. A substantial number of the case studies have included histomorphometric analysis of iliac crest bone biopsies (Table 6). However, only a few reports have included histology or histomorphometry of bone taken from or close to the subtrochanteric fracture site. Iliac crest biopsies generally have revealed extremely low bone turnover, a finding consistent with BP treatment,^(137–139) especially in patients treated concomitantly with a BP and another antiresorptive agent, such as estrogen,⁽¹⁴⁰⁾ or with BPs and GCs.⁽¹⁴¹⁾

Table 5. Case Series and Reports of Atypical Fractures

Author/date/reference	Number of patients	Age (range)	Gender (M/F)	BP exposure	BP duration (years)	Bilateral fractures/radiographic changes (n)	Prodrome (n)	Oral GCs (n)	Serum 25 (OH)D < 20 ng/mL (n/available)	Hip T-score > -2.5 (n/available)
Goh, 2007 ⁽¹⁰⁾	9	55-71	0M/9F	9 ALN	2.5-5	1/3 (thick cortex)	5	1	NA	5/5
Kwek, 2008 ⁽¹²⁾	17 ^a	55-77	0M/17F	16 ALN, 1 ALN > RIS	2-10	4/5	13	1	NA	8/12
Neviaser, 2008 ⁽¹⁰⁰⁾	19 ^b	NA	NA	19 ALN	Mean 6.9 (in 10 patients)	NA/NA	NA	NA	NA	NA
Wernecke, 2008 ⁽¹²³⁾	1 ^c	72	0M/1F	ZA > PAM	11	1/0	1	0	NA	1
Odvina, 2005 ⁽¹¹⁶⁾	5	52-68	1M/4F	5 ALN	3-8	2/NA	NA	2	None (range 28-180)	3/3
Odvina, 2010 ⁽¹¹⁵⁾	11	38-77	0M/11F	9 ALN 2 RIS	2-11	3/NA	5	4	2/9 (range 17.0-33.0)	5/8
Visekruna, 2008 ⁽¹³⁾	3	51-75	0M/3F	3 ALN	5-10	2/NA	2	3	None (range 32-48)	3
Somford, 2009 ⁽¹¹⁹⁾	1	76	0M/1F	ALN	8	1/0	1	1	1 (16.8)	1
Demiralp, 2007 ⁽¹²⁵⁾	1	65	0M/1F	ALN	7	1/0	1	1	NA	0
Armamento-Villareal, 2009 ⁽¹⁰⁹⁾	7	43-75	1M/6F	6 ALN 1 RIS	2-10	2/NA	NA	0	(30.6)	4/5
Lee, 2007 ⁽¹⁷⁰⁾	1	73	0M/1F	ALN	1.6	0/1 (thick lateral cortex)	1	0	None (24)	1
Schilcher, 2009 ⁽¹⁰¹⁾	5	>75	0M/5F	NA	3.5-8.5 (mean 5.8)	1/NA	NA	NA	NA	NA
Ing-Lorenzini, 2009 ⁽¹¹²⁾	8	57-86	1M/7F	5 ALN 1 RIS > ALN 1 ALN > IBN 1 PAM	1.3-10.3	4/3 (thick lateral cortex)	2	3	NA	3/4
Schneider, 2006 ⁽¹¹⁸⁾	1	59	0M/1F	ALN	7	0/0	1	NA	NA	1
Sayed Noor, 2008 ⁽¹¹⁷⁾	1	72	0M/1F	ALN	7	0/1 (thick cortex with local lateral cortical reaction)	1	NA	NA	NA
Sayed Noor, 2009 ⁽¹²⁸⁾	2	55-78	0M/2F	2 ALN	9	0/1 (cortical hypertrophy with lateral cortical reaction)	2	0	NA	NA
Goddard, 2009 ⁽¹⁷¹⁾	1	67	0M/1F	ALN > IBN	17	1/0	0	0	NA	NA
Cheung, 2007 ⁽¹²²⁾	1	82	0M/1F	ALN	10	1/0	0	0	"Normal"	1
Bush, 2008 ⁽¹⁴⁵⁾	1	61	1M/0F	ZA	1.5	0/1 (thick diaphyseal cortex)	0	0	NA	NA
Capeci, 2009 ⁽¹¹⁰⁾	7	53-75	0M/7F	7 ALN	5-13	3/4 (cortical stress reaction)	4	NA	0/3 (21-39)	NA

(Continued)

Table 5. (Continued)

Author/date/reference	Number of patients	Age (range)	Gender (M/F)	BP exposure	BP duration (years)	Bilateral fractures/radiographic changes (n)	Prodrome (n)	Oral GCs (n)	Serum 25 (OH)D < 20 ng/mL (n/available)	Hip T-score > -2.5 (n/available)
Husada, 2005 ⁽¹²⁹⁾	1	72	0M/1F	ALN	NA	1/0	1	NA	NA	NA
Edwards, 2010 ⁽¹⁷²⁾	1	60	0M/1F	ALN	6	1/1	1	1	NA	1
Cermak, 2009 ⁽¹¹¹⁾	3	59-70	0M/3F	ALN	5.5-12	1/1	2	0	NA	NA
Ali, 2009 ⁽¹⁷³⁾	1	82	0M/1F	ALN	8	0/0	0	0	"Normal"	1
Koh, 2010 ⁽¹⁷⁴⁾	32 ^d	47-91	0M/32F	30 ALN 1 ALN > RIS 1 ZA	2-10	NA/NA	NA	NA	8/32 (median 26.7 µg/L)	NA
Grasko, 2009 ⁽¹⁷⁵⁾	1	57	1M/0F	PAM > ZA	9	0/0	1	1	NA	1
Napoli, 2010 ⁽¹⁴⁴⁾	1	56	0M/1F	PAM > ZA	6	0/0	1	1	0	1
Issacs, 2010 ⁽¹⁰⁸⁾	40	NA	NA	40 ALN	7.1 (mean)	NA/18	29	NA	NA	NA
Girgis, 2010 ⁽¹⁰⁷⁾	20	78	NA	15 ALN 2 RIS	5.1 ALN (mean) 3.0 RIS (mean)	NA/NA	NA	OR 5.2	OR 3.5	NA
Glennon, 2009 ⁽¹⁷⁶⁾	6	60-87	0M/6F	5 ALN 1 RIS	1.5-16 ALN 3.0 RIS	0/1	5	NA	"Normal"	NA
Bunning, 2010 ⁽¹⁰²⁾	4	49-59	1M/3F	1 PAM > ZA 2 ALN 1 No BP	5-5.5	(cortical hypertrophy with lateral cortical reaction) 1/1 1	4	NA	NA	3
Lee, 2009 ⁽¹¹³⁾	1	82	0M/1F	ALN	8	1/1	NA	NA	None	1
Leung, 2009 ⁽¹¹⁴⁾	6	73-81	0M/6F	ALN	0.5-6	0/0	1	0	2	2
Schneider, 2009 ⁽¹⁷⁷⁾	3	59-66	0M/3F	ALN	5-9	0/2 (cortical hypertrophy with lateral cortical reaction)	2	NA	NA	NA
Somford, 2009 ⁽¹²¹⁾	3	65-79	0M/3F	ALN	4-12	1/1	3	3	0	1
Giusti, 2010 ⁽¹¹¹⁾	8	36-75	0M/8F	ALN (3) PAM (2) PAM -> RIS (1) RIS (2)	2.5-8 ALN 5-6 RIS 3-7 PAM	2/2 3 (cortical hypertrophy with lateral cortical reaction)	5	5	0	3
Dell, 2010 ⁽⁹⁹⁾	102	45-92	3M/99F	Oral BPs (97) No BPs (5)	5.5	26 (complete fracture or stress fracture)	71	NA	NA	NA

