Perspective

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

Running Title: Atypical Femoral Fractures Task Force Report

Elizabeth Shane (Co-Chair)[1,*], David Burr (Co-Chair)[2,*], Peter R. Ebeling[3], Bo Abrahamsen[4], Robert A. Adler[5], Thomas D. Brown[6], Angela M. Cheung[7], Felicia Cosman[8], Jeffrey R. Curtis[9], Richard Dell[10], David Dempster[1], Thomas A. Einhorn[11], Harry K. Genant[12], Piet Geusens[13], Klaus Klaushofer[14], Kenneth Koval[15], Joseph M. Lane[16], Fergus McKiernan[17], Ross McKinney[18], Alvin Ng[19], Jeri Nieves[8], Regis O'Keefe[20], Socrates Papapoulos[21], Howe Tet Sen[19], Marjolein C.H. van der Meulen[22], Robert S. Weinstein[23], Michael Whyte[24]

Initial Date Submitted July 19, 2010; Date Revision Submitted August 23, 2010; Date Final Disposition Set September 7, 2010
Journal of Bone and Mineral Research

DOI 10.1002/jbmr.253

[1]Columbia University
[2]Indiana University School of Medicine
[3]University of Melbourne
[4]Copenhagen University Hospital Gentofte
[5]McGuire Veteran's Administration Medical Center
[6]University of Iowa
[7]University Health Network & University of Toronto
[8]Helen Hayes Hospital
[9]University of Alabama at Birmingham
[10]Kaiser Permanente Bellflower
[11]Boston Medical Center
[12]University of California at San Francisco
[13]Maastricht University Medical Center, The Netherlands & University Hasselt, Belgium
[14]Hanusch Hospital – Ludwig Boltzmann Institute of Osteology
[15]Dartmouth-Hitchcock Medical Center
[16]Hospital for Special Surgery
[17]Marshfield Clinic
[18]Duke University School of Medicine
[19]Singapore General Hospital
[20]University of Rochester
[21]Leiden University Medical Center
[22]Cornell University
[23]University of Arkansas for Medical Sciences
[24]Shriners Hospital for Children

[*]Corresponding Authors

Elizabeth Shane, M.D., Columbia University, College of Physicians and Surgeons, PH 8 West-864, 630 West 168th Street, New York, NY 10032. Phone: (212) 305-6289, Fax: (212) 305-6486, E-mail: es54@columbia.edu

David Burr, Ph.D., Indiana University School of Medicine, Dept of Anatomy and Cell Biology, MS 5035, 635 Barnhill Dr., Indianapolis, IN 46202. Phone: (317) 274-7496, Fax: (317)278-2040, E-mail: dburr@iupui.edu.

Conflict/Duality of Interest Summary and Disclosures

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

The committees, task forces, and editorial boards of the ASBMR and its publications carry out the work of the Society on behalf of the membership. The distinct functions of the committees, task forces, and editorial boards are intended to address the broad mission of the ASBMR: to promote excellence in research and education, to integrate basic and clinical science in the field of bone and mineral metabolism, and to facilitate the translation of research into clinical practice and the betterment of human health. Chairs and members of committees, task forces, and editorial boards must assure that they act in these roles in a manner free from commercial bias and that they resolve any conflict or duality of interest or disclose them and then recuse themselves from related deliberations and voting.

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 speaker's 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 (e.g., you serve on a bone related organization's board, committee, journal; a family member contracts with ASBMR, etc.)

Name	Affiliation/Representation	Conflicts	Commercial Entity/# of Relationships
Elizabeth Shane, Task Force Co-Chair	Columbia University	Yes	Merck, 1; Novartis, 1; Eli Lilly, 1; Bone Editorial Board, 6
David Burr, Task Force Co-Chair	Indiana University School of Medicine	Yes	Eli Lilly, 1, 2, 3; Amgen, 2, 3; Procter and Gamble, 1, 2; NephroGenex, 1; Bone 6; J Musculoskeletal and Neuronal Interactions 6; Osteoporosis International 6; Calcified Tissue International 6; J Biomechanics 6
Bo Abrahamsen	Copenhagen University Hospital Gentofte	Yes	Amgen, 2; Nycomed, 2; Eli-Lilly, 3; Merck, 3; Novartis, 1
Robert A. Adler	McGuire Veteran's Administration Medical Center	Yes	Novartis, 1; Eli Lilly, 1, 2; Amgen, 1; Genentech, 1; Merck, 1, 2; GTX, Inc., 2; ISCD, 6 (Scientific Advisory Committee); Endocrine Research, 6 (Editorial Board); Journal of Clinical Densitometry, 6 (Editorial Board)
Thomas D. Brown (Reviewer Scientist)	University of Iowa	Yes	Smith & Nephew Orthopaedics, 2; Journal of Biomechanics, 6 (Editorial Advisory Board); Journal of Bone & Joint Surgery, 6 (Deputy Editor for Research); Journal of Orthopaedic Trauma, 6 (Editorial Board)
Angela M. Cheung	University Health Network University of Toronto	Yes	Amgen, 1, 2; Astra Zeneca, 1; Eli Lilly, 1, 2; Merck, 1; Novartis, 1; Alliance for Better Bone Health (Sanofi Aventis/Warner Chilcott), 1
Felicia Cosman	Helen Hayes Hospital	Yes	Eli Lilly, 1, 2, 3; Novartis, 2, 3; Merck, 2; Amgen, 2, 3; Zosano 2
Jeffrey R. Curtis	University of Alabama at Birmingham	Yes	Merck, 1, 2; Procter and Gamble, 1; Novartis, 1, 3; Eli Lilly, 1, 2, 3; Amgen 1,2
Richard Dell	Kaiser Permanente Bellflower	No	
David Dempster	Columbia University	Yes	Eli Lilly, 2, 3; Merck, 2; Amgen, 2, 3; Genentech, 3
Peter R. Ebeling	University of Melbourne	Yes	Merck 1,2; Novartis, 1, 3; Amgen, 1, 2; Sanofi-Aventis, 3; Osteoporosis International, 6
Thomas A. Einhorn	Boston Medical Center	Yes	Eli Lilly, 2; Novartis, 2; Amgen, 2; Smith and Nephew, 2; Osteotech, 2; Associate Editor, Bone, 6, Editorial Board, JBMR, 6, Deputy Editor, The Journal of Bone and Joint Surgery, 6, Editorial Board, Journal of Orthopaedic Research
Harry Genant	University of California at San Francisco	Yes	Merck, 2; Amgen, 2; Eli Lilly, 2; GSK, 2; Novartis, 2; Servier, 2; Roche, 2; Genentech, 2; BMS, 2; Wyeth, 2; Synarc, 5

Name	Affiliation/Representation	Conflicts	Commercial Entity/# of Relationships
Piet Geusens	Maastricht University Medical Center, The Netherlands & University Hasselt, Belgium	Yes	MSD, 1; Amgen, 1, 3; Procter and Gamble, 1, 3; Servier, 1; Novartis, 1; Wyeth, 1; Pfizer, 1; Swerinng Plough, 1; Abott, 1
Klaus Klaushofer	Hanusch Hospital – Ludwig Boltzmann Institute of Osteology	Yes	Amgen, 1; Eli Lilly, 1; MSD, 1; Novartis, 1; Procter and Gamble, 1; Servier, 1
Kenneth Koval	Dartmouth-Hitchcock Medical Center	No	
Joseph M. Lane	Hospital for Special Surgery	Yes	Amgen, 2; Biomimetrics, 2; D'Fine, 2; GrafLys Inc., 2; Innovative Clinical Solutions, 2; Kuros Biosurgery, 2; Zimmor, 2; Eli Lilly, 3; Novartis, 3; Sanofi-Aventis, 3; Warner Chilcott, 3
Fergus McKiernan	Marshfield Clinic	Yes	Amgen, 2
Ross McKinney (Ethicist)	Duke University School of Medicine	Yes	Gilead Sciences, 6 (DSMB Member)
Alvin Ng	Singapore General Hospital	No	
Jeri Nieves	Helen Hayes Hospital	No	
Regis O'Keefe	University of Rochester	Yes	Osteogenix, 2; LAGeT, 5
Socrates Papapoulos	Leiden University Medical Center	Yes	Alliance for Better Bone Health, 1, 2; Amgen, 2; Merck, 2; Novartis, 2; Roche/GSK, 2; Wyeth, 2; International Osteoporosis Foundation, 6 (Board Member); European Calcified Tissues Society, 6 (Board Member); ESCEO-IOF Working Group on Subtrochanteric Fractures, 6 (Member); Osteoporosis International 6; Bone 6
Howe Tet Sen	Singapore General Hospital	No	
Marjolein C.H. van der Meulen	Cornell University	Yes	Journal of Orthopaedic Research, 6 (Deputy Editor)
Robert S. Weinstein	University of Arkansas for Medical Sciences	No	
Michael Whyte	Shriners Hospital for Children	Yes	Enobia Pharma, 1, 2; Merck, 5; Bone 6; Clinical Cases in Bone and Mineral Metabolism 6; J Clinical Densitometry 6

ASBMR Disclosure

The American Society for Bone and Mineral Research (ASBMR) is the premier professional, scientific and medical society established to promote excellence in bone and mineral research and to facilitate the translation of that research into clinical practice. The ASBMR has a membership of nearly 4,000 physicians, basic research scientists, and clinical investigators from around the world. The ASBMR has a hard-earned reputation for scientific integrity.

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

Although task force members were required to disclose their potential conflicts of interest and their disclosures are published with this document, ASBMR recognizes that this might not go far enough to demonstrate to some that the final output of the Task Force is free of all bias. In an effort to address this concern, 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.

MICROABSTRACT

In recent years, there have been reports of atypical fractures of the subtrochanteric region of the hip and the femoral shaft in patients receiving long-term bisphosphonate therapy. Thus, the ASBMR leadership appointed a multi-disciplinary, international task force to address key questions related to case definition, epidemiology, risk factors, diagnostic imaging, future areas for research and clinical management related to the disorder. This report summarizes the findings and recommendations of the task force.

ABSTRACT

Introduction: 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.

Methods: A multi-disciplinary expert group reviewed pertinent published reports concerning atypical femur fractures, as well as pre-clinical studies that could provide insight into their pathogenesis.

Results and Conclusions: 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 and absence of comminution, be present to designate a femoral fracture as atypical. Minor features include their associations with cortical thickening, a periosteal reaction of the lateral cortex, a medial spike when the fracture is complete, prodromal pain, bilaterality, co-morbid 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 biological 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 to 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 under-reporting may mask the true incidence of the problem.

Recommendations: 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 epidemiological and clinical data to establish the true incidence of and risk factors for this condition and to inform orthopaedic and medical management.

Key words: osteoporosis, bone, pain, fracture, atypical, subtrochanteric, femoral diaphysis, bisphosphonates

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 current 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 non-invasive 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 orthopaedic 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, multi-disciplinary group of 28 individuals with expertise in clinical and basic bone biology, endocrinology, epidemiology, radiology, biomechanics and orthopaedic surgery. The expert committee also included a basic scientist (T.D.B.) working in the bone field but not in the areas of osteoporosis and BPs, and a physician and bioethicist (R.M.) 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", "anti-resorptive", "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 subsequently reviewed by four members of the ASBMR Task Force in order to construct the relevant sections of this document. 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 radiological changes, co-morbid 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 (<20ng/mL), the presence of BMD T score > -2.5 (osteopenia or normal BMD), information on bone histology, the 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 Figure 1.

RESULTS AND DISCUSSION

1. 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 most commonly observed 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 trauma 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 (Figure 2A). Complete

atypical femoral fractures are generally transverse although they may have a short oblique configuration, and are not comminuted. Alternatively, the fracture may be incomplete, 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 (Figure 2B), abnormalities indicative of a stress fracture. In addition, there may be generalized bilateral thickening of the both 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 co-morbid 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, pathological fractures associated with local primary or metastatic bone tumors, and peri-prosthetic 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 (femoral neck, intertrochanteric). Minor features have commonly been described in association with atypical fractures, but may or may not be present in individual cases. Although atypical femoral fractures have been reported most prominently in individuals who have been treated with BPs, such fractures 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.

