Atypical Femoral Fractures: An Orthopaedic Surgeon's Perspective

Clifford B. Jones

Published online: 20 April 2013
© Springer Science+Business Media New York 2013

Abstract Atypical femoral fractures are uncommon fractures that are often associated with extended bisphosphonate use. They occur in the proximal or middle diaphyseal portion of the femur with a short oblique pattern and have relatively thickened cortices. Prodromal pain symptoms vary and bilateral involvement is common. Because delayed or complicated healing adversely affects treatment, fixation with a load-sharing intramedullary nail seems to fair better than load-bearing plate stabilization. If a delayed union is noted, it is best to wait up to one year before surgical intervention. Optimization of the patient's metabolism is also required.

Keywords Atypical femoral fracture · Pathogenesis · Bisphosphonates · Stress fracture treatment

Introduction

Atypical femoral fractures (AFF) are described as diaphyseal femoral fractures with short oblique pattern and thickened cortices. Other pseudonyms are “bisphosphonate femoral fractures” and “stress femoral fractures.” Several case reports and case series have reported associations between these AFF and bisphosphonate (BP) usage—especially after more than five years of treatment [1•]. The etiology appears to be multifactorial. Successful orthopaedic treatment requires meticulous operative intervention, usually with intramedullary nails (IMN), optimization of the patient's metabolism, appropriate pharmacological intervention, and patience until osseous union [2•]. A review of atypical femoral fractures characteristics, epidemiology, and treatment will be discussed.

Characteristics

Major and Minor Features

In 2010, a multidisciplinary team created a task force from the American Society for Bone and Mineral Research (BMR) and published a report on atypical femoral fractures [3•]. Major and minor features of complete and incomplete fractures were defined. Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral extension, pathological fractures associated with primary or metastatic bone tumors, and periprosthetic fractures. Major features consist of either a subtrochanteric or diaphyseal location, a transverse or short oblique pattern, minimal or no associated trauma mechanism, the presence of a medial spike when the fracture is complete, and the absence of comminution. Minor features include cortical thickening, lateral cortex periosteal reaction (beaking or flaring), prodromal pain, bilaterality, delayed healing, comorbid conditions (such as vitamin D deficiency, rheumatoid arthritis, and hypophosphatasia), and concomitant drug exposures including BP, other antiresorptive agents, glucocorticoids, and proton pump inhibitors. All of the major features are required to be diagnosed as an atypical femoral fracture. Although sometimes associated with these fractures, none of the minor features are required for diagnosis. Prolonged BP usage impedes bone remodeling via osteoclast inhibition. This leads to summation of microdamage, unrepaired osseous flaws, and the ensuing weakened osseous strength can result in cortical thickening [4–9]. Despite being a minor feature, bisphosphonate usage greater than five years has not associated with cortical thickening, another minor feature [10].

Age

Older and thinner individuals have mainly major features of AFF, while younger and heavier patients tend to have both

C. B. Jones (✉)
Orthopaedic Associates of Michigan, Michigan State University/
CHM, Grand Rapids, MI 49503, USA
e-mail: clifford.jones@oamichigan.com

major and minor features [11]. Patients with major features of AFF have a constant incidence of about 6/100,000 persons, while patients with major and minor features of AFF increase with time [11]. Therefore, two different patient populations may be present with differing characteristics but with similar AFF patterns. Further analysis of the etiology, patients, patterns, and potential treatment outcomes are needed and will be beneficial.

Epidemiology

Incidence

In the elderly osteoporotic population, subtrochanteric and diaphyseal femoral fractures represent 3 % and 5 %, respectively, of the total femoral fractures [12, 13]. Atypical femoral fractures are much less common, but actual numbers are unknown. In a recent analysis from a single patient registry of nearly 2 million patients over the age of 45 with a femoral fracture, only 142 patients, or 1.78/100,000/year, had characteristic signs of an atypical femoral fracture [14•]. In the United States, the incidence of proximal diaphyseal fractures is twenty to 30 per 100,000 patient-years [13, 15•]. The incidence rises in correlation with increasing BP usage [14•]. The ASBMR task force reported an incidence of two per 100,000 cases per year compared to 78 per 100,000 cases per year, with two versus eight years of BP usage, respectively [3•]. In contradistinction to the increasing incidence, another analysis demonstrated an incidence of six per 100,000 person-years with no correlation with increased BP exposure [11]. In summary, the incidence is rare but many maybe underdiagnosed because of misdiagnosis, incomplete fracture characteristics, and misclassification [3•, 16•, 17].