NA = data not available; n = number; None = no cases outside the range; BP = bisphosphonate; ALN = alendronate; RIS = risedronate; IBN = ibandronate; ZA = zoledronate; PAM = pamidronate; GC = glucocorticoid; OR = odds ratio.

^aThis report included 8 from Goh, with substantial overlap likely.⁽¹⁰⁾

^bThis report included 10 from Lenart.⁽¹⁷²⁾

^cUnclear whether included in Neviaser.⁽¹⁰⁰⁾

^dThis report included 17 from Kwek.⁽¹²⁾

Table 6. Histomorphometric and Pathologic Assessments

Author/date/ reference	Number of patients biopsied	Site	Parameters	Findings
Goh, 2007 ⁽¹⁰⁾	5	Fracture site	Qualitative	No malignancy
Bush, 2008 ^{(145),a}	1	Fracture site	Qualitative	No malignancy; no osteoclasts
Wernecke, 2008 ^{(123),a}	1	L Femoral head, neck, marrow	Qualitative	L: No myeloma
		R Fracture site	Qualitative	R: Thin, sclerotic trabeculae Absent osteoclast/osteoblast activity
Somford, 2009 ⁽¹²¹⁾	2	Fracture site	Qualitative	No malignancy; no "osteoporosis"
Ing-Lorenzini, 2009 ⁽¹¹²⁾	2	Fracture site	Qualitative	Absent fracture healing/remodeling in cortex 1/2; periosteal bridging
Aspenberg, 2010 ⁽¹⁶⁹⁾	1	Fracture site	Qualitative	Few osteocytes distant from fracture; increased Oc.N and Ot.N near fracture; loss of osteonal regular structure indicating enhanced remodeling
Somford, 2009 ⁽¹¹⁹⁾	1	Fracture site and iliac crest	Static	Increased resorption and reduced formation at both sites; Oc.N sixfold higher at femoral cortex than iliac crest
Lee, 2009 ⁽¹¹³⁾	1	Fracture site	Static	Absence of osteoclasts and osteoblasts; few osteocytes; hypercellular marrow No inflammation or malignancy; irregular/disorganized collagen matrix
Donnelly, 2010 ⁽³²⁾	14 ^c	Fracture site	Static, Material Properties	Normal architecture and OS; reduced heterogeneity
Odovina, 2005 ⁽¹¹⁶⁾	9	Iliac crest	Static and Dynamic	Reduced bone turnover in all; no double labels 9/9; single labels 5/9
Cheung, 2007 ⁽¹²²⁾	1	Iliac crest	Static and Dynamic	Reduced osteoblast/osteoclast activity; thin but extensive osteoid
Visekruna, 2008 ⁽¹³⁾	2	Iliac crest	Static and Dynamic	Case 1: Increased Oc.N; lower OS and O.Wi; no double labels; limited single labels Case 3: Increased Oc.N and Ob.N; lower OS and O.Wi; double and single labels; low activation frequency
Armamento-Villareal, 2009 ⁽¹⁰⁹⁾	7 ^b	Iliac crest	Static and Dynamic	Reduced bone turnover 5/7; normal turnover 2/7
Odovina, 2010 ⁽¹¹⁵⁾	6	Iliac crest	Static and Dynamic	Ob.S and OS absent or low 6/6; Oc.S absent or low 3/6; ES normal 5/5; double labels absent 4/6; single labels present 4/6
Giusti, 2010 ⁽¹¹⁾	1	Iliac crest	Static and Dynamic	Decreased Oc.N, ES, and OS; reduced turnover; few labels
Armamento-Villareal, 2006 ⁽¹²⁶⁾	1	Iliac crest	Qualitative	Pre-ALN: increased OS and labels; post-ALN: 6 years, no osteoid or labels
Leung, 2009 ⁽¹¹⁴⁾	1	Iliac crest	Qualitative	Decreased Oc.N and Ob.N; reduced bone turnover; no labels
Napoli, 2010 ⁽¹⁴⁴⁾	1	Iliac crest		Unsuccessful; bone too "hard"

Oc.N = osteoclast number; Ob.N = osteoblast number; OS = osteoid surface; O.Wi = osteoid width; Oc.S = osteoclast surface; Ob.S = osteoblast surface.

^aCancer patients treated with high-dose BPs, i.v.

^bBiopsies performed on 15 patients, but only 7 had femoral shaft fractures.

^cAll BP-treated, average duration 7.4 years; 4 atypical femoral fractures, 1 subtrochanteric, 9 intertrochanteric.