2. Review carefully the current 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 pre-clinical 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 United States Food and Drug Administration (US FDA).

Insights Into the Pathogenesis of Atypical Femoral Fractures From Basic Studies

The radiologic presentation of atypical femoral fractures bears striking similarities to stress fractures (1) and may also resemble 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) have all 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 may often also have a more generalized thickening of both medial and lateral cortices bilaterally. This may be a normal genetically-determined variant of femoral shape, but has often been observed in those who have sustained an atypical femoral fracture. However, there is no evidence that BPs are associated with this more generalized cortical thickening as they are not known to stimulate periosteal apposition, nor do their anti-remodeling effects lead to enhanced endosteal formation.

Atypical femoral fractures in patients on BPs have occurred in the setting of co-morbid conditions with known adverse effects on bone quality (e.g., DM) (10-13). A relatively large proportion of the patients have also 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 increased risk of fracture (18). In vitro (19) and in vivo studies (20,21) demonstrate that AGE accumulation increases the brittleness of bone.

a. Bisphosphonate 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 non-enzymatic 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. Non-enzymatic cross-links are formed through the interaction of collagen and sugars via oxidation reactions. They are associated with the accumulation of advanced glycation end-products (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 one year of treatment with a wide range of BP doses, the PYD/DPD ratio was significantly increased in vertebral cancellous bone and tibial cortical bone from BP treated dogs compared to 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 post-yield 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 rib of dogs after 3 years of treatment with incadronate (29). However, caution should be exercised when interpreting the results of these studies as they involved BP administration to normal rather than osteoporotic dogs.

There are limited data on collagen crosslinks in humans treated with BPs. Using Fourier Transformed Infrared Spectroscopy (FTIR), Durchschlag et al. (30) showed that BP treatment prevented the maturation of collagen found in patients not treated with bisphosphonates, and reduced collagen maturity in newly formed bone. Boskey et al. (31) reported no change in collagen maturity in women treated with alendronate. Donnelly et al. (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.

b. Bisphosphonate effects on bone mineralization density distribution (BMDD)

Bone mineralization density distribution (BMDD) is a measure of 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 biological and mechanical optimum. Therefore, even small deviations from the normal BMDD may have biological 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 et al. (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 eight 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 preferentially affected. Narrowing of the BMDD by BPs may be transient. After 5 – 10 years of BP treatment, BMDD was restored to within the normal premenopausal range (40-43).

c. Effects of reducing remodeling on microdamage accumulation

Excessive bone remodeling results in microarchitectural deterioration with 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 efficiently removed. Even in the

absence of BP treatment, age-related reductions in bone turnover result in microdamage accumulation (28). There is a 3-fold 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 inter-individual variability in the amounts. BPs may exacerbate damage accumulation, as they impair targeted remodeling to a greater extent than remodeling not targeted to damage repair (i.e., stochastic remodeling) (46,47), thereby allowing microdamage to persist for longer compared to non-treated 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 just ~40% with risedronate is associated with a 3-fold increase in microdamage compared to untreated controls (48), and suppression by ~20% with raloxifene is associated with a doubling of damage (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 analysis 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.

d. Effects of reducing remodeling on tissue mechanical properties

Microdamage accumulation with BP treatment is not only a function of reduced repair, but BP-treated bone is also 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 one year with either risedronate or alendronate at doses equivalent to those used to treat postmenopausal osteoporosis (52). Vertebrae were then removed and loaded cyclically in compression (5 Hz for 100,000 cycles at loads ranging from 100-300% 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).

Pre-clinical studies show that treatment with BPs is associated with reduced bone toughness (48,53,54). Following 1-3 years of BPs at doses similar to or above those used in postmenopausal women, toughness was 20-30% lower compared to control animals (48,53). It was initially thought 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 one-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, 3-fold 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 the 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.

e. ***Affinity and retention of bisphosphonates 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 could eventually increase the risk of fracture, even in the face of increased bone mass. However, the toughness of the femoral diaphysis

in non-osteoporotic dogs treated for as long as three 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 ~3%/yr (59), based on biopsies from the rib, which is known to have a relatively high rate of turnover compared to 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 five year old beagle dogs that have cortical bone that is structurally very similar to human bone, the rate of turnover in the femoral cortex is about 1%/yr (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 et al. (11) and 7 years according to the current review.

f. Effects of bisphosphonates 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 ^{99m}technetium 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 eventually result in consolidation of the damage and a complete fracture of the stressed site.

e. Effects of bisphosphonates on angiogenesis

Effects of BPs on stress fracture repair could be exacerbated if BPs are also anti-angiogenic. 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, as both are coupled. However, dissociation between the two is possible during skeletal development in animal models, and studies of growing animals showed no anti-angiogenic effect of clodronate (69). Still, primary studies in non-skeletal tissues suggest that angiogenesis may indeed 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 1-4 hours after initiation of the stress fracture (71,72), and upregulation of osteogenic genes in the cambium layer of the periosteum within three days. Early upregulation of 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.

h. Summary of pre-clinical studies

The pre-clinical data provide a mixed picture of the effects of the BPs on bone's matrix composition and mechanical properties. BPs reduce bone remodeling, preventing the loss of bone and the 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 absorption 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 absorption 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

a. General epidemiology of subtrochanteric and femoral shaft fractures

Fractures located in the subtrochanteric region or femoral shaft (diaphysis) account for 7-10% 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 pre-fracture 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

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 both in males and females (82), similar to that reported by Singer et al. (83). The age-specific incidence (per 100,000) rates for subtrochanteric fractures increased between 65 and 85 year categories in both males and females in Iran (84), in the United States (US) (85), and in the United Kingdom (86). Although femoral shaft fractures were more common among males than females up to age 49, this gender difference was reversed in the 60–69 year age group (82). Thus, subtrochanteric fractures share features of typical osteoporosis-related fractures including: 1) higher incidence among women than men 2) a steep increase in incidence with age and 3) more common 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 US (74).

The epidemiology of femoral neck, trochanteric and intertrochanteric hip fractures was compared to subtrochanteric and femoral shaft fractures in the US 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, trochanter and intertrochanteric regions) decreased from about 600/100,000 to 400/100,000 person-years in the decade after 1996. In contrast, subtrochanteric and femoral shaft fracture rates did not change, with an annual incidence less than 30/100,000 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 (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 et al. (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 Caucasian women > 65 years followed for as long as 24 years indicate that the incidence of subtrochanteric fractures is very low (3/10,000 patient years) compared to the overall incidence of hip fracture (103/10,000 patient years) (91). After excluding high energy, pathologic or periprosthetic fractures, 48 subtrochanteric fractures occurred in 45 women (3.4% of hip fractures), nine 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-naïve group. As fracture radiographs were not available, features of atypia were not ascertained. However, in 33 of the 45 women from 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 compared to those with the thinnest cortices (92). Although lateral cortical thickening is commonly described in patients with atypical fractures, thickness of the lateral cortex was not related to fracture risk. As only six women of 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.

b. 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 to one intertrochanteric and one femoral neck fracture case that presented during the same time period (2000 to 2007). BP use was documented in 15 of the 41 (37%) subtrochanteric and femoral shaft cases, compared with nine of the 82 (11%) intertrochanteric and femoral neck cases, resulting in an odds ratio (OR) of 4.44 (95% 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 cases compared with both hip fracture control groups ($P = 0.001$). 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 cases on a BP and in three of 26 patients who were not taking a BP (OR, 15.33; 95% CI, 3.06-76.90; $p<0.001$).

In a cross-sectional study of 11,944 Danish people over age 60, Abrahamsen et al. (94) compared age-specific fracture rates and BP exposure in various kinds of proximal femur fractures identified by 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 to two controls (n =10,374). In this register-based matched cohort study, the hazard ratio for subtrochanteric or diaphyseal fracture with alendronate was 1.46 (0.91–2.35, P = 0.12), similar to the hazard ratio of 1.45 (1.21–1.74, $P < 0.001$) 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 were also 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 fracture 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), 4.7/1000 versus 3.1/1000, respectively. In contrast, there was a decline in femoral neck/intertrochanteric hip fracture incidence with increasing dose-years of alendronate from lowest (22.8/1000) to highest quartile (10.9/1000). The hazard ratio for subtrochanteric/diaphyseal fracture with alendronate was 1.50 (1.31–1.72) compared with 1.29 (1.21–1.37) for femoral neck/intertrochanteric hip fracture. Although rates of all fractures were higher in alendronate users than nonusers, highly compliant patients had significantly lower risk of femoral neck/intertrochanteric fractures (HR 0.47; 0.34-0.65) and subtrochanteric/diaphyseal fractures (HR 0.28; 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 to 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 four years. Recently, however, Black et al.(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 3-4.5 years. In FLEX, 1099 women originally randomized to alendronate were re-randomized to alendronate five or 10 mg/day or placebo. The total duration of alendronate was 10 years for those randomized to alendronate and five years for those randomized to placebo. In the HORIZON trial, 7736 women were randomized to zoledronate 5 mg or placebo and followed for three years. All 284 hip and femur fractures were re-evaluated to identify femoral shaft fractures and assess features of atypia. However, the reevaluation was based on the radiographic report, as radiographs were available for only one subject. Twelve subtrochanteric/diaphyseal fractures (4%) were found in 10 subjects, three 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 was not significantly increased, even among

women treated for as long as 10 years. Although the FLEX data that compare five and 10 years of alendronate 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 four 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 CPT coding in patients older than 45 over a three-year period between 2007 and 2009. After excluding those above the subtrochanteric region and below the distal femoral flair, periprosthetic, pathologic and high trauma fractures, 600 radiographs were reviewed, of which 102 (~17%) had features of atypia (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 2/100,000 cases per year for 2 years of BP use to 78/100,000 cases per year for eight years of BP use. These data suggest that atypical femoral fractures are rare in both the general population and in 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 six years. Important strengths of this study include the expert adjudication of all 600 radiographs that occurred in the region of interest and availability of data on filled prescriptions for oral BPs.

c. Summary of Epidemiological Studies

It is important not to equate the anatomical 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 epidemiological context is that

the total number of these fractures marks the upper boundary of any potential harm due to atypical femoral fractures. Notably, subtrochanteric and diaphyseal fractures together account for only about 5-10% of all hip/femoral fractures; of these, only a subset is atypical (17-29%). The proportion of subtrochanteric and diaphyseal fractures that have features of atypia depends on whether fractures due 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 three of the eight patients with atypical fragility fractures of the femur reported by Schilcher et al. (101), in one of 20 cases in the Neviaser case series (100), in five of 102 cases reported by Dell et al. (99), in one of four cases reported by Bunning et al. (102), in three of 26 cases in the Lenart study (93), and also in patients with hypophosphatasia (2,103).

Epidemiological 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 upon diagnostic codes for case finding that may misclassify fracture location (104) and do not assess the radiological hallmarks of atypia. Thus, a stable total number of subtrochanteric fractures could potentially mask a shift from typical, osteoporotic subtrochanteric fractures towards more atypical fractures, as might be suggested by Dell's results (99) and those reported by Bhattacharyya and Wong (90).

If BPs are targeted to patients with 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 78/100,000 incidence figure reported by Dell et al. (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 upon the quality in seven areas, as indicated in Tables 3 and 4.

a. 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 five in patients with BP treatment for malignancy (myeloma or metastatic renal cell carcinoma). In 19 cases, BP use was not identified. The subjects ranged in age from 36-92 years. Only nine fractures were in men, but sex was not identified in three large case series (100,107,108). The majority (160/189) occurred after oral alendronate monotherapy: 12 were treated with oral risedronate (of these, one was followed by oral alendronate while two were previously treated with alendronate and another was previously treated with pamidronate), four with the combination of intravenous pamidronate followed by intravenous zoledronic acid (myeloma), four with either oral or intravenous pamidronate (osteoporosis), two with intravenous zoledronic acid (renal cell carcinoma and osteoporosis), two 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 one case. The median duration was seven years. The presence or absence of prodromal pain was assessed in 227 of 310 cases; it was present in 70% (158 of 227). Concomitant GC use was assessed in 76 of 310 cases; it was present in 34% (26 of 76) and increased the risk of subtrochanteric fractures in one large series (OR 5.2) (107).