Associations

Atypical femoral fractures are associated with Asian descent, bilateral fractures, prodromal pain, glucocorticoid and proton-pump inhibitor usage, rheumatoid arthritis, diabetes mellitus, vitamin D3 deficiencies, and delayed fracture healing [3•, 18–20]. BP usage has been the most commonly associated culprit for atypical femoral fractures [21]. With an increased odds ratio of three to 140, BP has increased the risk of an AFF [3•, 11, 18, 19, 22–24]. In a registry of 2 million patients, 128 of the 142 patients with an AFF had BP exposure [14•]. A further increased risk of an AFF with BP usage greater than five years has been implicated [16•, 22, 25]. However, based upon experimental evidence and scientific design, the ASBMR task force has not completely confirmed this link [3•]. Furthermore, AFF have been diagnosed in patients with no prior BP exposure [26, 27].

Pathogenesis

Microdamage accumulation with impaired stress fracture healing, reduced heterogeneity of organic matrix and mineral properties, and increased glycation end products have been implicated as possible pathological mechanisms for AFF initiation. BP causes osteoclast inactivation and apoptosis. Without normally functioning osteoclastic remodeling, microdamage accumulation occurs [17, 28]. Impairment of stress fracture healing with BP usage has also been studied [29, 30]. In response to stress and strain, normal bone remodeling creates constant changes and heterogeneity in the bone matrix and mineral density, resulting in reduced stress–strain concentration, while abnormal homogeneity increases the risk of crack initiation and proliferation [31–33]. Glycation end products are increased with BP usage and are associated with inferior biomechanical properties and enhanced fracture risk [34]. To date, most studies evaluating the pathogenesis of AFF are in animals. More human studies are required to determine the pathogenesis and potential cures of AFF initiation.

Treatment

Operative Intervention

Since only case reports and small series of atypical fractures have been reported, large controlled studies evaluating vitamin D, calcium, and bone turnover markers have not been evaluated. Furthermore, a paucity of studies specifically evaluating anabolic agents is noted [35, 36]. Therefore, because successful nonoperative rates are extremely low [37, 38•], early operative intervention before the fracture completion or immediately after presenting with an acute fracture is best [38•]. Early intervention reduces length of stay, hospitalization costs, pain, and disability (Fig. 1). The three operative treatment options are intramedullary nailing (IMN), open reduction internal fixation (ORIF), and arthroplasty. To date, no randomized controlled trials exist that compare IMN to ORIF.

Total Joint Arthroplasty

The use of total joint arthroplasty as intervention for atypical femoral fractures has not been reported. Replacing the fracture with an immediate weight bearing implant that is not reliant on fracture healing sounds encouraging in this population, but is it? For very proximal diaphyseal or subtrochanteric fractures, short segment fixation, delayed healing, and the need for weight bearing in this elderly deconditioned population are problematic. This technique will still require bony fixation of the greater trochanter or

Fig. 1 A 67-year-old female presented with 6 months of prodromal right thigh pain not associated with trauma and unrelieved with partial weight bearing and crutches. She was not discontinued from her 7-year history of BP usage. Radiographs of the right femur demonstrate lateral cortical transverse incomplete fracture line (solid arrow) with associated periosteal callus formation (**a, b**). She had BP stopped, vitamin D3 doubled because of low levels, and initiation of teriparatide (T score of -2.8). The treatment was intramedullary nailing with a nail of small radius of curvature, far distal insertion, and cephalomedullary screws to protect the femoral neck. At 3 months postoperatively, she had complete resolution of pain and radiographs demonstrating complete resolution of her fracture line (**c, d**)

abductors. Dysfunctional abductors or trochanteric non-union may result in worse outcomes than primary fracture repair, including pain, limping, and gait disturbances [39–41]. Arthroplasty may be a good option for management of failures fixation and femoral head screws cut out/violation [42, 43].

Open Reduction and Internal Fixation

Open reduction and internal fixation requires direct or indirect fracture reduction, fracture site compression, and plate application. Because these are diaphyseal fractures,

reduction with compression, anatomic alignment, and balanced fixation is paramount. Hybrid fixation consisting of standard cortical screw fixation for compression of the fracture site and of the plate to the bone, locked screw supplementation for improved fixation in short segments and osteoporotic bone, with stout dynamic compression plates are beneficial.