Although a number of reports mention lack of double tetracycline labels in the biopsy, this too is a common and expected finding in BP-treated subjects,^(138,139) even in those who have been treated for only 6 months.⁽¹³⁰⁾ Moreover, lack of double label or so little double label that mineral apposition rate cannot be evaluated reliably is seen in a significant proportion of untreated postmenopausal women.^(142,143) Static parameters of bone formation are also low in biopsies from patients with atypical femoral fractures, consistent with those seen in BP-treated patients with osteoporosis. It is important to note that a finding of low turnover in biopsies from BP-treated patients with atypical femoral fractures has not been universal.^(109,119) In most cases, only a single transiliac biopsy, usually taken soon after the fracture, has been studied. Therefore, the turnover status prior to the fracture or before beginning BPs is not known. However, in one report,⁽¹²⁶⁾ a 35-year-old man was biopsied before beginning alendronate and again 7 years later, after a low-trauma subtrochanteric femur fracture. The first biopsy revealed low trabecular bone volume, reduced trabecular connectivity, and increased osteoid surface and tetracycline uptake, consistent with high-turnover osteoporosis. In contrast, the postfracture biopsy showed lack of osteoid and tetracycline labels, confirming conversion of high- to low-turnover bone.

In several cases, biopsy samples were obtained at or close to the site of the subtrochanteric fracture, the location that is likely to provide more information on the underlying pathogenetic mechanism, although there is no opportunity for tetracycline labeling and dynamic assessment of bone turnover in this setting. Moreover, analysis at the biopsy site may be misleading because the fracture itself will lead to an acceleration of remodeling in the region of the fracture. Caution should be used in interpreting measurements of bone turnover taken from a biopsy at the fracture site. Ing-Lorenzini and colleagues⁽¹¹²⁾ obtained biopsies from two patients but described the histologic appearance of only one of those, a 65-year-old postmenopausal woman who had received alendronate for 5 years and ibandronate for 1 year before suffering a subtrochanteric right femoral shaft insufficiency fracture. Five years earlier and 2 years after starting alendronate, she had sustained a subtrochanteric fracture of her left femur. This patient also had been treated with tibolone, inhaled GCs, and a PPI. A biopsy taken from the lateral cortex exactly at the level of the second fracture showed a fracture line extending from the periosteal to the endosteal surface with evidence of partial bone bridging across the fracture line on the periosteal surface. The fracture line was filled with blood, and there was no evidence of intracortical remodeling.

Lee⁽¹¹³⁾ obtained a biopsy of endocortical bone from the proximal end of the fracture in an 82-year-old woman who had sustained bilateral atypical femoral fractures. She had been treated with alendronate for 8 years. Osteoclasts were not seen in the sample, and osteocytes were few in number. Polarized light revealed the presence of both lamellar and woven bone. The bone marrow was hypercellular, but there was no evidence of inflammation, malignancy, or myelosclerosis. Goh and colleagues⁽¹⁰⁾ performed qualitative histology on biopsies removed intraoperatively during repair of subtrochanteric fractures in 5 alendronate-treated patients, but they simply reported that there was no evidence of neoplasia.

Napoli and colleagues⁽¹⁴⁴⁾ described one of the few reported cases of atypical femoral fracture in a cancer patient (multiple myeloma) treated with high-dose intravenous BPs. Following a stem cell transplant, the patient was given pamidronate for 2 years and zoledronate for 4 years, in addition to high-dose GCs. An attempt to obtain an iliac crest biopsy was unsuccessful because the biopsy needle was unable to penetrate the "rock hard" bone. Wernecke and colleagues⁽¹²³⁾ reported another case of a patient with multiple myeloma who had been treated with intravenous BPs (pamidronate and zoledronate) for 9 years and presented with sequential, bilateral subtrochanteric stress fractures. Histologic examination of a biopsy taken from the femoral head during repair of the second fracture revealed an almost complete lack of osteoclasts and osteoblasts. A similar finding was described in curettage samples from the fracture site of a patient who had been treated with intravenous zoledronate for 1.5 years to prevent metastatic bone disease secondary to renal carcinoma.⁽¹⁴⁵⁾

In contrast to the preceding cases, the biopsy from the subtrochanteric fracture site obtained by Somford and colleagues⁽¹¹⁹⁾ revealed a very different cellular profile. This biopsy was taken from a 76-year-old woman with RA who had been treated with alendronate for 8 years prior to admission for a subtrochanteric stress fracture of her left femur, which subsequently fractured completely. She also had received GCs and methotrexate for 11 years and infliximab for 3 years before the fracture. Nine months after the left femur fracture, she sustained a subtrochanteric fracture of her right femur. At that time, biopsies were obtained from the iliac crest and the right femur approximately 1 cm above the fracture. In the ilium, cancellous bone microarchitecture was normal for her age, but static bone formation indices, such as osteoid surface and volume, were reduced substantially to within the range previously reported for patients with alendronate-treated, GC-induced osteoporosis.⁽¹⁴¹⁾ Unexpectedly, the eroded surface was about threefold higher than that of controls and 6.5 to 13 times the levels seen in patients with GC-induced osteoporosis and postmenopausal osteoporosis, respectively. Osteoclast number also was about four times higher than that recorded in alendronate-treated patients; however, this is not surprising because normal or elevated numbers of osteoclasts have been reported from biopsies of BP-treated patients.⁽¹⁴⁶⁾ In a biopsy taken close to the fracture site, eroded surface and osteoclast number were high, and static parameters of bone formation were low, although there are no normative data for this skeletal site. Osteoclast number at the fracture site was sixfold higher than at the iliac crest. At both sites, the morphologic appearance of the osteoclasts suggested that they were actively resorbing. The imbalance between resorption and formation displayed by this patient differs from the prevailing hypothesis regarding the pathogenesis of atypical fractures, which invokes severe suppression of turnover. It is possible that the excessive resorption was related to the fracture itself, but this seems unlikely, given that it also was evident in the iliac crest biopsy and that the femoral biopsy was located 1 cm above the fracture and was taken within 12 hours of the event. MRI evidence for excessive resorption at the site of atypical fractures also has been reported in a BP-treated patient,⁽¹²⁾ and the same phenomenon

has been seen in young athletes with early tibial stress injuries.^(147,148) Somford and colleagues⁽¹¹⁾ also took the opportunity to assess the mineralization density of the bone tissue at the fracture site because some have suggested that prolonged BP treatment may lead to hypermineralized and, therefore, brittle bone matrix. There was no evidence of hypermineralization and no change in hydroxyapatite crystal size, although the crystals were more mature than in control subjects, consistent with the known effects of alendronate on bone turnover and secondary mineralization.⁽¹¹⁹⁾