Bilateral fractures were assessed in 215 of the 310 cases and were present in 28% (60 of 215 cases). Bilateral radiological changes were assessed in 224 of the 310 cases and were present in 28% (63 of 224). Healing was assessed in 112 of the 310 cases, 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 <65 years (OR 3.6); and active RA (OR 16.5)(107). PPI use was assessed in 36 of the 310 cases, and was noted in 14 (39%) (112,119-121).

Serum 25-hydroxyvitamin D (25-OHD) concentrations were measured in 84 cases and five (6%) had vitamin D deficiency (25-OHD < 20 ng/mL). In one large series, serum 25-OHD concentrations <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 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 cases. However, as 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. BTMs obtained prior to the fracture would be more informative.

b. 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 may also occur in BP-naïve patients. Several unique radiographic and clinical features have emerged from these case reports and series. All of 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); 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 (e.g., estrogen, raloxifene, calcitonin); and use of GCs or PPIs in addition to the BP (118,119,125); presence of RA or DM; serum 25-OHD concentrations < 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, as 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 to the amount of BP received and perhaps suggests that duration may be more important than amount.

Guisti et al. conducted a systematic review of 141 women with postmenopausal osteoporosis treated with BPs who sustained subtrochanteric/diaphsyeal fractures (11). Their results are generally comparable to this Task Force report with regard to age, mean duration of BP use, proportions with bilateral fractures, prodromal pain, co-morbid conditions (DM, 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 co-morbid 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 due 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.

c. 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 have generally revealed extremely low bone turnover, a finding consistent with BP treatment (137-139), and especially in patients treated concomitantly with a BP and another antiresorptive agent, such as estrogen (140) or with BPs and GCs (141). 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 only been treated for six months (130). Moreover, lack of double label or so little double label that mineral apposition rate cannot be reliably evaluated 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 the majority of 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 post-fracture biopsy showed lack of osteoid and tetracycline labels, confirming conversion of high to low turnover.

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 as 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 et al. (112) obtained biopsies from two cases, but described the histological appearance of only one of these, a 65-year-old postmenopausal woman who had received alendronate for five years and ibandronate for one year before suffering a subtrochanteric right femoral shaft insufficiency fracture. Five years earlier and two years after starting alendronate, she had sustained a subtrochanteric fracture of her left femur. This patient had also 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 surfaces 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 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 eight years (113). 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 et al. (10) performed qualitative histology on biopsies removed intraoperatively during repair of subtrochanteric fractures in five alendronate-treated patients, but they simply reported that there was no evidence of neoplasia.

Napoli et al. (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 two years and zoledronate for four 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 et al. (123) reported another case of a patient with multiple myeloma who had been treated with intravenous BPs (pamidronate and zoledronate) for nine years and presented with sequential, bilateral subtrochanteric stress fractures. Histological 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 above cases, the biopsy from the subtrochanteric fracture site obtained by Somford et al. (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 eight years prior to admission for a subtrochanteric stress fracture of her left femur, which subsequently fractured completely. She had also received GCs and methotrexate for 11 years and infliximab for three 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 from the right femur approximately one 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 substantially reduced to within the range previously reported for patients with alendronate-treated, GC-induced osteoporosis (141). Unexpectedly, the eroded surface was about 3-fold higher than controls and 6.5 to 13 times the levels seen in GC-induced osteoporosis and postmenopausal osteoporosis, respectively. Osteoclast number was also about four times higher than that recorded in alendronate-treated subjects; however, this is not surprising as 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 6-fold higher than at the iliac crest. At both sites, the morphological 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 was also evident in the iliac crest biopsy and that the femoral biopsy was located a centimeter above the fracture and was taken within 12 hours of the event. MR evidence for excessive resorption at the site of

atypical fractures has also 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 et al (119) also took the opportunity to assess the mineralization density of the bone tissue at the fracture site, as 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 histological data currently available in patients with atypical fractures, most but not all studies indicate very low turnover at both the iliac crest and at the fracture site, although reports of increased turnover may be influenced by the fracture itself. Also, only static and qualitative histomorphometry 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 et al. (119) at both the ilium and the fracture site, and of Visekruna et al. (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 Research section).

d. Input from the pharmaceutical industry:

Four members of the Task Force (D.B., T.B., R.M., E.S.) conducted teleconference sessions with representatives of companies that market drugs used to treat osteoporosis in the United States (Amgen, Eli Lilly, Genentech, Merck, Novartis, Warner-Chilcott). These sessions were informational; they permitted the task force to develop some understanding of the number of atypical fractures cases reported to industry and the steps being taken by the individual companies to adjudicate cases reported to them. The sessions also permitted experts from industry to provide their input on the case definition for consideration by the Task Force.

The majority 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. The majority of cases were from the post-marketing 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, scientific literature and lay press. Although this system is useful for identifying rare events that are not detected in clinical trials, important limitations include under-reporting and poor quality reports with missing critical information. Additionally, it is impossible to calculate incidence rates; the numerator is uncertain because of under-reporting and the denominator is generally based upon 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 (1-3/1,000,000 patient years of exposure). However, as expected, the pharmaceutical companies were aware of cases that had not been reported in the medical literature.

e. Input from the United States Food and Drug Administration (US FDA):

Two Task Force members (D.B., E.S.) conducted a teleconference with representatives of the US 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 above, particularly substantial under-reporting.

2. Recommend the development of non-invasive 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 (MR), or computed tomography (CT) useful principally for detecting early or subtle pre-fracture features (12,93,100,119,145).

Conventional radiographs of the femur, acquired in antero-posterior and lateral projections, will usually suffice to demonstrate a range of characteristic findings in complete or incomplete fractures (Fig. 2A)(149-152). 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 (Fig. 2B) (12,93,100,145). 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 may also 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 moderately early evolution, the findings may be quite subtle and non-diagnostic (Fig. 4A, 4C, 5A) (149,150). 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 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 (Fig. 4B, 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 the stress fractures.

Like bone scintigraphy, MR imaging can detect the reactive hyperemia and periosteal new-bone formation of an evolving stress or insufficiency fracture (Fig. 5C) (151-155). Typically, on T1-weighted images there will be diffuse decreased signal due to water partially replacing the normal fatty marrow components and due to 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 specificity, generally surpassing that of bone scintigraphy.

Similarly the application of advanced multi-slice, or spiral CT imaging with its thin sections, relatively high resolution and multi-planar reformation capability render this technique quite useful in detecting subtle reactive periosteal new-bone formation and the small, discrete radiolucency of the evolving fracture and its focal intra-cortical bone resorption (156-158).

While scintigraphy, MRI and CT 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-x-ray absorptiometry (DXA) may occasionally 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 (Fig. 5D) (104).

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

Recommendations to Facilitate Future Research

a. Create specific diagnostic and procedural codes for cases of atypical femoral fractures

To facilitate case ascertainment in administrative datasets and identification of incident cases, specific diagnostic and procedural codes (ICD and/or Current Procedural Terminology code) should be created for atypical femoral fractures, based upon the major features summarized in the Case Definition, as has recently been done for osteonecrosis of the jaw (ONJ; ICD9 733.45). Such codes would facilitate preliminary case ascertainment in administrative datasets, which would then 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 as compared with other osteoporotic fractures of the lower extremity that could otherwise 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.

b. 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 (i.e., a denominator). The registry must utilize 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 classical comminuted spiral fractures from non-comminuted 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 both from administrative and clinical data sources (Table 7). An external agency could also 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 between the recording of vital information, as 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, co-morbid diseases and concomitant medications, as summarized in Table 7.

Key Research Questions

a. Define measurable characteristics that are associated with atypical femoral fractures.

To develop a clinical profile and to 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 would also be important to determine prospectively the frequency of other characteristics reported in conjunction with atypical femoral fractures, such as:

- The frequency of periosteal reaction (i.e., callus) associated with a fracture, including the incidence of such reactions in the contralateral non-fractured femur

- The incidence and duration of prodromal thigh pain
- The frequency of bilateral fractures and symptoms

b. 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 both 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 co-morbid diseases. Without these data, it is possible to misinterpret an association between treatment and fractures as causation. Patients with Paget's disease receiving intermittent courses of BPs, and patients with malignancies receiving high doses of intravenous BPs should also 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 or denosumab, or in diseases characterized by extremely low bone turnover, such as osteopetrosis, hypoparathyroidism, myxedema or certain forms of renal bone disease. It will also 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 prevention and treatment of bone loss and fractures associated with GCs. However, there are no studies of long-term (>2-3 years) BP treatment in patients receiving GCs. Thus, while short-term (1-2 years) BP administration lowers the risk of typical osteoporotic fractures in patients with GIOP, it is possible that prolonged administration of two classes of drugs that suppress bone formation may increase the risk of atypical femoral fractures.

c. 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 bone mineral density using microradiographs, μCT 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.

d. Genetics

Although patients with X-linked hypophosphatemia (XLH) can have pseudofractures that resemble atypical femoral fractures (2), XLH is usually obvious and could only rarely 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 non-specific (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 from antiresorptives. Genome-wide association studies will probably not be helpful, because DNA samples from many atypical femoral fractures patients would be necessary.

e. 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.

f. 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 a critical 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, which have substantial intracortical bone remodeling, may be appropriate. However, these animals cannot be studied in conjunction with the osteoporotic condition, as attempts to make them estrogen deficient do not generally 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 (e.g., 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 end-points of such studies should not be overt fracture. Rather, animal models can be used to investigate alterations of the structural and material properties of the bone under different conditions, such as co-administration of GCs and BPs, or administration of BPs to diabetic animals. They could also 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 (e.g., treatment with PTH) should also be examined in such models.

5. Recommend clinical orthopaedics and medical management of subtrochanteric 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 orthopaedic surgeons who served on the Task Force. The Task Force developed a hierarchical approach to management dependent upon whether fracture was complete or incomplete.

a. History of thigh or groin pain in a patient on bisphosphonate therapy

A femoral fracture must be ruled out (10,12,93,100,110,115,124,159). Anterior-posterior 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 an 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.

b. Complete subtrochanteric/diaphyseal femoral fracture

Orthopaedic management includes stabilizing the fracture and addressing the medical management (see below) (10,12,93,100,110,115,124,159). 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 over-reamed (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 the passage of the nail and avoid malalignment. The contralateral femur must be evaluated radiographically, including scintigraphy or MR, whether or not symptoms are present (110).

c. 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 2-3 months of conservative therapy, prophylactic nail fixation should be strongly considered, as 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 the MRI.

Medical Management of Atypical Subtrochanteric Femoral and 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:

a. 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, 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 risedronate (163,164), patients with osteoporosis will have an anti-fracture benefit for at least 5 years. However, continued use of BP therapy beyond that time should be re-evaluated 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 re-evaluation) 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 five 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 non-vertebral fracture incidence was limited to those women without a fracture history but with femoral neck T-scores < -2.5 (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 risedronate, seven years of therapy did not further reduce the incidence of vertebral fractures below that observed with three and five years of therapy (163). Models to help determine absolute risk of fracture in patients who have already been treated for 4-5 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 > -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 4-5 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 re-started. However, patients should be followed by clinical assessment, bone turnover markers and BMD. Restarting osteoporosis therapy, either with BPs or a different class of agent, can be considered in those patients who appear to be at increasing fracture risk. Models to help assess risk in previously treated patients, after one 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 scans should be performed to identify stress reaction, stress fracture, or partial fracture of either femur. Other disorders, such as forms of osteomalacia, should also be considered (2).

b. Medical Management

For patients with a stress reaction, stress fracture, incomplete or complete subtrochanteric or femoral shaft fracture, potent antiresorptive agents should be discontinued. Dietary calcium and vitamin D status should be assessed, and adequate supplementation prescribed. 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 non-union 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 will likely 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 four to six weeks after surgical intervention.

Summary and Conclusions

BPs are highly effective at reducing 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 (transverse or short oblique orientation, absence of comminution, cortical thickening, stress fracture or stress reaction on the symptomatic and/or contralateral side, delayed healing) and unique clinical features (prodromal pain, bilaterality). The apparent increased risk for atypical femoral fractures in patients receiving GCs is a concern, as BPs are the mainstay for prevention of GC-induced osteoporotic fractures. Bone biopsies from the iliac crest and/or the fracture site generally show reduced bone formation consistent with BP action. Paradoxically, some cases 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 to typical and common femoral neck and intertrochanteric fractures. It must also be emphasized that BPs are important drugs for 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 epidemiological data to establish the true incidence of and risk factors for this condition, and studies to address their surgical and medical management.