Restoration of anatomic alignment is important but difficult: atypical femoral fractures fixed in varus with compression along the medial cortex and distraction/tension along the lateral cortex are likely to fail catastrophically. When the fracture is realigned and compressed, a mismatch occurs

with distraction or gapping along the medial cortex. Reduction the fracture “anatomically” at the fracture site results in overall varus alignment. This is undesirable and is associated with increased failure rates. Gapping can be corrected with creating a small osteotomy along the lateral cortex to remove the pathologic cortical bone and create a symmetrical fracture reduction with associated restoration of mechanical alignment. Plate fixation results in a “load bearing”, laterally based implant. Early weight bearing required by many elderly, deconditioned patients can disrupt the stability of the construct and ultimately result in early fixation failure even in the best of circumstances. Placement of an intramedullary fibular strut allograft that bypasses the fracture may be a suitable alternative with ORIF, creating a load bearing construct, and enhancing screw purchase and fixation [2•]. Since most plates do not protect or span the entire femur, a stress reaction and potential for fracture at the tip of the implant is possible. Fractures repaired with direct compressive reduction heal via osteoclast-dependent cutting cones and not enchondral bone formation. Healing rates and outcomes for atypical femoral fractures treated with ORIF is not known. More studies are required.

Intramedullary Nailing

Intramedullary nailing (IMN) requires either direct or indirect fracture reduction, relative stability that promotes callus formation, and intramedullary implant insertion. Indirect fracture reduction avoids fracture hematoma formation, disruption of the soft tissue envelope and the periosteum of the fractured femur, and potentially benefits fracture healing. Callus formation and maturation are less reliant on osteoclasts, which may be dysfunctional or dormant in the setting of atypical fractures. The IMN is a “load sharing”, centrally based implant when used in diaphyseal fractures. Immediate weight bearing is safe and encouraged. Furthermore, the intramedullary implant can span the entire femur with a large cephalomedullary screw proximally in the femoral head and a smaller interlocking screw at the distal aspect of the femur. Starting the nail just anterior to the universal start site will confirm an anatomic or slightly valgus reduction with optimal screw insertion trajectory into the head [44]. An attempt to insert the nail as far distal into the metaphyseal bone just proximal to articular surface should be desired. Therefore, the entire femur is truly protected with the implant and stress reaction at the tip of the implant will be avoided [45–47]. In my opinion, an interlocking screw distally should be inserted to avoid rotational and axial instability. In addition, the screw may avoid “windshield wiper” translation in the distal osteoporotic, voluminous, metaphyseal bone. Problems with distal nail insertion are related to the radius of curvature mismatch. Most

femoral nails have a larger-than-anatomic radius of curvature, which is tolerated in younger, straighter femora and enhances intramedullary insertion. However, the mismatch may result in anterior distal femoral cortical penetration and fracture at the tip of the implant. Utilizing a modern nail with more anatomic features, decreased radius of curvature, and utilizing techniques such as leaving the guide pin in until the nail is fully inserted and guiding the nail with blocking screws will facilitate central metaphyseal nail insertion (Fig. 2). Anterior nail abutment without cortical penetration is still not desirable since the anterior position can stress the cortical bone and positions the distal interlocking screw in a precarious anterior position. This anterior position of the screw may predispose the femur to periprosthetic distal fractures. Nails are typically sized based upon the “cortical chatter” of the reamers for a good snug intramedullary fit of the IMN within the canal. Since the bone of these patients is osteoporotic, cortical chatter or resistance may be absent, removing a useful reference for the surgeon, and possibly resulting in technical complications. Using fluoroscopic visualization and surgeon experience will result in an optimal match between the medullary canal and implant.

Fig. 2 A lateral radiograph of femur demonstrates matching anatomy and nail radius of curvature or bow

Fig. 3 A 62-year-old female presented after a low energy fall resulting in a left atypical femoral fracture treated with a cephalomedullary nail. She had an 11-year history of BP usage and a T score of -3.4 . She was started on teriparatide. Two weeks postoperatively, she complained of right knee pain with normal knee radiographs, which did not image her entire femur (a). A MRI demonstrated a degenerative medial meniscal

tear (b). Her arthroscopic medial meniscal debridement did not relieve her pain (c). Four weeks later, she presented with a right atypical femoral fracture (d, e), which was treated with a reconstruction nail (f, g, h) spanning her entire femur and femoral neck. Her displaced fracture, knee MRI, and knee arthroscopy could have been eliminated with complete femoral imaging initially