Summarizing the small amount of histologic data currently available in patients with atypical fractures, most, but not all, studies indicate very low turnover at both the iliac crest and the fracture site, although reports of increased turnover may be influenced by the fracture itself. Also, only static and qualitative histomorphometry analyses at the fracture site are available. Whether turnover at the iliac crest is lower than in the vast majority of BP-treated patients who have not sustained such fractures is not known. Double tetracycline labels are usually absent, but single labels are present in many cases, indicating that turnover is not always absent at the ilium. Also, where available, biochemical markers of bone turnover are often not reduced to the same degree as that seen in the biopsy and may be within the normal range.^(13,109,113–116,122,123) The findings of Somford and colleagues⁽¹¹⁹⁾ at both the ilium and the fracture site and of Visekruna and colleagues⁽¹²⁾ at the ilium suggest an alternate pathogenetic mechanism that involves increased resorption coupled with reduced bone formation. Clearly, more information is needed about bone histopathology at the site of atypical femur fractures (see “Key Research Questions” below).

Input from the pharmaceutical industry. Four members of the task force (DB, TB, RM, and ES) conducted teleconference sessions with representatives of companies that market drugs used to treat osteoporosis in the United States (ie, Amgen, Eli Lilly, Genentech, Merck, Novartis, and Warner-Chilcott). These sessions were informational; they permitted the task force to develop some understanding of the number of atypical fracture cases reported to the industry and the steps being taken by the individual companies to adjudicate cases reported to them. The sessions also permitted experts from the industry to provide their input on the case definition for consideration by the task force.

Most of the companies had examined the data from their large registration trials, and very few cases of atypical femoral fractures were detected. However, this approach was limited in most cases by reliance on diagnostic codes to search for subtrochanteric and diaphyseal fractures and lack of availability of radiographs to examine features of atypia in any subtrochanteric/diaphyseal fractures that occurred. Also, maximum treatment duration in these trials was lower than the median treatment duration in the published cases of atypical fractures. Most cases were from the postmarketing reporting system. These are unsolicited reports of medical events temporally associated with use of a pharmaceutical product and originating from health care professionals, patients, regulatory agencies, the scientific literature, and the lay press. Although this system is useful for identifying rare events that are not detected in clinical trials, important limitations

include underreporting and poor-quality reports with missing critical information. Additionally, it is impossible to calculate incidence rates; the numerator is uncertain because of underreporting, and the denominator generally is based on the amount of drug distributed. There was considerable variability among companies in the mechanisms in place to identify atypical femoral fractures and in the amount of information that was shared with the task force. The number of patient-years of exposure to drugs that are currently on the market for osteoporosis varied between 2 million and 54 million. In general, reporting rates of subtrochanteric and diaphyseal fractures, with or without atypical features, were very low (1 to 3 per 1 million patient-years of exposure). However, as expected, the pharmaceutical companies were aware of cases that had not been reported in the medical literature.

Input from the USFDA. Two task force members (DB and ES) conducted a teleconference with representatives of the FDA. Data from the FDA were consistent with industry and task force estimates of the number of atypical femoral fractures. However, officials emphasized that adverse-event reporting was subject to the same limitations noted earlier, particularly substantial underreporting.

Recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder

Imaging of the atypical femoral shaft fracture is relatively straightforward. Conventional radiography is the first line of approach, with more sophisticated imaging such as bone scintigraphy, magnetic resonance imaging (MRI), or computed tomography (CT) useful principally for detecting early or subtle prefracture features.^(12,93,100,119,145)

Conventional radiographs of the femur, acquired in anteroposterior and lateral projections, usually suffice to demonstrate a range of characteristic findings in complete or incomplete fractures^(149–152) (Fig. 2A). These consist of a substantially transverse fracture line, at least laterally, with variable obliquity extending medially (Fig. 3). There is often associated focal or diffuse cortical thickening, especially of the lateral cortex, where the fracture process generally initiates. When it is focal and substantial, this lateral cortical thickening may produce an appearance of cortical “beaking” or “flaring” adjacent to a discrete transverse fracture line^(12,93,100,145) (Fig. 2B). As the fracture evolves and propagates medially, ultimately displacing and becoming a complete fracture, an oblique component may be observed as a prominent medial “spike” (Fig. 2A). Conventional radiography also may show diffuse cortical thickening, suggesting chronic stress response, which may be unilateral or bilateral (Fig. 3). Similarly, discrete linear lateral cortical translucencies may be observed in the pre-fracture displacement phase, often with adjacent focal cortical thickening from periosteal new bone apposition^(12,93,100,145) In contrast, femoral stress fractures of athletes usually involve the medial cortex in the proximal one-third of the diaphysis.^(149–152)

While conventional radiographs may be suggestive or diagnostic of these stress or insufficiency fractures even in



Fig. 3. AP radiograph of the left femur demonstrates a substantially transverse femoral fracture and associated diffuse periosteal new bone formation (black arrow) and focal cortical thickening (white arrow) consistent with atypical femoral shaft fracture. (Courtesy of Joseph Lane, MD.)

moderately early evolution, the findings may be quite subtle and nondiagnostic^(149,150) (Figs. 4A, C, and 5A). In the setting of prodromal symptoms of aching deep thigh or groin pain and normal or equivocal radiographs, additional, more advanced diagnostic imaging procedures may be useful. Radionuclide



Fig. 4. Conventional AP radiographs of the right (A) and left femurs (C) demonstrate subtle focal cortical thickening on both periosteal and endosteal surfaces, as well callus on the periosteal surface (arrows), whereas bone scintigraphy (B) demonstrates focal increased radionuclide uptake in the corresponding proximal lateral femoral cortices, findings consistent with early, evolving, bilateral femoral insufficiency fractures. (Courtesy of Piet Geusens, MD.)

bone scintigraphy may be employed to document the presence of an evolving stress or insufficiency fracture.^(119,145,149–153) Typically, the appearance will be that of unilateral or bilateral increased uptake with a broad diffuse zone and a centrally located, focal region of extreme uptake usually in the lateral cortex (Figs. 4B and 5B). When only the diffuse pattern is observed, the differential diagnosis includes primary or secondary malignancy, bone infarction, and osteomyelitis. However, these conditions usually are centered in the medullary space of the femur and do not show the lateral cortical predilection of stress fractures.