REFERENCES:

1. Chisin R 2001 The Role of Various Imaging Modalities in Diagnosing Stress Fractures. In: Burr DB, Milgrom C (eds.) Musculoskeletal Fatigure and Stress Fractures. CRC Press, Boca Raton, pp 279-294.
2. Whyte MP 2009 Atypical femoral fractures, bisphosphonates, and adult hypophosphatasia. J Bone Miner Res **24**(6)**:**1132-4.
3. Li J, Waugh LJ, Hui SL, Burr DB, Warden SJ 2007 Low-intensity pulsed ultrasound and nonsteroidal anti-inflammatory drugs have opposing effects during stress fracture repair. J Orthop Res **25**(12)**:**1559-67.
4. Uthgenannt BA, Kramer MH, Hwu JA, Wopenka B, Silva MJ 2007 Skeletal self-repair: stress fracture healing by rapid formation and densification of woven bone. J Bone Miner Res **22**(10)**:**1548-56.
5. Burr DB, Milgrom C, Boyd RD, Higgins WL, Robin G, Radin EL 1990 Experimental stress fractures of the tibia. Biological and mechanical aetiology in rabbits. J Bone Joint Surg Br **72**(3)**:**370-5.
6. Li GP, Zhang SD, Chen G, Chen H, Wang AM 1985 Radiographic and histologic analyses of stress fracture in rabbit tibias. Am J Sports Med **13**(5)**:**285-94.
7. Muir P, Johnson KA, Ruaux-Mason CP 1999 In vivo matrix microdamage in a naturally occurring canine fatigue fracture. Bone **25**(5)**:**571-6.
8. Nunamaker D 2001 Bucked Shins in Horses. In: Burr DB, Milgrom C (eds.) Musculoskeletal Fatigue and Stress Fractures. CRC Press, Boca Raton, pp 279-294.
9. Verheyen K, Price J, Lanyon L, Wood J 2006 Exercise distance and speed affect the risk of fracture in racehorses. Bone **39**(6)**:**1322-30.
10. Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT, Howe TS 2007 Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br **89**(3)**:**349-53.
11. Guisti A, Hamdy NAT, Papapoulos SE 2010 (In press) Atypical fractures of the femur and bisphosphonate therapy: A systematic review of case/case series studies. Bone.
12. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS 2008 An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury **39**(2)**:**224-31.
13. Visekruna M, Wilson D, McKiernan FE 2008 Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab **93**(8)**:**2948-52.
14. Jilka RL, Weinstein RS, Parfitt AM, Manolagas SC 2007 Quantifying osteoblast and osteocyte apoptosis: challenges and rewards. J Bone Miner Res **22**(10)**:**1492-501.
15. Plotkin LI, Lezcano V, Thostenson J, Weinstein RS, Manolagas SC, Bellido T 2008 Connexin 43 is required for the anti-apoptotic effect of bisphosphonates on osteocytes and osteoblasts in vivo. J Bone Miner Res **23**(11)**:**1712-21.
16. Wang FS, Ko JY, Yeh DW, Ke HC, Wu HL 2008 Modulation of Dickkopf-1 attenuates glucocorticoid induction of osteoblast apoptosis, adipocytic differentiation, and bone mass loss. Endocrinology **149**(4)**:**1793-801.

17. Asada T, Kushida T, Umeda M, Oe K, Matsuya H, Wada T, Sasai K, Ikehara S, Iida H 2008 Prevention of corticosteroid-induced osteonecrosis in rabbits by intra-bone marrow injection of autologous bone marrow cells. Rheumatology (Oxford) **47**(5)**:**591-6.
18. Saito M, Marumo K Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporos Int **21**(2)**:**195-214.
19. Vashishth D, Gibson GJ, Khoury JI, Schaffler MB, Kimura J, Fyhrie DP 2001 Influence of nonenzymatic glycation on biomechanical properties of cortical bone. Bone **28**(2)**:**195-201.
20. Allen MR, Gineyts E, Leeming DJ, Burr DB, Delmas PD 2008 Bisphosphonates alter trabecular bone collagen cross-linking and isomerization in beagle dog vertebra. Osteoporos Int **19**(3)**:**329-37.
21. Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D 2009 Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. Osteoporos Int **20**(6)**:**887-94.
22. Hernandez CJ, Tang SY, Baumbach BM, Hwu PB, Sakkee AN, van der Ham F, DeGroot J, Bank RA, Keaveny TM 2005 Trabecular microfracture and the influence of pyridinium and non-enzymatic glycation-mediated collagen cross-links. Bone **37**(6)**:**825-32.
23. Wang X, Shen X, Li X, Agrawal CM 2002 Age-related changes in the collagen network and toughness of bone. Bone **31**(1)**:**1-7.
24. Zioupos P, Currey JD, Hamer AJ 1999 The role of collagen in the declining mechanical properties of aging human cortical bone. J Biomed Mater Res **45**(2)**:**108-16.
25. Vashishth D 2009 Advanced glycation end-products and bone fractures. BoneKey **6:**268-78.
26. Tang SY, Zeenath U, Vashishth D 2007 Effects of non-enzymatic glycation on cancellous bone fragility. Bone **40**(4)**:**1144-51.
27. Viguet-Carrin S, Roux JP, Arlot ME, Merabet Z, Leeming DJ, Byrjalsen I, Delmas PD, Bouxsein ML 2006 Contribution of the advanced glycation end product pentosidine and of maturation of type I collagen to compressive biomechanical properties of human lumbar vertebrae. Bone **39**(5)**:**1073-9.
28. Allen MR, Burr DB 2007 Three years of alendronate treatment results in similar levels of vertebral microdamage as after one year of treatment. J Bone Miner Res **22**(11)**:**1759-65.
29. Saito M, Mori S, Mashiba T, Komatsubara S, Marumo K 2008 Collagen maturity, glycation induced-pentosidine, and mineralization are increased following 3-year treatment with incadronate in dogs. Osteoporos Int **19**(9)**:**1343-54.
30. Durchschlag E, Paschalis EP, Zoehrer R, Roschger P, Fratzl P, Recker R, Phipps R, Klaushofer K 2006 Bone material properties in trabecular bone from human iliac crest biopsies after 3- and 5-year treatment with risedronate. J Bone Miner Res **21**(10)**:**1581-90.
31. Boskey AL, Spevak L, Weinstein RS 2009 Spectroscopic markers of bone quality in alendronate-treated postmenopausal women. Osteoporos Int **20**(5)**:**793-800.

32. Donnelly E, Meredith DS, Gladnick BP, Rebolledo BJ, Lane JM, Boskey AL 2010 Reduced matrix heterogeneity with bisphosphonate treatment in postmenopausal women with proximal femoral fractures American Society of Bone and Mineral Research Annual Meeting, Toronto, Canada.
33. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ 2000 Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone **27**(5)**:**687-94.
34. Roschger P, Rinnerthaler S, Yates J, Rodan GA, Fratzl P, Klaushofer K 2001 Alendronate increases degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. Bone **29**(2)**:**185-91.
35. Roschger P, Paschalis EP, Fratzl P, Klaushofer K 2008 Bone mineralization density distribution in health and disease. Bone **42**(3)**:**456-66.
36. Roschger P, Gupta HS, Berzlanovich A, Ittner G, Dempster DW, Fratzl P, Cosman F, Parisien M, Lindsay R, Nieves JW, Klaushofer K 2003 Constant mineralization density distribution in cancellous human bone. Bone **32**(3)**:**316-23.
37. Turner CH, Burr DB 2006 Principles of Bone Biomechanics. In: Lane NE, Sambrook PN (eds.) Osteoporosis and the Osteoporosis of Rheumatic Diseases. Mosby Elsevier, Philadelphia, pp 41-53.
38. Donnelly E, Gladnick BP, Meredith DS, Lane JM, Boskey AL 2010 Bisphosphonate treatment reduces cortical tissue heterogeneity in postmenopausal women with fractures Transactions Orthopaedic Research Society 56th Annual Meeting, New Orleans.
39. Donnelly E, Meredith DS, Nguyen JT, Gladnick BP, Unnanuntana A, Lane JM, Boskey AL 2010 Mean bone tissue composition, but not heterogeneity, is consistent across iliac crest and trochanteric sites American Society for Bone and Mineral Research, 23nd Annual Meeting, Toronto, Canada.
40. Borah B, Dufresne TE, Ritman EL, Jorgensen SM, Liu S, Chmielewski PA, Phipps RJ, Zhou X, Sibonga JD, Turner RT 2006 Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: sequential triple biopsy studies with micro-computed tomography. Bone **39**(2)**:**345-52.
41. Roschger P, Lombardi A, Misof BM, Maier G, Fratzl-Zelman N, Fratzl P, Klaushofer K 2010 Mineralization density distribution of postmenopausal osteoporotic bone is restored to normal after long-term alendronate treatment: qBEI and sSAXS data from the fracture intervention trial long-term extension (FLEX). J Bone Miner Res **25**(1)**:**48-55.
42. Ruffoni D, Fratzl P, Roschger P, Phipps R, Klaushofer K, Weinkamer R 2008 Effect of temporal changes in bone turnover on the bone mineralization density distribution: a computer simulation study. J Bone Miner Res **23**(12)**:**1905-14.
43. Zoehrer R, Roschger P, Paschalis EP, Hofstaetter JG, Durchschlag E, Fratzl P, Phipps R, Klaushofer K 2006 Effects of 3- and 5-year treatment with risedronate on bone mineralization density distribution in triple biopsies of the iliac crest in postmenopausal women. J Bone Miner Res **21**(7)**:**1106-12.

44. Mori S, Harruff R, Ambrosius W, Burr DB 1997 Trabecular bone volume and microdamage accumulation in the femoral heads of women with and without femoral neck fractures. Bone **21**(6)**:**521-6.
45. Schaffler MB, Choi K, Milgrom C 1995 Aging and matrix microdamage accumulation in human compact bone. Bone **17**(6)**:**521-25.
46. Li J, Mashiba T, Burr DB 2001 Bisphosphonate treatment suppresses not only stochastic remodeling but also the targeted repair of microdamage. Calcif Tissue Int **69**(5)**:**281-6.
47. Parfitt AM 2002 Targeted and nontargeted bone remodeling: relationship to basic multicellular unit origination and progression. Bone **30**(1)**:**5-7.
48. Allen MR, Iwata K, Phipps R, Burr DB 2006 Alterations in canine vertebral bone turnover, microdamage accumulation, and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. Bone **39**(4)**:**872-9.
49. Allen MR, Iwata K, Sato M, Burr DB 2006 Raloxifene enhances vertebral mechanical properties independent of bone density. Bone **39**(5)**:**1130-5.
50. Stepan JJ, Burr DB, Pavo I, Sipos A, Michalska D, Li J, Fahrleitner-Pammer A, Petto H, Westmore M, Michalsky D, Sato M, Dobnig H 2007 Low bone mineral density is associated with bone microdamage accumulation in postmenopausal women with osteoporosis. Bone **41**(3)**:**378-85.
51. Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux JP, Portero-Muzy N, Delmas PD 2007 Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: a bone biopsy study. J Bone Miner Res **22**(10)**:**1502-9.
52. Iwata K, Allen MR, Phipps R, Burr DB 2006 Microcrack initiation occures more easily in vertebrae from beagles treated with alendronate than with risedronate. Bone **38 (Suppl):**42.
53. Allen MR, Reinwald S, Burr DB 2008 Alendronate reduces bone toughness of ribs without significantly increasing microdamage accumulation in dogs following 3 years of daily treatment. Calcif Tissue Int **82**(5)**:**354-60.
54. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB 2001 Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. Bone **28**(5)**:**524-31.
55. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB 2000 Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res **15**(4)**:**613-20.
56. Nancollas GH, Tang R, Phipps RJ, Henneman Z, Gulde S, Wu W, Mangood A, Russell RG, Ebetino FH 2006 Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone **38**(5)**:**617-27.
57. Bagger YZ, Tanko LB, Alexandersen P, Ravn P, Christiansen C 2003 Alendronate has a residual effect on bone mass in postmenopausal Danish women up to 7 years after treatment withdrawal. Bone **33**(3)**:**301-7.
58. Burr DB, Diab T, Koivunemi A, Koivunemi M, Allen MR 2009 Effects of 1 to 3 years' treatment with alendronate on mechanical properties of the femoral shaft in