Bisphosphonate Holidays

Since bisphosphonates are associated with atypical femoral fractures, impede osseous remodeling via osteoclast inhibition and apoptosis, and can potentially soften the healing callus, it has been suggested that bisphosphonates should be stopped temporarily or permanently. Stopping bisphosphonates will allow one to assess the medical situation, enhance the metabolic environment, and correct any abnormalities. Once the fracture is treated operatively, medical therapy can resume. A paucity of literature exists for bisphosphonates' effect on fracture healing. In animal studies, the fracture callus is larger, has larger trabecular bone volume and increased mineral content, but has delayed hard callus remodeling during enchondral fracture repair [48–51]. In another animal study, delayed spinal fusion union was demonstrated in animals taking bisphosphonates [52]. In contradistinction to these theories, an in vitro human trabecular bone cell culture demonstrated that bisphosphonates induced osteoblastic proliferation and maturation. Furthermore, bisphosphonates upregulated bone morphogenetic protein (BMP) 2, type 1 collagen, and osteocalcin [53]. With ORIF, plate fixation results in absolute stability and cutting cone primary bone healing. This process is dependent on osteoclast functioning on the leading edge of this healing. In a human study, a prospective randomized trial of early (2 weeks) versus late (3 months) bisphosphonate treatment was examined in osteoporotic women with unstable distal radius fractures treated with volar locked plates [54]. No difference in time to union (6.7 versus 6.8 weeks) or clinical outcome was demonstrated. The study pitfalls include the fact that metaphyseal fractures uniformly heal at six weeks, this location is dependent on

callus and not cutting cone healing, and there is no mention of vitamin D and calcium levels. Since atypical femoral fractures occur in the diaphyseal instead of the metaphyseal location and usually demonstrate retarded callus formation, more information will be required before definitive recommendations can be made.

Bisphosphonates have different binding affinity and antiresorptive effectiveness properties [55]. Based upon these parameters, stopping or providing a drug “holiday” comes under strong consideration with these fractures. BP usage for more than five years has an increased risk of AFF of 2.74 [22]. Discontinuing therapy will potentially reverse bone-remodeling suppression and inhibition of callus remodeling, and potentiate fracture healing. The length of this holiday is based upon drug kinetics, bone turnover, and secondary fracture risk. If BP is discontinued after the initial AFF presentation, the risk of suffering a contralateral AFF was halved [56]. Denosumab or Teriparatide should be considered as alternative therapies in osteoporotic patients when bisphosphonates are discontinued [35, 36, 57].

Enhancement of Anabolic Metabolism

It is paramount to provide an environment that encourages appropriate and optimal healing. A balanced diet for patients with normal intestinal absorption and a supplemental diet for abnormally absorbing individuals is encouraged. Because fracture healing creates a transient catabolic setting, supplements for all patients are an option. Appropriate calcium, vitamin D, and vitamin C intake and/or supplementation are crucial. Minimum

daily calcium requirements are 1000–1200 mg/day total administered optimally in divided doses [58–60]. The minimum daily Vitamin D3 intake is controversial but should be 1000–2000 IU/day (75). Based upon initial vitamin D 1, 25 OH levels, at the onset vitamin D administration should be Vitamin D2 (ergocalciferol) for enhanced absorption and quicker normalization of vitamin D levels. Once the vitamin D levels become stabilized, changing over to vitamin D3 (cholecalciferol) is beneficial. Individual fracture risk assessment based upon FRAX scores can be estimated (92). Bone turnover markers such as CTX, NTX, and P1NP can estimate bone activity. A combination approach of FRAX with bone markers can help determine the need for initiation of denosumab or teriparatide treatment. The net anabolic effects of teriparatide should be considered for all high-risk patients especially with abnormal bone turnover markers and high FRAX scores.

Assessment of the Contralateral Femur

Bilateral AFF involvement is common, with estimates ranging from 28–44 % [3•, 61]. Any hip, groin, or thigh pain should be imaged with entire femoral length radiographs instead of limited hip images only (Fig. 3). If images are inconclusive or negative, more sensitive technology such as bone scan or MRI should be performed. Serial radiographic images in conjunction with or separate from the treated AFF should also be considered. Prophylactic contralateral femoral IMN is an option but controversial especially if asymptomatic clinically and radiographically [62, 63•, 64, 65].