Like bone scintigraphy, MRI can detect the reactive hyperemia and periosteal new bone formation of an evolving stress or insufficiency fracture^(151–155) (Fig. 5C). Typically, on T₁-weighted images there will be diffuse decreased signal owing to both water partially replacing the normal fatty marrow components and the focal cortical thickening that creates little signal on this sequence. On T₂-weighted images with fat saturation, there may be diffuse increased signal related to the associated inflammation and hyperemia. With relatively high resolution and multiplanar imaging, the evolving fracture line in the lateral cortex may be discerned on T₂-weighted images or on T₁-weighted images obtained with fat saturation and gadolinium-based contrast enhancement. The ability to image thin sections in multiple planes creates both high sensitivity and high specificity, generally surpassing that of bone scintigraphy.

Similarly, the application of advanced multislice or spiral CT imaging with its thin sections, relatively high resolution, and multiplanar re-formation capability renders this technique quite useful in detecting subtle reactive periosteal new bone formation and the small, discrete radiolucency of the evolving fracture and its focal intracortical bone resorption.^(156–158)



Fig. 5. Conventional AP radiograph of the pelvis (A) shows bilateral focal cortical thickening from periosteal new bone formation (arrows). Corresponding bone scintigraphy (B) demonstrates focal increased radionuclide uptake in the proximal lateral femoral cortices (arrows). MRI images of the femurs (C) demonstrate subtle decreased signal on T₁-weighted and increased signal on T₂-weighted images only of the right femur on this section. Similar findings on AP DXA hip images (D) show focal bilateral cortical thickening consistent with early, evolving femoral insufficiency fractures. (Courtesy of Fergus McKiernan, MD.)

While scintigraphy, MRI, and CT scanning are more costly and less convenient than conventional radiography, these advanced imaging techniques provide superior sensitivity and specificity for detecting early stages of stress or insufficiency fractures and therefore, in selected instances, could improve the clinical management of atypical femoral shaft fractures (Fig. 5A–C). Even the lower-resolution images of dual-energy X-ray absorptiometry (DXA) occasionally may detect the hypertrophic new bone formation of an evolving proximal subtrochanteric femoral shaft fracture and aid in the differentiation of proximal thigh pain in this condition⁽¹⁰⁴⁾ (Fig. 5D).

Identify the key questions that the scientific community should address, and recommend a research agenda to elucidate incidence, pathophysiology, and etiology of atypical femoral fractures and their potential relationship with BP usage

Recommendations to facilitate future research

Create specific diagnostic and procedural codes for cases of atypical femoral fractures. To facilitate case ascertainment in administrative data sets and identification of incident cases, specific diagnostic and procedural codes (ICD and/or CPT code) should be created for atypical femoral fractures based on the major features summarized in the case definition, as has been done recently for osteonecrosis of the jaw (ONJ, ICD-9 733.45). Such codes would facilitate preliminary case ascertainment in administrative data sets, which then would result in more efficient and targeted review of medical records and radiographic images. Having a specific code would permit better understanding of the relative incidence of these fractures compared with other osteoporotic fractures of the lower extremity that otherwise could be coded similarly. Without such a code, it will be more difficult to identify and confirm atypical fractures efficiently in future large population databases where the population at risk can be enumerated. Better precision in determining incidence rates of atypical fractures in large populations will permit examination of health economics and harm/benefit modeling.

Develop an international registry for cases of atypical femoral fractures. Because of the generally low incidence of these fractures, a centralized repository of standardized information will be required to generate the kinds of data and sufficient numbers of cases to understand the incidence, risk factors, and pathophysiology of atypical femoral fractures. The task force strongly recommends the establishment of an international registry spanning interested countries and health care plans with different patterns of BP usage. Local and national databases should be established to maximize case ascertainment. Data sources that contribute to the registry will be most informative if they can enumerate the population at risk (ie, a denominator). The registry must use a uniform case definition of atypical fractures. All future studies using patients treated or untreated for osteoporosis should collect radiographs of all femoral fractures. Some formal means should be established to collect all radiographs in an electronic repository to allow for review of the variability in fracture pattern. There should be

independent review of the radiographic studies to distinguish classic comminuted spiral fractures from noncomminuted transverse or short oblique atypical fractures of the femoral subtrochanteric and diaphyseal regions. Administrative data may be useful to assist in identifying possible cases, and an ideal scenario would link administrative data to medical and pharmacy records and radiographic images (not simply radiographic reports). Certain information on risk factors for fracture should be available from both administrative and clinical data sources (Table 7). An external agency also could follow up and validate FDA adverse-drug-report data in detail both to confirm all reported cases and to accumulate further accurate information on the epidemiology of this rare but important condition. This was considered to be a good model for national regulatory agencies to consider.

The registry should develop a focused standardized case report form to be completed for each case. A balance must be achieved in the recording of vital information because requiring too much information will make it time consuming to report cases and mean that fewer cases will be reported. Ideally, a case report should include information on demographics, fractures, BP exposure (if any), comorbid diseases, and concomitant medications, as summarized in Table 7.