a canine model: implications for subtrochanteric femoral fracture risk. J Orthop Res **27**(10)**:**1288-92.
59. Parfitt AM 1983 The physiologic and clinical significance of bone histomorphometric data. In: Recker RR (ed.) Bone Histomorphometry: Techniques and Interpretation. CRC Press, Boca Raton, pp 143-224.
60. Forwood MR, Burr DB, Takano Y, Eastman DF, Smith PN, Schwardt JD 1995 Risedronate treatment does not increase microdamage in the canine femoral neck. Bone **16**(6)**:**643-50.
61. Cao Y, Mori S, Mashiba T, Westmore MS, Ma L, Sato M, Akiyama T, Shi L, Komatsubara S, Miyamoto K, Norimatsu H 2002 Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. J Bone Miner Res **17**(12)**:**2237-46.
62. MacDonald MM, Schindeler A, Little DG 2007 Bisphosphonate treatment and fracture repair. BoneKey **4:**236-251.
63. Martinez MD, Schmid GJ, McKenzie JA, Ornitz DM, Silva MJ 2010 Healing of non-displaced fractures produced by fatigue loading of the mouse ulna. Bone **46**(6)**:**1604-12.
64. Li J, Miller MA, Hutchins GD, Burr DB 2005 Imaging bone microdamage in vivo with positron emission tomography. Bone **37**(6)**:**819-24.
65. Milgrom C, Finestone A, Novack V, Pereg D, Goldich Y, Kreiss Y, Zimlichman E, Kaufman S, Liebergall M, Burr D 2004 The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. Bone **35**(2)**:**418-24.
66. Barrett JG, Sample SJ, McCarthy J, Kalscheur VL, Muir P, Prokuski L 2007 Effect of short-term treatment with alendronate on ulnar bone adaptation to cyclic fatigue loading in rats. J Orthop Res **25**(8)**:**1070-7.
67. Allen MR, Burr DB 2005 Human femoral neck has less cellular periosteum, and more mineralized periosteum, than femoral diaphyseal bone. Bone **36**(2)**:**311-6.
68. Wood J, Bonjean K, Ruetz S, Bellahcene A, Devy L, Foidart JM, Castronovo V, Green JR 2002 Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther **302**(3)**:**1055-61.
69. Deckers MM, Van Beek ER, Van Der Pluijm G, Wetterwald A, Van Der Wee-Pals L, Cecchini MG, Papapoulos SE, Lowik CW 2002 Dissociation of angiogenesis and osteoclastogenesis during endochondral bone formation in neonatal mice. J Bone Miner Res **17**(6)**:**998-1007.
70. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, Clezardin P 2002 Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res **62**(22)**:**6538-44.
71. Kidd LJ, Stephens AS, Kuliwaba JS, Fazzalari NL, Wu AC, Forwood MR 2010 Temporal pattern of gene expression and histology of stress fracture healing. Bone **46**(2)**:**369-78.
72. Wohl GR, Towler DA, Silva MJ 2009 Stress fracture healing: fatigue loading of the rat ulna induces upregulation in expression of osteogenic and angiogenic genes that mimic the intramembranous portion of fracture repair. Bone **44**(2)**:**320-30.

73. Salminen S, Pihlajamaki H, Avikainen V, Kyro A, Bostman O 1997 Specific features associated with femoral shaft fractures caused by low-energy trauma. J Trauma **43**(1)**:**117-22.
74. Nieves JW, Bilezikian JP, Lane JM, Einhorn TA, Wang Y, Steinbuch M, Cosman F 2010 Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int **21**(3)**:**399-408.
75. Mullaji AB, Thomas TL 1993 Low-energy subtrochanteric fractures in elderly patients: results of fixation with the sliding screw plate. J Trauma **34**(1)**:**56-61.
76. Salminen ST, Pihlajamaki HK, Avikainen VJ, Bostman OM 2000 Population based epidemiologic and morphologic study of femoral shaft fractures. Clin Orthop Relat Res (372)**:**241-9.
77. Ekstrom W, Nemeth G, Samnegard E, Dalen N, Tidermark J 2009 Quality of life after a subtrochanteric fracture: a prospective cohort study on 87 elderly patients. Injury **40**(4)**:**371-6.
78. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C 2009 Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int **20**(10)**:**1633-50.
79. Holt G, Smith R, Duncan K, Hutchison JD, Gregori A 2008 Gender differences in epidemiology and outcome after hip fracture: evidence from the Scottish Hip Fracture Audit. J Bone Joint Surg Br **90**(4)**:**480-3.
80. Penrod JD, Litke A, Hawkes WG, Magaziner J, Doucette JT, Koval KJ, Silberzweig SB, Egol KA, Siu AL 2008 The association of race, gender, and comorbidity with mortality and function after hip fracture. J Gerontol A Biol Sci Med Sci **63**(8)**:**867-72.
81. Johnell O, Kanis JA 2004 An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos Int **15**(11)**:**897-902.
82. Weiss RJ, Montgomery SM, Al Dabbagh Z, Jansson KA 2009 National data of 6409 Swedish inpatients with femoral shaft fractures: stable incidence between 1998 and 2004. Injury **40**(3)**:**304-8.
83. Singer BR, McLauchlan GJ, Robinson CM, Christie J 1998 Epidemiology of fractures in 15,000 adults: the influence of age and gender. J Bone Joint Surg Br **80**(2)**:**243-8.
84. Soveid M, Serati AR, Masoompoor M 2005 Incidence of hip fracture in Shiraz, Iran. Osteoporos Int **16**(11)**:**1412-6.
85. Melton LJ, 3rd, Crowson CS, O'Fallon WM 1999 Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. Osteoporos Int **9**(1)**:**29-37.
86. Knowelden J, Buhr AJ, Dunbar O 1964 Incidence of Fractures in Persons over 35 Years of Age. A Report to the M.R.C. Working Party on Fractures in the Elderly. Br J Prev Soc Med **18:**130-41.
87. Baron JA, Karagas M, Barrett J, Kniffin W, Malenka D, Mayor M, Keller RB 1996 Basic epidemiology of fractures of the upper and lower limb among Americans over 65 years of age. Epidemiology **7**(6)**:**612-8.
88. Donaldson LJ, Cook A, Thomson RG 1990 Incidence of fractures in a geographically defined population. J Epidemiol Community Health **44**(3)**:**241-5.

89. Wong PC 1966 Fracture epidemiology in a mixed southeastern Asian community (Singapore). Clin Orthop Relat Res **45:**55-61.
90. Bhattacharyya T, Wang JZ 2010 Divergent Trends between Typical and Atypical Hip Fractures and Prevalance of Bisphosphonate Use in the US Elderly, 1996-2007 ASBMR 2010 Annual Meeting, Toronto, Canada.
91. Kelly MP, Wustrack R, Bauer DC, Burch S, Palermo L, Wilt K, Cauley JA, Ensrud KE, Black DM 2010 Incidence of subtrochanteric and diaphyseal fractures in older while women: Data from the Study of Osteoporotic Fractures ASBMR 2010 Annual Meeting, Toronto, Canada.
92. Wustrack R, Black DM, Burch S, Wilt K, Ensrud KE, Cauley JA, Napoli N, Kelly MP 2010 Are women with thicker cortices in the femoral shaft at higher risk of subtrochanteric/diaphyseal fractures?: The Study of Osteoporotic Fractures ASBMR 2010 Annual Meeting, Toronto, Canada.
93. Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, van der Meulen MC, Lorich DG, Lane JM 2009 Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int **20**(8)**:**1353-62.
94. Abrahamsen B, Eiken P, Eastell R 2009 Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res **24**(6)**:**1095-102.
95. Abrahamsen B, Eiken P, Eastell R 2010 Subtrochanteric and diaphyseal femur fractures in patients during long-term alendronate therapy: expanded and extended national register-based cohort study 37th European Symposium on Calcified Tissues (ECTS 2010), Glasgow, Scotland, United Kingdom.
96. Vestergaard P, Amtssygehus A 2010 Risk of Femoral Shaft and Subtrochanteric Fractures in Users of Bisphophonates, Raloxifene and Strontium Ranelate ASBMR 2010 Annual Meeting, Toronto, Canada.
97. Black DM, Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, Cauley J, Leung PC, Boonen S, Santora A, de Papp A, Bauer DC 2010 Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med **362**(19)**:**1761-71.
98. Shane E 2010 Evolving data about subtrochanteric fractures and bisphosphonates. N Engl J Med **362**(19)**:**1825-7.
99. Dell R, Greene D, Ott S, Silverman S, Eisemon E, Funahashi T, Adams A 2010 A retrospective analysis of all atypical femur fractures seen in a large California HMO from the years 2007 to 2009 ASBMR 2010 Annual Meeting, Toronto, Canada.
100. Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG 2008 Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma **22**(5)**:**346-50.
101. Schilcher J, Aspenberg P 2009 Incidence of stress fractures of the femoral shaft in women treated with bisphosphonate. Acta Orthop **80**(4)**:**413-5.
102. Bunning RD, Rentfro RJ, Jelinek JS 2010 Low-energy femoral fractures associated with long-term bisphosphonate use in a rehabilitation setting: a case series. PM R **2**(1)**:**76-80.

103. Gagnon C, Sims NA, Mumm S, McAuley SA, Jung C, Poulton IJ, Ng KW, Ebeling PR 2010 Lack of sustained response to teriparatide in a patient with adult hypophosphatasia. J Clin Endocrinol Metab **95**(3)**:**1007-12.
104. McKiernan FE, Ton Q, Neviaser A, Lane JM 2010 Searching for Atypical Subtrochanteric Femoral Shaft Fractures ASBMR 2010 Annual Meeting, Toronto, Canada.
105. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW, Jr., Dequeker J, Favus M 1995 Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med **333**(22)**:**1437-43.
106. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet **348**(9041)**:**1535-41.
107. Girgis CM, Sher D, Seibel MJ 2010 Atypical femoral fractures and bisphosphonate use. N Engl J Med **362**(19)**:**1848-9.
108. Issacs JD, Shidiak L, Harris I 2010 Femoral Insufficiency Fractures Associated with Prologned Alendronate Therapy Annual Meeting of the American Academy of Orthopedic Surgeons, New Orleans, LA, USA.
109. Armamento-Villareal R, Napoli N, Diemer K, Watkins M, Civitelli R, Teitelbaum S, Novack D 2009 Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tissue Int **85**(1)**:**37-44.
110. Capeci CM, Tejwani NC 2009 Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. J Bone Joint Surg Am **91**(11)**:**2556-61.
111. Cermak K, Shumelinsky F, Alexiou J, Gebhart MJ 2009 Case reports: subtrochanteric femoral stress fractures after prolonged alendronate therapy. Clin Orthop Relat Res **468**(7)**:**1991-6.
112. Ing-Lorenzini K, Desmeules J, Plachta O 2009 Low-energy femoral fractures associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital. Drug Saf **32:**775-785.
113. Lee JK 2009 Bilateral atypical femoral diaphyseal fractures in a patient treated with alendronate sodium. Int J Rheum Dis **12**(2)**:**149-54.
114. Leung F, Lau TW, To M, Luk KDK, Kung AWC 2009 Atypical femoral diaphyseal and subtrochanteric fractures and their association with bisphosphonates. BMJ Case Reports (epub March 5).
115. Odvina CV, Levy S, Rao S, Zerwekh JE, Rao DS 2010 Unusual mid-shaft fractures during long-term bisphosphonate therapy. Clin Endocrinol (Oxf) **72**(2)**:**161-8.
116. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY 2005 Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab **90**(3)**:**1294-301.