Conclusion

Atypical femoral fractures are associated with long-term bisphosphonate treatment for osteoporosis, but do not have a causal relationship. Osteoporosis-related hip fractures are several times more common than atypical femoral fractures. A diagnostic evaluation of hip pain in an older patient with a history of osteoporosis and bisphosphonate usage should probably include a femoral diaphyseal image. Treatment of atypical femoral fractures with an intramedullary nail and metabolic optimization should be desired.

Conflict of Interest Clifford B. Jones has served on the board for the American Orthopaedic Association's Own the Bone; payment for lectures including service on speaker's bureaus from A.O. North America; payment for manuscript preparation from *The Journal of Bone and Joint Surgery* Trauma Newsletter; stock/stock options from Orthopaedic Associates of Michigan and Midtowne Surgery Center ASC (partial owner); reimbursement for travel expenses incurred from A.O. North America.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
1. • Weaver MJ, Miller MA, Vrahas MS. The orthopaedic implications of diphosphonate therapy. *J Am Acad Orthop Surg.* 2010;18(6):367–74. *Prospective clinical trials have shown that diphosphonates increase bone mineral density and reduce the risk of fracture. Diphosphonates are generally well tolerated, with a low incidence of side effects. They may be administered orally or intravenously; infusions are the most potent. Few studies have directly studied the effect of diphosphonates on the rate of fracture or time to union. Concern exists regarding the long-term safety of diphosphonates, particularly in patients with osteoporosis. New evidence suggests that long-term therapy may increase the risk of fracture of the femoral shaft, with possible morphologic and prodromal warning signs.*
  2. • Unnanuntana A, Saleh A, Mensah KA, et al. Atypical femoral fractures: what do we know about them?: AAOS Exhibit Selection. *J Bone Joint Surg Am.* 2013;95(2):e8 1–13. *The causal relationship between prolonged bisphosphonate use and the occurrence of atypical femoral fractures has not yet been established. If a patient sustains an atypical femoral fracture, bisphosphonates must be stopped, and an anabolic agent should be employed with daily calcium and vitamin D supplementation. As fractures treated by intramedullary nailing heal by endochondral repair, such nailing is a preferred method of fixation for atypical femoral fractures. Atypical femoral fractures are relatively rare events, and the balance between patient efficacy and safety still favors bisphosphonate therapy for the treatment of osteoporosis. Bisphosphonates appear to have lingering efficacy against fractures even after the treatment is discontinued, so a drug holiday should be considered for most patients who take bisphosphonates for 5 years or more.*
  3. • Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2010;25(11):2267–94. *Reports linking long-term use of bisphosphonates (BPs) with atypical fractures of the femur led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address key questions related to this problem. A multidisciplinary expert group reviewed pertinent published reports concerning atypical femur fractures, as well as preclinical studies that could provide insight into their pathogenesis. A case definition was developed so that subsequent studies report on the same condition. The task force defined major and minor features of complete and incomplete atypical femoral fractures and recommends that all major features, including their location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete, and absence of comminution, be present to designate a femoral fracture as atypical. Minor features include their association with cortical thickening, a periosteal reaction of the lateral cortex, prodromal pain, bilaterality, delayed healing, comorbid conditions, and concomitant drug exposures, including BPs, other antiresorptive agents, glucocorticoids, and proton pump inhibitors.*
  4. Mashiba T, Hirano T, Turner CH, et al. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res.* 2000;15(4):613–20.