Key research questions

Define measurable characteristics that are associated with atypical femoral fractures. To develop a clinical profile and to

Table 7. Information That Should Be Included in Future Reports of Atypical Femoral Fractures

- Standard demographic data (age, gender, height, weight, race, ethnicity)
- Anatomic location of the fracture (subtrochanteric or diaphyseal)
- Key radiographic features of atypia (see Table 1)
- Information on osteoporosis therapies
 - Doses, routes, duration of, and adherence to osteoporosis therapy
 - Indication for therapy (eg, osteoporosis, osteopenia, bone loss prevention, cancer, Paget disease)
- Prior fracture history
- Concomitant medications: GCs, thiazolidenediones, PPIs, anticonvulsants, statins, HRT, SERMs
- Comorbid medical conditions: Diabetes, RA, chronic kidney disease, malabsorption, errors of phosphate metabolism, joint replacement
- Family history (for genetic studies)
- Bone mineral density: before treatment and at time of fracture
- Biochemistries
 - Serum calcium, creatinine, 25(OH)D, PTH
 - Biochemical markers of bone turnover (P1NP, osteocalcin, total or bone alkaline phosphatase, C-telopeptide)
- Surgical management of the fracture (intramedullary rod, locking plates): documentation of delayed healing

determine which patients are susceptible, it is important to define quantitatively features that are considered part of the etiopathology of atypical femoral fractures. For example, case reports and series suggest that cortical thickening at the fracture site is one feature of atypia. However, because cortical thickness varies throughout the diaphysis and also by age, gender, and possibly race, studies that evaluate this characteristic must specify the specific regions for analysis and measurement. A normal range by age, gender, and diaphyseal location should be developed as a first step toward identifying the significance of cortical thickening in the pathogenesis of atypical fractures. It also would be important to determine prospectively the frequency of other characteristics reported in conjunction with atypical femoral fractures, such as

- The frequency of periosteal reaction (ie, callus) associated with a fracture, including the incidence of such reactions in the contralateral nonfractured femur
- The incidence and duration of prodromal thigh pain
- The frequency of bilateral fractures and symptoms

Identify the true incidence of atypical femoral fractures and their association with BPs and/or other conditions characterized by low bone turnover. The precise incidence of atypical femoral fractures is unknown. To clarify the pathogenesis and causality, it is necessary to understand the true incidence of these fractures in the general population of patients without known osteoporosis who are unexposed to BPs, in patients with osteoporosis both exposed and unexposed to BPs and other agents used to treat osteoporosis, and in specific populations distinguished by concomitant drug exposures and comorbid diseases. Without these data, it is possible to misinterpret an association between treatment and fractures as causation. Patients with Paget disease receiving intermittent courses of BPs and patients with malignancies receiving high doses of intravenous BPs also should be assessed, with appropriate controls for duration of treatment, BMD, and other relevant parameters. To determine whether atypical femoral fractures are a class effect of BPs or generally related to low bone turnover, it is essential to determine whether such fractures occur with other antiresorptive drugs, such as estrogen, raloxifene, and denosumab, or in diseases characterized by extremely low bone turnover, such as osteopetrosis, hypoparathyroidism, myxedema, and certain forms of renal bone disease. It also will be important to determine whether the risk of atypical femoral fractures increases with greater inhibition of remodeling. The association between atypical femoral fractures and concomitant GC therapy is a concern and requires investigation. BPs represent the cornerstone of strategies for the prevention and treatment of bone loss and fractures associated with GCs. However, there are no studies of long-term (>2 to 3 years) BP treatment in patients receiving GCs. Thus, while short-term (1 to 2 years) BP administration lowers the risk of typical osteoporotic fractures in patients with glucocorticoid-induced osteoporosis (GIOP), it is possible that prolonged administration of two classes of drugs that suppress bone formation may increase the risk of atypical femoral fractures.

Acquisition of biopsy data, especially from the site of fracture. Bone biopsy data should be collected whenever possible. Both specimens from the fracture site and tetracycline double-labeled transiliac bone biopsies would be desirable, although the former may be misleading as an indicator of the bone-remodeling rate prior to the fracture. Guidelines for the biopsy size and quality control should be developed. A concerted effort should be made to gather normative data for all these variables from the subtrochanteric femoral shaft. Carefully selected autopsy material would serve for all but the dynamic indices of bone formation. In addition, however, it might be helpful to assess local BMD using microradiographs, micro-computed tomography (μ CT), or quantitative backscattered electron microscopy to provide some assessment of collagen organization and to evaluate necrotic bone by measurements of osteocyte apoptosis and/or lacunar density. The information that ideally should be collected from biopsy specimens is summarized in Table 8. Measurement of mechanical properties, especially tissue properties, would be desirable. It is also important to know whether microcracks accumulate at the site of the femoral fracture and whether there is evidence of healing at the site.

Genetics. Although patients with X-linked hypophosphatemia (XLH) can have pseudofractures that resemble atypical femoral fractures,⁽²⁾ XLH is usually obvious and only rarely could explain this problem. However, because atypical femoral fractures may resemble the pseudofractures that characterize adult hypophosphatasia,⁽²⁾ studies to examine the gene that encodes the tissue nonspecific (bone) isoenzyme of alkaline phosphatase (*TNSALP*) for mutations or polymorphisms will be of research interest for atypical femoral fracture patients. This could clarify whether carriers for hypophosphatasia develop atypical femoral fractures

Table 8. Information to Be Collected from Transiliac and/or Femoral Fracture Biopsies

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- Cortical and cancellous microarchitecture: Bone volume (BV/TV), trabecular thickness (Tb.Th), separation (Tb.Sp) and number (Tb.N); cortical area (Ct.Ar), thickness (Ct.Th), and porosity (Ct.Po)
 - Mineral and matrix quality, including mineral density distribution, heterogeneity of matrix characteristics, and mineral particle size and shape
 - Collagen cross-links and advanced glycation end products
 - Collagen organization (lamellar/woven)
 - Osteoblast and osteoclast surface
 - Osteoblast and osteoclast numbers, with surface referent
 - Prevalence of osteoblast and osteocyte apoptosis per total number of cells
 - Amount of necrotic bone, as determined by measurements of lacunar density and empty lacunae
 - Osteoid surface, volume, and average thickness
 - Reversal surface, with bone surface referent
 - Bone-formation rates and activation frequency, when possible
 - Bone vascularity
 - Tissue mechanical properties
-

from antiresorptive agents. Genome-wide association studies probably will not be helpful because DNA samples from many atypical femoral fracture patients would be necessary.

Bone turnover markers. Retrospective analysis of BTM data from fracture patients but prior to the introduction of BP therapy and before the fracture should be performed where possible. Although specific BTMs may not be available, serum total alkaline phosphatase is a commonly performed test and may be useful in assessing whether bone turnover was low before or became suppressed during therapy in these individuals.