117. Sayed-Noor AS, Sjoden GO 2008 Subtrochanteric displaced insufficiency fracture after long-term alendronate therapy--a case report. Acta Orthop **79**(4)**:**565-7.
118. Schneider JP 2006 Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics **61**(1)**:**31-33.
119. Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE 2009 Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. J Bone Miner Res **24**(10)**:**1736-40.
120. Giusti A, Hamdy NA, Papapoulos SE 2010 Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. Bone **47**(2)**:**169-80.
121. Somford MP, Geurts GF, den Teuling JW, Thomassen BJ, Draijer WF 2009 Long-Term Alendronate Use Not without Consequences? Int J Rheumatol **2009:**253432.
122. Cheung RK, Leung KK, Lee KC, Chow TC 2007 Sequential non-traumatic femoral shaft fractures in a patient on long-term alendronate. Hong Kong Med J **13**(6)**:**485-9.
123. Wernecke G, Namduri S, Dicarlo EF, Schneider R, Lane J 2008 Case Report of Spontaneous, Nonspinal Fractures in a Multiple Myeloma Patient on Long-term Pamidronate and Zoledronic Acid. HSS J **4**(2)**:**123-7.
124. Lenart BA, Lorich DG, Lane JM 2008 Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med **358**(12)**:**1304-6.
125. Demiralp B, Ilgan S, Ozgur Karacalioglu A, Cicek EI, Yildrim D, Erler K 2007 Bilateral femoral insuffiency fractures treated with inflatable intramedullary nails: a case report. Arch Orthop Trauma Surg **127**(7)**:**597-601.
126. Armamento-Villareal R, Napoli N, Panwar V, Novack D 2006 Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. N Engl J Med **355**(19)**:**2048-50.
127. Kumm DA, Rack C, Rutt J 1997 Subtrochanteric stress fracture of the femur following total knee arthroplasty. J Arthroplasty **12**(5)**:**580-3.
128. Sayed-Noor AS, Sjoden GO 2009 Case reports: two femoral insufficiency fractures after long-term alendronate therapy. Clin Orthop Relat Res **467**(7)**:**1921-6.
129. Husada G, Libbeerecht K, Peeters T, Populaire J 2005 Bilateral Mid-Diaphyseal Femoral Stress Fractures in the Elderly. European J Trauma (1)**:**68-71.
130. Arlot M, Meunier PJ, Boivin G, Haddock L, Tamayo J, Correa-Rotter R, Jasqui S, Donley DW, Dalsky GP, Martin JS, Eriksen EF 2005 Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. J Bone Miner Res **20**(7)**:**1244-53.
131. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E 2007 Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res **22**(10)**:**1479-91.

132. Cheung AM, Adachi JD, Josse RG, Bleakney R, Khan A, Jamal SA 2010 Bone Density and Structure of Patients on Bisphosphonates with Atypical Femur Fractures ASBMR 2010 Annual Meeting, Toronto, Canada.
133. Juby A, Davis S 2010 Subtrochanteric hip fracture in Edmonton, Alberta, Canada - case reports ASBMR 2010 Annual Meeting, Toronto, Canada.
134. Nitche J, Sagebien C, Masella R, Redziniak D, Wimalawansa SJ 2010 Subtrochanteric Femoral Stress Fractures in Patients on Chronic Bisphosphonate Therapy: A Case Series ASBMR 2010 Annual Meeting, Toronto, Canada.
135. Warren C, Gilchrist NL, Coates M, Helmore J, McKie J, Hooper G 2010 Atypical Substrochanteric and Shaft of Femur Fractures - Are They Related to Bisphosphonate Therapy?: Blinded Radiological Review ASBMR 2010 Annual Meeting, Toronto, Canada.
136. Zanchetta MB, Sarli M, Massari FE, Spivacow R, Buttazzoni M, Silveria F, Bogado CE, Zanchetta JR 2010 Bone Microarchitecture Assessment in Postmenopausal Women with Atypical Fractures and Long Term Bisphosphonate Use ASBMR 2010 Annual Meeting, Toronto, Canada.
137. Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ 1997 Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest **100**(6)**:**1475-80.
138. Eriksen EF, Melsen F, Sod E, Barton I, Chines A 2002 Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. Bone **31**(5)**:**620-5.
139. Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, Garcia-Hernandez PA, Supronik J, Lewiecki EM, Ochoa L, Miller P, Hu H, Mesenbrink P, Hartl F, Gasser J, Eriksen EF 2008 Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. J Bone Miner Res **23**(1)**:**6-16.
140. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, Emkey R, Meunier PJ, Miller SS, Mulloy AL, Recker RR, Weiss SR, Heyden N, Musliner T, Suryawanshi S, Yates AJ, Lombardi A 2000 Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab **85**(2)**:**720-6.
141. Chavassieux PM, Arlot ME, Roux JP, Portero N, Daifotis A, Yates AJ, Hamdy NA, Malice MP, Freedholm D, Meunier PJ 2000 Effects of alendronate on bone quality and remodeling in glucocorticoid-induced osteoporosis: a histomorphometric analysis of transiliac biopsies. J Bone Miner Res **15**(4)**:**754-62.
142. Hauge E, Mosekilde L, Melsen F 1999 Missing observations in bone histomorphometry on osteoporosis: implications and suggestions for an approach. Bone **25**(4)**:**389-95.
143. Whyte MP, Bergfeld MA, Murphy WA, Avioli LV, Teitelbaum SL 1982 Postmenopausal osteoporosis. A heterogeneous disorder as assessed by histomorphometric analysis of Iliac crest bone from untreated patients. Am J Med **72**(2)**:**193-202.

144. Napoli N, Novack D, Armamento-Villareal R 2010 Bisphosphonate-associated femoral fracture: implications for management in patients with malignancies. Osteoporos Int **21**(4)**:**705-8.
145. Bush L, Chew F 2008 Subtrochanteric femoral insufficiency fracture following bisphosphonate therapy for osseous metastases. Radiology Case Reports (3)**:**232.
146. Weinstein RS, Roberson PK, Manolagas SC 2009 Giant osteoclast formation and long-term oral bisphosphonate therapy. N Engl J Med **360**(1)**:**53-62.
147. Gaeta M, Minutoli F, Scribano E, Ascenti G, Vinci S, Bruschetta D, Magaudda L, Blandino A 2005 CT and MR imaging findings in athletes with early tibial stress injuries: comparison with bone scintigraphy findings and emphasis on cortical abnormalities. Radiology **235**(2)**:**553-61.
148. Mori S, Kawaguchi Y 2001 The Histological Appearnace of Stress Fracturesq. In: Burr DB, Milgrom C (eds.) Musculoskeletal Fatigue and Stress Fractures. CRC Press, Boca Raton, pp 151-159.
149. Clement DB, Ammann W, Taunton JE, Lloyd-Smith R, Jesperson D, McKay H, Goldring J, Matheson GO 1993 Exercise-induced stress injuries to the femur. Int J Sports Med **14**(6)**:**347-52.
150. Ivkovic A, Bojanic I, Pecina M 2006 Stress fractures of the femoral shaft in athletes: a new treatment algorithm. Br J Sports Med **40**(6)**:**518-20; discussion 520.
151. Deutsch AL, Coel MN, Mink JH 1997 Imaging of stress injuries to bone. Radiography, scintigraphy, and MR imaging. Clin Sports Med **16**(2)**:**275-90.
152. Spitz DJ, Newberg AH 2002 Imaging of stress fractures in athletes. Radiol ClinNorlh Am **40:**313-331.
153. Zwas ST, Elkanovitch R, Frank G 1987 Interpretation and classification of bone scintigraphic findings in stress fractures. J Nucl Med **28**(4)**:**452-7.
154. Lee JK, Yao L 1988 Stress fractures: MR imaging. Radiology **169**(1)**:**217-20.
155. Shin AY, Morin WD, Gorman JD, Jones SB, Lapinsky AS 1996 The superiority of magnetic resonance imaging in differentiating the cause of hip pain in endurance athletes. Am J Sports Med **24**(2)**:**168-76.
156. Tyrrell PN, Davies AM 1994 Magnetic resonance imaging appearances of fatigue fractures of the long bones of the lower limb. Br J Radiol **67**(796)**:**332-8.
157. Yousem D, Magid D, Fishman EK, Kuhajda F, Siegelman SS 1986 Computed tomography of stress fractures. J Comput Assist Tomogr **10**(1)**:**92-5.
158. Berger FH, de Jonge MC, Maas M 2007 Stress fractures in the lower extremity. The importance of increasing awareness amongst radiologists. Eur J Radiol **62**(1)**:**16-26.
159. Das De S, Setiobudi T, Shen L A rational approach to management of alendronate-related subtrochanteric fractures. J Bone Joint Surg Br **92**(5)**:**679-86.
160. Cohen A, Addesso V, McMahon DJ, Staron RB, Namerow P, Maybaum S, Mancini D, Shane E 2006 Discontinuing antiresorptive therapy one year after cardiac transplantation: effect on bone density and bone turnover. Transplantation **81**(5)**:**686-91.
161. Hershman DL, McMahon DJ, Crew KD, Shao T, Cremers S, Brafman L, Awad D, Shane E Prevention of bone loss by zoledronic acid in premenopausal women

undergoing adjuvant chemotherapy persist up to one year following discontinuing treatment. J Clin Endocrinol Metab **95**(2)**:**559-66.
162. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR 2006 Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA **296**(24)**:**2927-38.
163. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA 2004 Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int **75**(6)**:**462-8.
164. Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, Pack S, Wenderoth D, Cooper C, Reginster JY 2003 Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone **32**(2)**:**120-6.
165. Schwartz AV, Bauer DC, Cummings SR, Cauley JA, Ensrud KE, Palermo L, Wallace RB, Hochberg MC, Feldstein AC, Lombardi A, Black DM 2010 Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: The FLEX trial. J Bone Miner Res.
166. Alkhiary YM, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, Einhorn TA 2005 Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). J Bone Joint Surg Am **87**(4)**:**731-41.
167. Rubery PT, Bukata SV 2010 Teriparatide may accelerate healing in delayed union of Type III odontoid fractures: a report of 3 cases. J Spinal Disord Tech **Published Online January 4, 2010**.
168. Chintamaneni S, Finzel K, Gruber BL 2010 Successful treatment of sternal fracture nonunion with teriparatide. Osteoporos Int **21**(6)**:**1059-63.
169. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, Garcia-Hernandez PA, Recknor CP, Einhorn TA, Dalsky GP, Mitlak BH, Fierlinger A, Lakshmanan MC 2009 Teriparatide for Acceleration of Fracture Repair in Humans: A Prospective, Randomized, Double-blind Study of 102 Postmenopausal Women with Distal Radial Fractures. J Bone Miner Res.
170. Lee P, van der Wall H, Seibel MJ 2007 Looking beyond low bone mineral density: multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. J Endocrinol Invest **30**(7)**:**590-7.
171. Goddard MS, Reid KR, Johnston JC, Khanuja HS 2009 Atraumatic bilateral femur fracture in long-term bisphosphonate use. Orthopedics **32**(8).
172. Edwards MH, McCrae FC, Young-Min SA 2010 Alendronate-related femoral diaphysis fracture--what should be done to predict and prevent subsequent fracture of the contralateral side? Osteoporos Int **21**(4)**:**701-3.
173. Ali T, Jay RH 2009 Spontaneous femoral shaft fracture after long-term alendronate. Age Ageing **38**(5)**:**625-6.
174. Koh JS, Goh SK, Png MA, Kwek EB, Howe TS 2010 Femoral cortical stress lesions in long-term bisphosphonate therapy: a herald of impending fracture? J Orthop Trauma **24**(2)**:**75-81.

175. Grasko JM, Herrmann RP, Vasikaran SD 2009 Recurrent low-energy femoral shaft fractures and osteonecrosis of the jaw in a case of multiple myeloma treated with bisphosphonates. J Oral Maxillofac Surg **67**(3)**:**645-9.
176. Glennon DA 2009 Subtrochanteric stress fractures in six patients on long term bisphosphonate therapy: a case series. . Bone **44 (Suppl 1):**S77–8.
177. Schneider JP 2009 Bisphosphonates and low-impact femoral fractures: current evidence on alendronate-fracture risk. Geriatrics **64**(1)**:**18-23.