5. Mashiba T, Mori S, Burr DB, et al. The effects of suppressed bone remodeling by bisphosphonates on microdamage accumulation and degree of mineralization in the cortical bone of dog rib. *J Bone Miner Metab.* 2005;23(Suppl):36–42.
6. Mashiba T, Turner CH, Hirano T, et al. Effects of high-dose etidronate treatment on microdamage accumulation and biomechanical properties in beagle bone before occurrence of spontaneous fractures. *Bone.* 2001;29(3):271–8.
7. Armamento-Villareal R, Napoli N, Diemer K, et al. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. *Calcif Tissue Int.* 2009;85(1):37–44.
8. Armamento-Villareal R, Napoli N, Panwar V, et al. Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. *N Engl J Med.* 2006;355(19):2048–50.
9. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab.* 2008;93(8):2948–52.
10. Unnanuntana A, Ashfaq K, Ton QV, et al. The effect of long-term alendronate treatment on cortical thickness of the proximal femur. *Clin Orthop Relat Res.* 2012;470(1):291–8.
11. Feldstein AC, Black D, Perrin N, et al. Incidence and demography of femur fractures with and without atypical features. *J Bone Miner Res.* 2012;27(5):977–86.
12. Martinet O, Cordey J, Harder Y, et al. The epidemiology of fractures of the distal femur. *Injury.* 2000;31 Suppl 3:C62–3.
13. Wang Z, Bhattacharyya T. Trends in incidence of subtrochanteric fragility fractures and bisphosphonate use among the US elderly, 1996–2007. *J Bone Miner Res.* 2011;26(3):553–60.
14. • Dell RM, Adams AL, Greene DF, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. *J Bone Miner Res.* 2012;27(12):2544–50. *The incidence of BP fractures within a defined population was calculated and examined the incidence rates according to duration of bisphosphonate use. All femur fractures from January 1, 2007 until December 31, 2011 in 1,835,116 patients older than 45 years who were enrolled in the Healthy Bones Program at Kaiser Southern California, an integrated health care provider, were calculated. The results showed that 142 patients had atypical fractures; of these, 128 had bisphosphonate exposure. There was no significant correlation between duration of use (5.5 +/- 3.4 years) and age (69.3 +/- 8.6 years) or bone density (T-score 2.1 +/- 1.0). There were 188,814 patients who had used bisphosphonates. The age-adjusted incidence rates for an atypical fracture were 1.78/100,000/year (95% confidence interval [CI], 1.5–2.0) with exposure from 0.1 to 1.9 years, and increased to 113.1/100,000/year (95% CI, 69.3–156.8) with exposure from 8 to 9.9 years. We conclude that the incidence of atypical fractures of the femur increases with longer duration of bisphosphonate use. The rate is much lower than the expected rate of devastating hip fractures in elderly osteoporotic patients. Patients at risk for osteoporotic fractures should not be discouraged from initiating bisphosphonates, because clinical trials have documented that these medicines can substantially reduce the incidence of typical hip fractures. The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years.*
15. • Nieves JW, Bilezikian JP, Lane JM, et al. Fragility fractures of the hip and femur: incidence and patient characteristics. *Osteoporos Int.* 21(3):399–408. *In females, the overall hospital discharge rates of hip fracture decreased from about 600/100,000 to 400/100,000 person-years from 1996 to 2006. Subtrochanteric, femoral shaft, and lower femur rates remained stable, each approximately 20 per 100,000 person-years. Similar trends but lower rates existed in males. No significant trends were found in any of these fractures during the more recent years of 2002–2006. The overall incidence of hip fracture was < 300/100,000 person-years; incidence of subtrochanteric and femoral shaft fractures combined was < 25/100,000 person-years and distal femur fracture incidence was < 18/100,000 person-years in females; rates were lower in males. The incidence of hip and other femur fractures increased exponentially with age. No evidence of an increasing incidence of any femoral fracture was found. Hip fracture incidence is declining, but the incidence of each of the more rare femur fractures (distal to the lesser trochanter) is stable over time.*
16. • Neviaser AS, Lane JM, Lenart BA, et al. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma.* 2008;22(5):346–50. *There were 59 females and 11 males. The average age was 74.7 years. Twenty-five (36 %) were being treated with alendronate. None of the patients had used or were using other bisphosphonates. Nineteen (76 %) of these 25 patients demonstrated a simple, transverse fracture with a unicortical beak in an area of cortical hypertrophy. This fracture pattern was seen in only one patient (2 %) not being treated with alendronate. Alendronate use was a significant risk factor for the fracture pattern (odds ratio [OR]) 139.33, 95 % CI [19.0–939.4], $P < 0.0001$. This pattern was 98 % specific to alendronate users. The average duration of alendronate use in those with the pattern was significantly longer than those who did not exhibit the pattern but were taking alendronate, 6.9 years versus 2.5 years of use, respectively ($P = 0.002$). Only one patient with the fracture pattern had been taking alendronate for less than 4 years. Low-energy fractures of the femoral shaft with a simple, transverse pattern and hypertrophy of the diaphyseal cortex are associated with alendronate use. This may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair resulting from its prolonged use.*
17. Brennan O, Kennedy OD, Lee TC, et al. Effects of estrogen deficiency and bisphosphonate therapy on osteocyte viability and microdamage accumulation in an ovine model of osteoporosis. *J Orthop Res.* 2011;29(3):419–24.
18. Giusti A, Hamdy NA, Dekkers OM, et al. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. *Bone.* 2011;48(5):966–71.
19. Giusti A, Hamdy NA, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. *Bone.* 2010;47(2):169–80.
20. Lo JC, Huang SY, Lee GA, et al. Clinical correlates of atypical femoral fracture. *Bone.* 2012;51(1):181–4.
21. Odvina CV, Zerwekh JE, Rao DS, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab.* 2005;90(3):1294–301.
22. Park-Wyllie LY, Mamdani MM, Juurlink DN, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA.* 2011;305(8):783–9.
23. Schilcher J, Koeppen V, Ranstam J, et al. Atypical femoral fractures are a separate entity, characterized by highly specific radiographic features. A comparison of 59 cases and 218 controls. *Bone.* 2013;52(1):389–92.
24. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med.* 2011;364(18):1728–37.
25. Lenart BA, Lorch DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med.* 2008;358(12):1304–6.
26. Adachi JD, Lyles K, Boonen S, et al. Subtrochanteric fractures in bisphosphonate-naïve patients: results from the HORIZON-recurrent fracture trial. *Calcif Tissue Int.* 2011;89(6):427–33.
27. Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res.* 2009;24(6):1095–102.
28. Koh JS, Goh SK, Png MA, et al. Femoral cortical stress lesions in long-term bisphosphonate therapy: a herald of impending fracture? *J Orthop Trauma.* 2010;24(2):75–81.