The development of an animal model to study pathogenesis. It is unlikely that pathogenesis and fracture mechanism can be fully understood from clinical data alone given the low incidence of these fractures and the variability in patient characteristics. Once the risk factors contributing to atypical femoral fractures are better understood, animal models incorporating risk factors may provide insights into mechanisms at the cellular and tissue levels. Because bone remodeling is likely an important component of the response, in vivo animal models that exhibit intracortical remodeling are particularly critical. Several different animal models have been used to study the pathogenesis of stress fractures. Existing rodent models^(3,4,66) may not be appropriate because of their lack of haversian remodeling, but attempts should be made to adapt fatigue-loading techniques that have been developed in rodents to larger animals. Nonhuman primates would be acceptable but are expensive. Several smaller animal models, such as rabbits and dogs, that have substantial intracortical bone remodeling may be appropriate. However, these animals cannot be studied in conjunction with the osteoporotic condition because attempts to make them estrogen-deficient generally do not result in bone loss. Sheep have some intracortical remodeling and can be made estrogen-deficient. However, they have some reproductive anomalies and are seasonal breeders, which may limit their usefulness. Minipigs might offer a suitable alternative, although adult minipigs can be difficult to handle and are expensive.

Because of the similarity of the signs and symptoms preceding atypical femoral fractures to stress fractures, it may be desirable to combine variable loading regimens (eg, increased mechanical loading or fatigue injury) with a concurrent pharmacologic regimen that could accelerate the development of bone fragility. Animals do not appear to fracture spontaneously, even following prolonged treatment with high doses of second- and third-generation BPs. For this reason, the endpoints of such studies should not be overt fracture. Rather, animal models can be used to investigate alterations in the structural and material properties of the bone under different conditions, such as coadministration of GCs and BPs or administration of BPs to diabetic animals. They also could be used to explore possible regional differences in the biodistribution of various BPs, bone histomorphometry and microarchitecture, bone healing, and bone vascularity. Efforts at management of stress-induced lesions (eg, treatment with parathyroid hormone) also should be examined in such models.

Recommend clinical orthopedic and medical management of atypical femoral fractures based on available information

Surgical treatment strategy for atypical subtrochanteric and femoral shaft fractures

Because of the propensity for delayed healing, the morbidity of these fractures is particularly high. The task force recognized that there are no controlled studies evaluating surgical treatment strategies for atypical subtrochanteric and femoral shaft fractures. The recommendations outlined here therefore are opinion-based and represent the consensus of the orthopedic surgeons who served on the task force. The task force developed a hierarchical approach to management that depends on whether the fracture is complete or incomplete.

History of thigh or groin pain in a patient on BP therapy. A femoral fracture must be ruled out.^(10,12,93,100,110,115,124,159) Anteroposterior and lateral plain radiographs of the hip, including the full diaphysis of the femur, should be performed. If the radiograph is negative and the level of clinical suspicion is high, a technetium bone scan or MRI of the femur should be performed to detect a periosteal stress reaction. The advantage of the technetium bone scan is that both legs will be imaged.

Complete subtrochanteric/diaphyseal femoral fracture. Orthopedic management includes stabilizing the fracture and addressing the medical management^(10,12,93,100,110,115,124,159) (see below). Since BPs inhibit osteoclastic remodeling, endochondral fracture repair is the preferred method of treatment. Intramedullary reconstruction full-length nails accomplish this goal and protect the entire femur. Locking plates preclude endochondral repair, have a high failure rate, and are not recommended as the method of fixation. The medullary canal should be overreamed (at least 2.5 mm larger than the nail diameter) to compensate for the narrow intramedullary diameter (if present), facilitate insertion of the reconstruction nail, and prevent fracture of the remaining shaft. The proximal fragment may require additional reaming to permit passage of the nail and avoid malalignment. The contralateral femur must be evaluated radiographically, including scintigraphy or MRI, whether or not symptoms are present.⁽¹¹⁰⁾

Incomplete subtrochanteric/femoral shaft fractures. Prophylactic reconstruction nail fixation is recommended for incomplete fractures accompanied by pain.^(10,12,93,100,110,115,124,159) 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, weight bearing may be continued but should be limited and vigorous activity avoided. Reduced activity should be continued until there is no bone edema on MRI.

Medical management of atypical subtrochanteric/femoral shaft fractures

There are also no controlled studies evaluating medical treatment strategies for atypical subtrochanteric and femoral shaft fractures. The recommendations outlined here therefore are opinion-based and represent the consensus of the clinicians who served on the task force. The task force considered two main aspects of medical management:

Prevention. Decisions to initiate pharmacologic treatment, including BPs, to manage patients with osteoporosis should be made based on an assessment of benefits and risks. Patients who are deemed to be at low risk of osteoporosis-related fractures should not be started on BPs. For patients with osteoporosis in the spine and normal or only moderately reduced femoral neck or total-hip BMD, one could consider alternative treatments for osteoporosis, such as raloxifene or teriparatide, depending on the severity of the patient's condition. It is apparent that therapy must be individualized and clinical judgment must be used because there will not always be sufficient evidence for specific clinical situations. BP therapy should be strongly considered to protect patients from rapid bone loss and increased fracture rates associated with clinical scenarios such as organ transplantation, endocrine or chemotherapy for breast or prostate cancer, and initiation of aromatase inhibitors and GCs. However, long-term BP therapy may not always be necessary in these clinical conditions.^(160,161) More research is needed to determine the most effective dose and duration of BPs in patients with secondary causes of rapid bone loss.

The optimal duration of BP treatment is not known. Based on studies with alendronate⁽¹⁶²⁾ and risendronate,^(163,164) patients with osteoporosis will have an antifracture benefit for at least 5 years. However, continued use of BP therapy beyond that time should be reevaluated annually, assessing factors such as BMD, particularly in the hip region, fracture history, newly diagnosed underlying conditions or initiation of other medications known to affect skeletal status, and new research findings in a rapidly evolving field. For those who are considered to remain at moderately elevated fracture risk, continuation of BP therapy should be strongly considered. Recent or multiple fractures (including asymptomatic vertebral fractures on lateral DXA imaging or lateral spine X-ray at the time of reevaluation) should suggest assessment or reassessment for underlying secondary causes and reevaluation of the treatment plan. Such patients are known to be at high risk of future fracture, and thus discontinuation of osteoporosis treatment is inadvisable. However, whether continuing BPs beyond 5 years will reduce that risk is unclear. In the FLEX trial, the incidence of clinical (but not morphometric) vertebral fractures was significantly lower in those on 10 years of continued alendronate versus those who stopped after 5 years⁽¹⁶²⁾; reduction in nonvertebral fracture incidence was limited to women without a fracture history but with femoral neck *T*-scores that were -2.5 or less.⁽¹⁶⁵⁾ While conclusions from this trial need to be tempered by its limitations, primarily the small study sample, these are the only long-term fracture data available with alendronate treatment. With regard to risendronate, 7 years of therapy did not further reduce the

incidence of vertebral fractures below that observed with 3 and 5 years of therapy.⁽¹⁶³⁾ Models to help determine absolute risk of fracture in patients who have already been treated for 4 to 5 years are needed to help guide these decisions.