TABLES

Table I. Atypical Femoral Fracture: Major and Minor Features*

*Major Features***

- 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
- Non-comminuted
- 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***
- 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 (e.g., vitamin D deficiency, RA, hypophosphatasia)
- Use of pharmaceutical agents (e.g., BPs, GCs, proton pump inhibitors)

* Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors and peri-prosthetic fractures

** All Major Features are required to satisfy the case definition of atypical femoral fracture. None of the Minor Features are required but have been sometimes associated

with these fractures.
*** Often referred to in the literature as “beaking” or “flaring”

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

- 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 anti-angiogenic effects

Table 3. Hierarchy of Data Quality For Atypical Femoral Fractures

---

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

A. Patient Characteristics

1. Age
2. Gender

B. Description of Atypical Subtrochanteric and Femoral Shaft Fracture

1. Location in femoral shaft from just distal to the lesser trochanter to just proximal to the supracondylar flair of the distal femoral metaphysis
2. Presence of transverse or short oblique configuration of fracture
3. Low level of trauma
4. Non-comminuted
5. Presence of thickened cortices with or without a periosteal callus

C. Bisphosphonate Exposure History

1. Specific drug(s)
2. Specific dose history
3. Duration of and adherence to therapy before diagnosis of fracture

D. Bisphosphonate Therapy Indication

1. Disease (osteoporosis, osteopenia, myeloma, etc.)
2. History of prior low trauma fracture

E. Co-Morbid Conditions

1. Presence of vitamin D deficiency (<20 ng/mL)
2. Presence of other co-morbid conditions
    - RA
    - Other diseases requiring corticosteroids
    - Diabetes
    - Cancer
    - Hypophosphatasia

F. Concomitant Medication History

1. Identity of concomitant medications, including
    - Glucocorticoids
    - Proton pump inhibitors
    - Other antiresorptive drugs (estrogen, raloxifene, calcitonin, denosumab)
2. Doses of concomitant medications and duration of therapy prior to subtrochanteric fracture

G. Investigations

1. Bone densitometry
2. Bone turnover markers

3. Bone histomorphometry, including an assessment of bone turnover

Table 4. Classification of Data Quality

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

Best Evidence:	Information complete for all seven categories
Good Evidence:	Information complete for categories A-E, F1 and G1
Acceptable Evidence:	Information complete for categories A-D, but E, F1 and G1 not all complete
Marginal Evidence:	Information complete only for B1 and C1
Insufficient Evidence:	Information unavailable for B1, C1, & D1, regardless of other information provided

Table 5. Case Series and Reports of Atypical Fractures

Author/Date	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-OHD <20 ng/mL (n/available)	Hip T score > -2.5 (n/available)
Goh (10) 2007	9	55-71	0M/9F	9 ALN	2.5 to 5	1/3 (thick cortex)	5	1	NA	5/5
Kwek (12) 2008	17 [a]	55-77	0M/17F	16 ALN, 1 ALN -> RIS	2 to 10	4/5	13	1	NA	8/12
Neviaser (100) 2008	19 [b]	NA	NA	19 ALN	Mean 6.9 (in 10 patients)	NA/NA	NA	NA	NA	NA
Wernecke (123) 2008	1 [c]	72	0M/1F	ZA -> PAM	11	1/0	1	0	NA	1
Odvina (116) 2005	5	52-68	1M/4F	5 ALN	3-8	2/NA	NA	2	None (range, 28-180)	3/3
Odvina (115) 2010	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 (13) 2008	3	51-75	0M/3F	3 ALN	5-10	2/NA	2	3	None (range, 32-48)	3
Somford (119) 2009	1	76	0M/1F	ALN	8	1/0	1	1	1 (16.8)	1
Demiralp (125) 2007	1	65	0M/1F	ALN	7	1/0	1	1	NA	0

Armamento-Villareal (109) 2009	7	43-75	1M/6F	6 ALN 1 RIS	2-10	2/NA	NA	0	(30.6)	4/5
Lee (170) 2007	1	73	0M/1F	ALN	1.6	0/1 (thick lateral cortex)	1	0	None (24)	1
Schilcher (101) 2009	5	> 75	0M/5F	NA	3.5-8.5 (mean, 5.8)	1/NA	NA	NA	NA	NA
Ing-Lorenzini (112) 2009	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 (118) 2006	1	59	0M/1F	ALN	7	0/0	1	NA	NA	1
Sayed Noor (117) 2008	1	72	0M/1F	ALN	7	0/1 (thick cortex with local lateral cortical reaction)	1	NA	NA	NA
Sayed Noor (128) 2009	2	55,78	0M/2F	2 ALN	9	0/1 (cortical hypertrophy with lateral cortical reaction)	2	0	NA	NA
Goddard (171) 2009	1	67	0M/1F	ALN -> IBN	17	1/0	0	0	NA	NA
Cheung (122) 2007	1	82	0M/1F	ALN	10	1/0	0	0	“Normal”	1
Bush (145) 2008	1	61	1M/0F	ZA	1.5	0/1 (thick diaphyseal cortex)	0	0	NA	NA
Capeci (110)	7	53-75	0M/7F	7 ALN	5-13	3/4 (cortical stress	4	NA	0/3 (21-39)	NA

2009						reaction)				
Husada (129) 2005	1	72	0M/1F	ALN	NA	1/0	1	NA	NA	NA
Edwards (172) 2010	1	60	0M/1F	ALN	6	1/1	1	1	NA	1
Cermak (111) 2009	3	59-70	0M/3F	ALN	5.5-12	1/1	2	0	NA	NA
Ali (173) 2009	1	82	0M/1F	ALN	8	0/0	0	0	"Normal"	1
Koh (174) 2010	32 [d]	47-91	0M/32F	30 ALN 1 ALN -> RIS 1 ZA	2-10	NA/NA	NA	NA	8/32, (Median 26.7 mcg/L)	NA
Grasko (175) 2009	1	57	1M/0F	PAM -> ZA	9	0/0	1	1	NA	1
Napoli (144) 2010	1	56	0M/1F	PAM -> ZA	6	0/0	1	1	0	1
Issacs (108) 2010	40	NA	NA	40 ALN	7.1 (mean)	NA/18	29	NA	NA	NA
Girgis (107) 2010	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 (176) 2009	6	60-87	0M/6F	5 ALN 1 RIS	1.5 - 16 ALN 3.0 RIS	0/1 (cortical hypertrophy with lateral cortical reaction)	5	NA	"Normal"	NA
Bunning (102) 2010	4	49-59	1M/3F	1 PAM -> ZA 2 ALN 1 No BP	5 - 5.5	1/1 1 (cortical hypertrophy with lateral cortical reaction)	4	NA	NA	3

Lee (113) 2009	1	82	0M/1F	ALN	8	1/1	NA	NA	None	1
Leung (114) 2009	6	73 - 81	0M/6F	ALN	0.5 - 6	0/0	1	0	2	2
Schneider (177) 2009	3	59 - 66	0M/3F	ALN	5 - 9	0/2 (cortical hypertrophy with lateral cortical reaction)	2	NA	NA	NA
Somford (121) 2009	3	65 - 79	0M/3F	ALN	4 - 12	1/1	3	3	0	1
Giusti (11) 2010	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 (85)	102	45 - 92	3M/99F	Oral BIS (97) No Bis (5)	5.5	26 (complete fracture or stress fracture)	71	NA	NA	NA

a: This report included 8 from Goh, with substantial overlap likely (10); b: This report included 10 from Lenart (172); c: Unclear whether included in Neviaser (100); d: This report included 17 from Kwek (12)

Abbreviations:

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

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)*	1	Fracture site	Qualitative	No malignancy; No osteoclasts
Wernecke, 2008 (123)*	1	L- Fem head, neck, marrow R – Fracture site	Qualitative Qualitative	L – No myeloma 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 6-fold 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***	Fracture site	Static, Material Properties	Normal architecture and OS; Reduced heterogeneity
Odvina, 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**	Iliac crest	Static and Dynamic	Reduced bone turnover, 5/7 Normal turnover, 2/7
Odvina, 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 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 yrs, 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

* Cancer patients treated with high-dose BPs, iv

** Biopsies performed on 15 patients, but only 7 had femoral shaft fractures

***All BP treated, average duration 7.4 yrs; 4 atypical femoral fractures, 1 subtrochanteric, 9 inter-trochanteric

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

- Standard demographic data (age, gender, height, weight, race, ethnicity)
- Anatomical location of the fracture (subtrochanteric or diaphyseal)
- Key radiographic features of atypia (Table 1)
- Information on osteoporosis therapies
    - Doses, routes, duration of and adherence to osteoporosis therapy
    - Indication for therapy (e.g., osteoporosis, osteopenia, bone loss prevention, cancer, Paget's disease)
- Prior fracture history
- Concomitant medications
    - GCs, thiazolidenediones, proton pump inhibitors, anticonvulsants, statins, HRT, SERMs
- Co-morbid medical conditions
    - Diabetes, RA, chronic kidney disease, malabsorption, errors of phosphate metabolism, joint replacement
- Family history (for genetic studies)
- Bone mineral density
    - Pre-treatment and at time of fracture
- Biochemistries
    - Serum calcium, creatinine, 25-OHD, 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

Table 8. Information To Be Collected From Transiliac and/or Femoral Fracture Biopsies

- 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, mineral particle size and shape
- Collagen cross-links and advanced glycation endproducts
- 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

FIGURE LEGENDS

Figure 1: Locations of common hip and femur fractures. Figure courtesy of Thomas Einhorn, M.D.

Figure 2. Antero-posterior (AP) radiographs showing an atypical femoral shaft fracture (A) pre- and (B) post-operatively, 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. Figure courtesy of Thomas Einhorn, M.D.

Figure 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. Figure courtesy of Joseph Lane, M.D.

Figure 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), while bone scintigraphy (C) demonstrates focal increased radionuclide uptake in the corresponding proximal lateral femoral cortices, findings consistent with early, evolving, bilateral, femoral insufficiency fractures. Figure courtesy of Piet Geusens, M.D.

Figure 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). MR images of the femurs (C) demonstrate subtle decreased signal on T1-weighted and increased signal on T-2 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. Figure courtesy of Fergus McKiernan, M.D.