29. Kidd LJ, Cowling NR, Wu AC, et al. Bisphosphonate treatment delays stress fracture remodeling in the rat ulna. *J Orthop Res*. 2011;29(12):1827–33.
30. Sloan AV, Martin JR, Li S, et al. Parathyroid hormone and bisphosphonate have opposite effects on stress fracture repair. *Bone*. 2010;47(2):235–40.
31. Tai K, Dao M, Suresh S, et al. Nanoscale heterogeneity promotes energy dissipation in bone. *Nat Mater*. 2007;6(6):454–62.
32. Roschger P, Paschalis EP, Fratzl P, et al. Bone mineralization density distribution in health and disease. *Bone*. 2008;42(3):456–66.
33. Roschger P, Rinnerthaler S, Yates J, et al. Alendronate increases degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. *Bone*. 2001;29(2):185–91.
34. Tang SY, Allen MR, Phipps R, et al. Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. *Osteoporos Int*. 2009;20(6):887–94.
35. Huang HT, Kang L, Huang PJ, et al. Successful teriparatide treatment of atypical fracture after long-term use of alendronate without surgical procedure in a postmenopausal woman: a case report. *Menopause*. 2012;19(12):1360–3.
36. Pietrogrande L, Raimondo E. Teriparatide in the treatment of non-unions: scientific and clinical evidences. *Injury*. 2013;44 Suppl 1:S54–7.
37. Ha YC, Cho MR, Park KH, et al. Is surgery necessary for femoral insufficiency fractures after long-term bisphosphonate therapy? *Clin Orthop Relat Res*. 2010;468(12):3393–8.
38. • Banffy MB, Vrahas MS, Ready JE, et al. Nonoperative versus prophylactic treatment of bisphosphonate-associated femoral stress fractures. *Clin Orthop Relat Res*. 2011;469(7):2028–34. *Five of the six stress fractures treated nonoperatively progressed to fracture completion and displacement at an average of 10 months (range, 3–18 months). The average hospital stay was 3.7 days for patients treated prophylactically and 6.0 days for patients treated after fracture completion. The data suggest nonoperative treatment of bisphosphonate-related femoral stress fractures is not a reliable way to treat these fractures, as the majority progress to fracture completion. Prophylactic fixation of femoral stress fractures also reduces total hospital admission time.*
39. Kohl S, Evangelopoulos DS, Siebenrock KA, et al. Hip abductor defect repair by means of a vastus lateralis muscle shift. *J Arthroplasty*. 2012;27(4):625–9.
40. Fehm MN, Huddleston JI, Burke DW, et al. Repair of a deficient abductor mechanism with Achilles tendon allograft after total hip replacement. *J Bone Joint Surg Am*. 2010;92(13):2305–11.
41. Pritchett JW. Fracture of the greater trochanter after hip replacement. *Clin Orthop Relat Res*. 2001;390:221–6.
42. Abouelela AA. Salvage of failed trochanteric fracture fixation using the Revitan curved cementless modular hip arthroplasty. *J Arthroplasty*. 2012;27(7):1382–8.
43. Hsieh PH, Chang YH, Chen SH, et al. Staged arthroplasty as salvage procedure for deep hip infection following intertrochanteric fracture. *Int Orthop*. 2006;30(4):228–32.
44. Ostrum RF, Marcantonio A, Marburger R. A critical analysis of the eccentric starting point for trochanteric intramedullary femoral nailing. *J Orthop Trauma*. 2005;19(10):681–6.
45. Collinge CA, Beltran CM. Does Modern Nail Geometry Affect Positioning in the Distal Femur of Elderly Patients with Hip Fractures? A Comparison of Otherwise Identical Intramedullary Nails with a 200 cm versus 150 cm Radius of Curvature. *J Orthop Trauma*. 2013.