Based on current case reports and series, the median BP treatment duration in patients with atypical subtrochanteric and femoral shaft fractures is 7 years. For patients without a recent fracture and with femoral neck *T*-scores greater than -2.5 after the initial therapeutic course, consideration may be given to a "drug holiday" from BPs. Because some patients with atypical femoral fractures while on BPs were on concomitant therapy with GCs, estrogen, tamoxifen, or PPIs, continued BP therapy should be reevaluated, particularly in those deemed to be at low or only modestly elevated fracture risk. Whether discontinuation of BPs after 4 to 5 years in the lower-risk group will lead to fewer atypical subtrochanteric fractures is not known.

If BPs are discontinued, there are no data to guide when or whether therapy should be restarted. However, patients should be followed by clinical assessment, bone turnover markers, and BMD determination. Restarting osteoporosis therapy, either with BPs or with a different class of agent, can be considered in patients who appear to be at increasing fracture risk. Models to help assess risk in previously treated patients, after 1 or more years off therapy, are needed to help guide these therapeutic decisions. It seems apparent that there can be no general rule and that decisions to stop and/or restart therapy must be individualized.

More than half of patients reported with atypical femoral fractures have had a prodrome of thigh or groin pain before suffering an overt break. Thus it is important to educate physicians and patients about this symptom and for physicians to ask patients on BPs and other potent antiresorptive agents about thigh or groin pain. Complaints of thigh or groin pain in a patient on BPs require urgent radiographic evaluation of both femurs (even if pain is unilateral). If plain radiographs are normal or equivocal and clinical suspicion is high, MRI or radionuclide scintigraphy should be performed to identify stress reaction, stress fracture, or partial fracture of either femur. Other disorders, such as forms of osteomalacia, also should be considered.⁽²⁾

Medical management. 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 should be prescribed. A few case reports and anecdotal findings suggest that teriparatide therapy can improve or hasten healing of these fractures.^(13,123) Additionally, consistent with a large body of animal data,⁽¹⁶⁶⁾ some clinical evidence^(167,168) indicates that teriparatide benefits nonunion of fractures, although a controlled trial in patients with Colles' fracture showed little effect.⁽¹⁶⁹⁾ Given the relative rarity of atypical femoral fractures and ethical issues surrounding potential randomization to placebo, it seems unlikely that there will be a randomized, controlled trial of teriparatide for subtrochanteric and femoral shaft fractures. Therefore, the level of evidence for efficacy likely will remain low. However, in the absence of evidence-based approaches, teriparatide should be considered in patients who

suffer these fractures, particularly if there is little evidence of healing by 4 to 6 weeks after surgical intervention.

Summary and Conclusions

BPs are highly effective at reducing the risk of spine and nonspine fractures, including typical and common femoral neck and intertrochanteric fractures. However, there is evidence of a relationship between long-term BP use and a specific type of subtrochanteric and femoral shaft fracture. These fractures are characterized by unique radiographic features (ie, transverse or short oblique orientation, absence of comminution, cortical thickening, stress fracture or stress reaction on the symptomatic and/or contralateral side, and delayed healing) and unique clinical features (ie, prodromal pain and bilaterality). The apparent increased risk for atypical femoral fractures in patients receiving GCs is a concern because BPs are the mainstay for prevention of GC-induced osteoporotic fractures. Bone biopsies from the iliac crest and/or fracture site generally show reduced bone formation consistent with BP action. Paradoxically, some patients show biopsy evidence of enhanced bone resorption. Biochemical BTMs are often normal but may be increased. These fractures can occur in patients who have not been treated with BPs, and their true incidence in both treated and untreated patients is unknown. However, they 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). It must be emphasized that these fractures are rare, particularly when considered in the context of the millions of patients who have taken BPs and also when compared with typical and common femoral neck and intertrochanteric fractures. It also must be emphasized that BPs are important drugs for the prevention of common osteoporotic fractures. However, atypical femoral fractures are 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. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Given the relative rarity of atypical femoral fractures, to facilitate future research, specific diagnostic and procedural codes should be created for cases of atypical femoral fractures, an international registry should be established, and the quality of case reporting should be improved. Research directions should include development of animal models, increased surveillance, and additional epidemiologic data to establish the true incidence of and risk factors for this condition and studies to address their surgical and medical management.

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 the Society. The ASBMR protects itself and its reputation by ensuring impartial decision making. Accordingly, the ASBMR requires that all ASBMR officers, councilors, committee chairs, editors-in-chief, associate editors,

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Relationship key: (1) Research grant or financial support from commercial entities; (2) consultant or member of advisory board to a commercial entity; (3) participant in a speakers' bureau; (4) employment or executive positions in pharmaceutical, medical device, or diagnostic companies, including industry scientists in the bone and mineral field; (5) stock holdings in pharmaceutical, medical device, or diagnostic companies; (6) any other situation or transaction in which you have a formal role or interest (eg, you serve on a bone-related organization's board, committee, or journal; a family member contracts with ASBMR; etc.).

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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, two

additional individuals were assigned to the Atypical Femoral Fractures Task Force—an ethicist and a scientist knowledgeable about the musculoskeletal system who does not work directly on osteoporosis or bisphosphonates or with pharmaceutical companies who make or market bisphosphonates. The role of these

individuals was to provide ethical oversight to the work of the task force. Both individuals have verified and attested that they witnessed no commercial bias during the task force’s deliberations, during discussions with the pharmaceutical industry, or in the preparation of the final document by the task force.

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