Figure 1

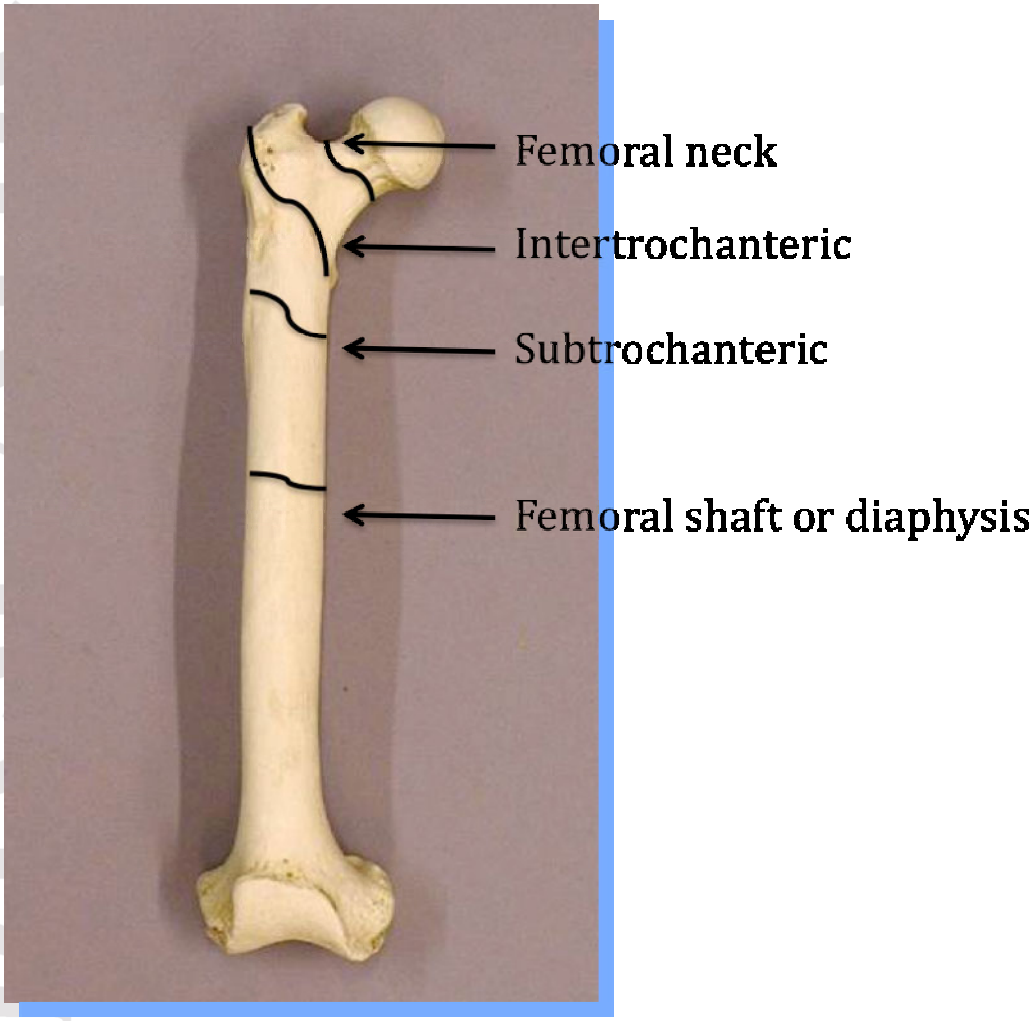
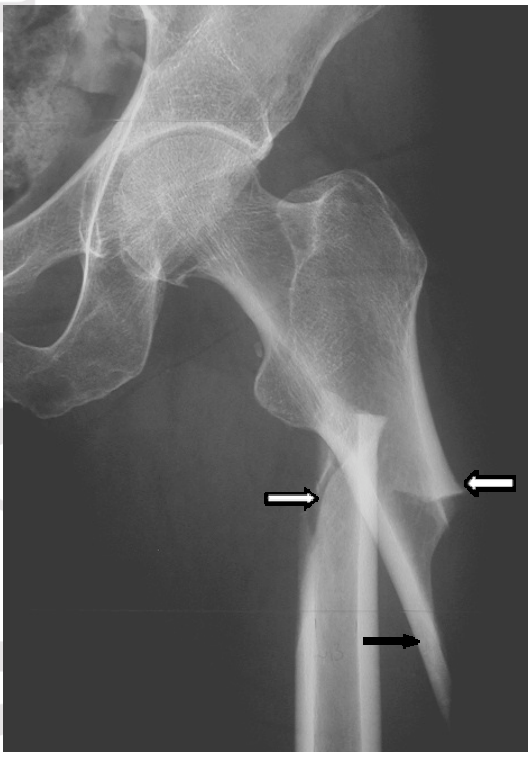
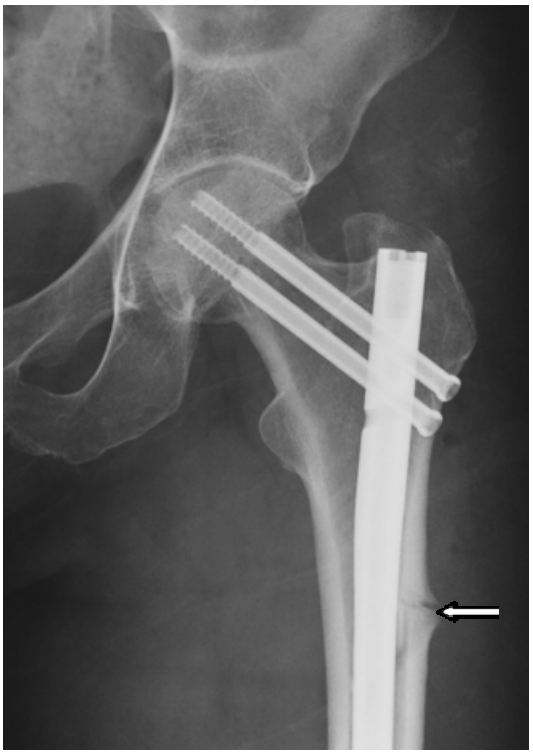


Figure 2



Panel A



Panel B

Figure 3

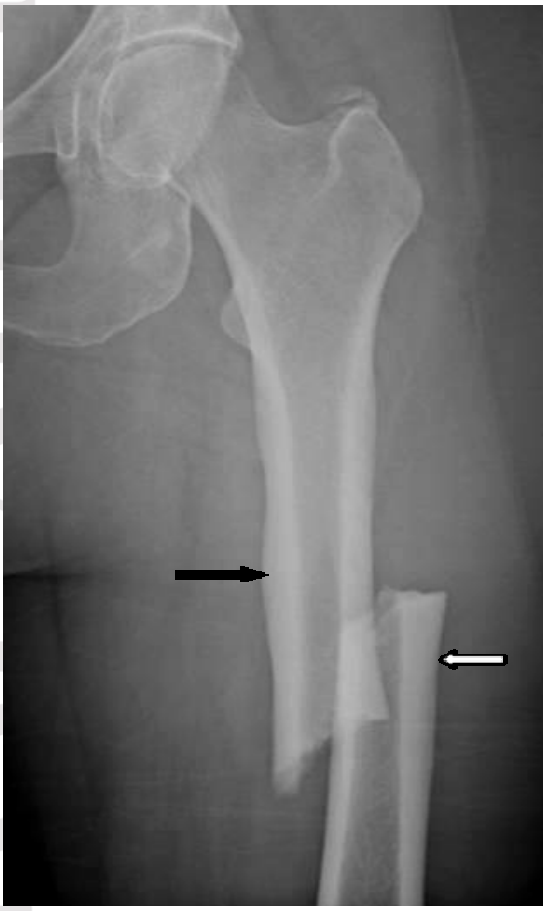
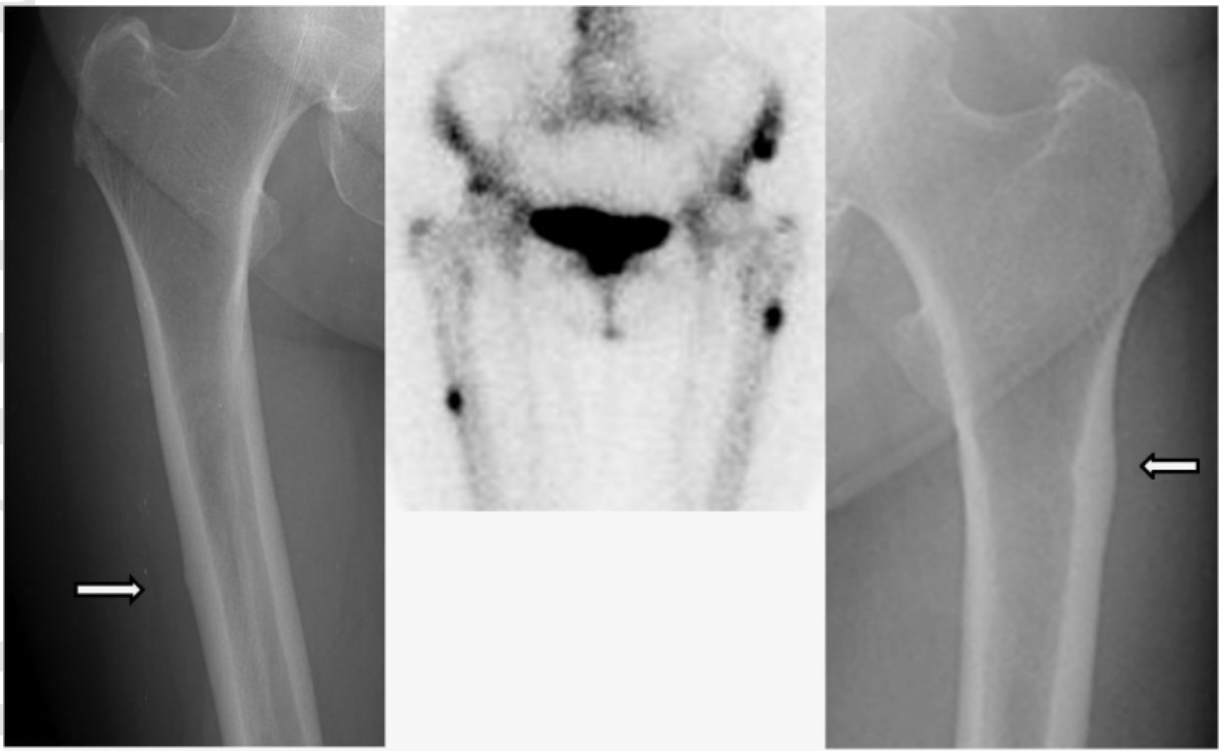


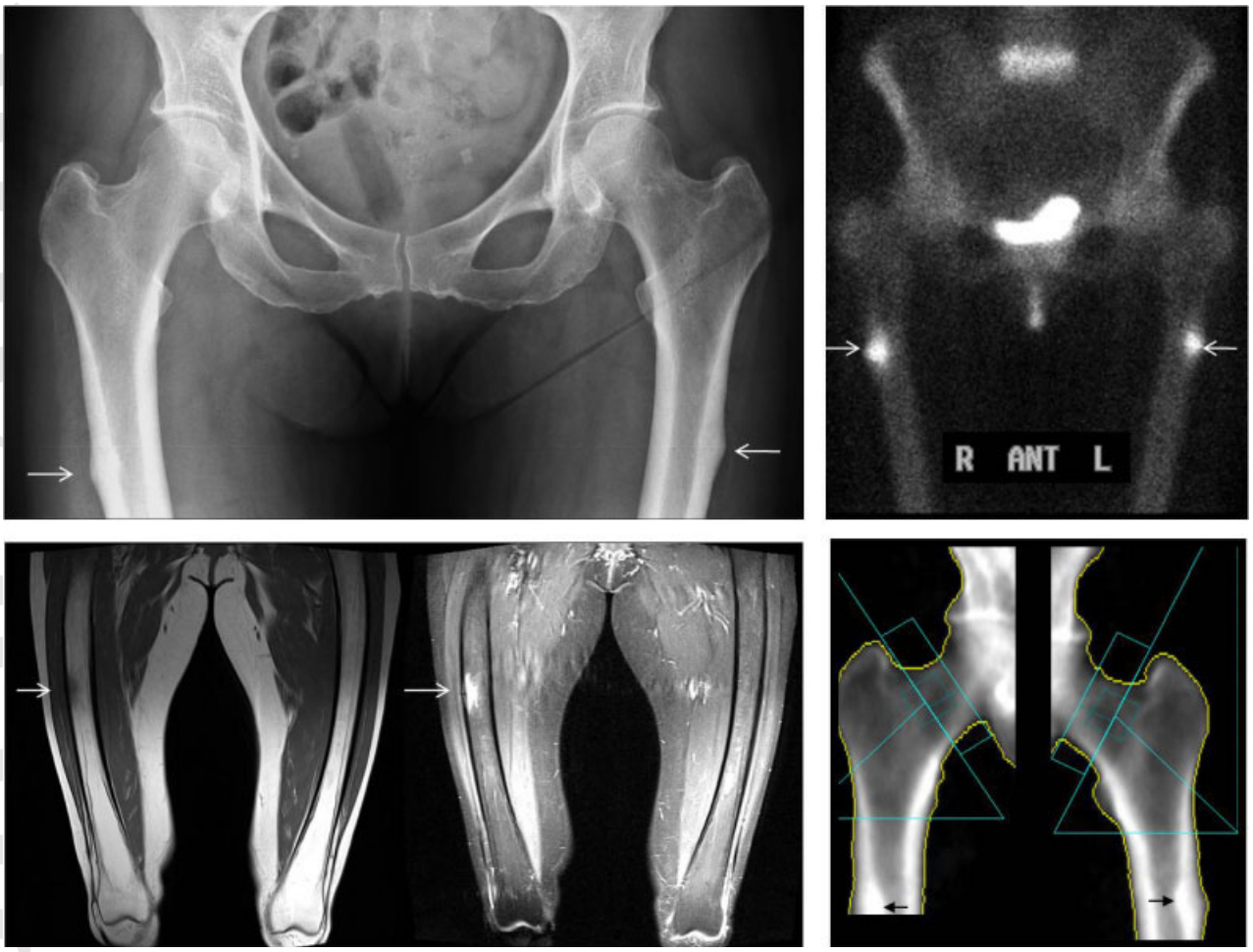
Figure 4



Panel A **Panel B** **Panel C**

Figure 5

Panel A **Panel B**



Panel C **Panel D**