46. Patton JT, Cook RE, Adams CI, et al. Late fracture of the hip after reamed intramedullary nailing of the femur. *J Bone Joint Surg Br*. 2000;82(7):967–71.
47. Collinge C, Liporace F, Koval K, et al. Cephalomedullary screws as the standard proximal locking screws for nailing femoral shaft fractures. *J Orthop Trauma*. 2010;24(12):717–22.
48. Matos MA, Tannuri U, Guarniero R. Effect of ifosfamide on bone healing. *J Musculoskelet Neuronal Interact*. 2006;6(3):247–50.
49. Matos MA, Tannuri U, Guarniero R. The effect of zoledronate during bone healing. *J Orthop Traumatol*. 2010;11(1):7–12.
50. Amanat N, McDonald M, Godfrey C, et al. Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. *J Bone Miner Res*. 2007;22(6):867–76.
51. Amanat N, Brown R, Bilston LE, et al. A single systemic dose of pamidronate improves bone mineral content and accelerates restoration of strength in a rat model of fracture repair. *J Orthop Res*. 2005;23(5):1029–34.
52. Huang RC, Khan SN, Sandhu HS, et al. Alendronate inhibits spine fusion in a rat model. *Spine (Phila Pa 1976)*. 2005;30(22):2516–22.
53. Im GI, Qureshi SA, Kenney J, et al. Osteoblast proliferation and maturation by bisphosphonates. *Biomaterials*. 2004;25(18):4105–15.
54. Gong HS, Song CH, Lee YH, et al. Early initiation of bisphosphonate does not affect healing and outcomes of volar plate fixation of osteoporotic distal radial fractures. *J Bone Joint Surg Am*. 2012;94(19):1729–36.
55. Dunford JE, Thompson K, Coxon FP, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther*. 2001;296(2):235–42.
56. Dell R, Greene, D, Tran, D. Stopping bisphosphonate treatment decreases the risk of having a second atypical femur fracture. Paper 190. Annual Meeting of the American Academy of Orthopaedic Surgery. San Francisco, CA 2012, Feb 7–11.
57. Chiang CY, Zebaze RM, Ghasem-Zadeh A, et al. Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy. *Bone*. 2013;52(1):360–5.
58. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. preventive services task force recommendation statement. *Ann Intern Med*. 2013.
59. Nestle M, Nesheim MC. To supplement or not to supplement: the U.S. preventive services task force recommendations on calcium and vitamin D. *Ann Intern Med*. 2013.
60. Moyer VA. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. preventive services task force recommendation statement. *Ann Intern Med*. 2013.
61. Rizzoli R, Akesson K, Bouxsein M, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. *Osteoporos Int*. 2011;22(2):373–90.
62. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg Am*. 2009;91(11):2556–61.
63. • Edwards BJ, Bunta AD, Lane J, et al. Bisphosphonates and nonhealing femoral fractures: analysis of the FDA adverse event reporting system (FAERS) and international safety efforts: a systematic review from the research on adverse drug events and reports (RADAR) project. *J Bone Joint Surg Am*. 2013;95(4):297–307. *Nonhealing femoral fractures are unusual adverse drug reactions associated with bisphosphonate use, as up to 26 % of published cases of atypical femoral fractures exhibited delayed healing or nonhealing.*
64. Edwards MH, McCrae FC, Young-Min SA. Alendronate-related femoral diaphysis fracture—what should be done to predict and prevent subsequent fracture of the contralateral side? *Osteoporos Int*. 2010;21(4):701–3.
65. Somford MP, Draijer FW, Thomassen BJ, et al. 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*. 2009;24(10):1736–40.