# Atypical femur fractures: a review of the evidence and its implication to clinical practice

*Ther Adv Musculoskel Dis*
(2011) 3(6) 301–314
DOI: 10.1177/1759720X11416270



**Christian M. Girgis and Markus J. Seibel**

*Abstract*: Whilst bisphosphonates are an established modality in the treatment of osteoporosis, there have been increasing concerns regarding the risk of an unusual form of femur fracture amongst patients receiving bisphosphonates for prolonged periods. These fractures, referred to as 'atypical', have been characterized by a number of clinical and radiographic features that distinguish them from 'typical' osteoporotic fractures. The evidence base is currently split between a large number of case series demonstrating an association between the occurrence of atypical fractures and bisphosphonate use and several population-based studies that do not confirm such an association. Hence, a degree of uncertainty surrounds this important issue. In this review, we examine the emerging evidence on atypical femur fractures, assess hypotheses on their biomechanical evolution and discuss the wider clinical implications of this phenomenon.

*Keywords*: Atypical femur fractures, osteoporosis, bisphosphonates, adverse drug reactions

## Introduction

Bisphosphonates are highly effective in the treatment of osteoporosis. Numerous large clinical trials have demonstrated their efficacy in reducing bone turnover, increasing bone mineral density and reducing vertebral and non-vertebral fracture risk in patients with osteoporosis [Cranney *et al.* 2002a, 2002b]. A recent study estimated that between 2001 and 2008, 144,670 low-energy fractures were prevented amongst women who took bisphosphonates in the United States [Siris *et al.* 2011]. Bisphosphonates are also generally well tolerated and considered to have an excellent safety profile even at higher doses [Dunstan *et al.* 2007].

However, since 2005, there have been increasing concerns regarding the potential risk of an unusual type of femur fracture amongst patients on bisphosphonate therapy [Odvina *et al.* 2005]. Similar fractures were later described by Lenart and colleagues as 'atypical' in that they involved the strongest part of the femur, namely the subtrochanteric and diaphyseal region, and were characterized by features distinctly different from 'typical' osteoporotic femur fractures [Lenart *et al.* 2008]. Such 'atypical' features include a history of prodromal thigh pain, the development of circumferential cortical thickening and cortical stress lesions that may precede a complete transverse or oblique fracture of the subtrochanteric femur [Lenart *et al.* 2008; Goh *et al.* 2007]. Although a clear causal link between bisphosphonates and such atypical femur fractures has not been established, the widespread use of these otherwise effective agents has come under scrutiny amidst increasing public and medical concerns of this potential complication. In response to this, drug regulatory authorities have issued statements acknowledging the efficacy of bisphosphonates but advising caution regarding their 'long-term' use (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm). Likewise, the International Osteoporosis Foundation and the American Society of Bone and Mineral Research have published position statements that acknowledge the issue, define atypical femur fractures and guide further research [Rizzoli *et al.* 2011; Shane *et al.* 2010].

In this review, we summarize the past 6 years of data on atypical femur fractures, discuss what is currently known of their association with bisphosphonate use and examine the basis of the widely held hypothesis of 'severe suppression of bone turnover'.

Correspondence to:
**Markus J. Seibel, MD, PhD, FRACP**
Bone Research Program, ANZAC Research Institute, 1A Hospital Road, Concord, Sydney, NSW 2139, Australia
**markus.seibel@sydney.edu.au**

**Christian M. Girgis, BSc, MBBS**
Garvan Institute of Medical Research, Darlinghurst, Sydney and University of Sydney, Sydney, Australia

## Case reports and series

In 2005, Odvina and colleagues described a series of unusual fractures that occurred spontaneously in patients who had been treated with alendronate for 3–8 years [Odvina *et al.* 2005]. Of the nine patients reported, two had sustained bilateral femur shaft fractures, two had unilateral femur shaft fractures, two had proximal femur fractures and the remainder had a combination of pelvic, vertebral and metatarsal fractures. The unusual nature of the femur fractures as noted by their midshaft location, spontaneous development and the delay or absence in fracture healing prompted the investigators to perform bone biopsies on all nine patients. Histomorphometric analysis of trans-iliac biopsies demonstrated marked suppression of bone formation, with reduced or absent osteoblastic surface in five patients, reduced osteoclastic surface in six patients and reduced eroded surface in five patients. On this basis, the authors proposed that the prolonged use of alendronate had led to severe suppression of bone turnover, which in turn resulted in microdamage accumulation and the subsequent development of insufficiency fractures. However, the validity of this hypothesis was limited by the small number of cases, inconsistencies in histomorphometric results amongst cases, the demonstration of normal bone markers in most patients, and the general consideration that a degree of bone suppression may be expected in patients on long-term bisphosphonate therapy.

Following this initial publication, a number of additional reports emerged which described a similar pattern of unusual insufficiency fracture amongst patients on long-term bisphosphonate therapy. Visekruna and colleagues described three patients who sustained minimal-trauma, 'chalk-stick type' femoral shaft fractures while on alendronate therapy (5–10 years' duration) [Visekruna *et al.* 2008]. Notable features included the concomitant use of other antiresorptive agents, the presence of systemic inflammatory conditions (i.e. Crohn's disease, rheumatoid arthritis), low or undetectable biochemical markers of bone turnover, bilaterality of the femur fracture in two of the three patients and iliac bone biopsy findings consistent with suppression of turnover. Several months after the discontinuation of alendronate, the only patient to show signs of fracture healing had been receiving teriparatide whereas the other two had not.

However, not all reports support the hypothesis of severe suppression of bone turnover in the development of these fractures. Lee and colleagues reported the case of a 73-year-old woman who sustained multiple atraumatic femoral and pelvic insufficiency fractures 18 months after the commencement of alendronate therapy [Lee *et al.* 2007]. In spite of biochemical evidence of reduced bone resorption (i.e. urinary deoxypyridinoline to creatinine ratio $<3$ nmol/mmol), the fractures healed while the patient remained on alendronate therapy, thus casting doubt on the proposed hypothesis that bisphosphonates would be directly responsible for these fractures. Furthermore, a patient with rheumatoid arthritis who developed bilateral femoral shaft fractures while taking long-term alendronate and glucocorticoid therapy demonstrated evidence of significantly increased, rather than reduced, bone resorption and a reduction in bone formation both at the iliac crest and femoral cortex [Somford *et al.* 2009].

It was in 2008 that the term 'atypical femur fracture' was coined and a clear definition of these fractures was proposed [Lenart *et al.* 2008]. A case series describing 15 patients who had developed minimal trauma fractures while receiving alendronate reported that 10 of these patients demonstrated a unique, atypical fracture pattern, defined by a simple transverse or oblique ($\leq 30^{\circ}$) fracture, cortical beaking and diffuse cortical thickening of the femoral shaft. Importantly, these 10 patients had been on alendronate for a significantly longer period than the five patients without this pattern ($7.3 \pm 1.8$ *versus* $2.8 \pm 1.3$ years, $p < 0.001$). For a comparison of the radiographical appearance of atypical *versus* typical subtrochanteric femur fractures, see Figure 1.

The association between the atypical fracture pattern and prolonged bisphosphonate use was further validated by two case series. The first of these described eight patients with the atypical fracture pattern of whom five had been on alendronate from 16 months to 8 years, two had been on ibandronate for 4 months and 1 year and one had been on pamidronate until 1 year prior to the fracture [Ing-Lorenzini *et al.* 2009]. Seven patients were also on proton-pump inhibitors, four on long-term steroid therapy and four patients eventually developed a stress fracture or complete fracture of the contralateral femur. Capeci and Tejwani also described seven patients

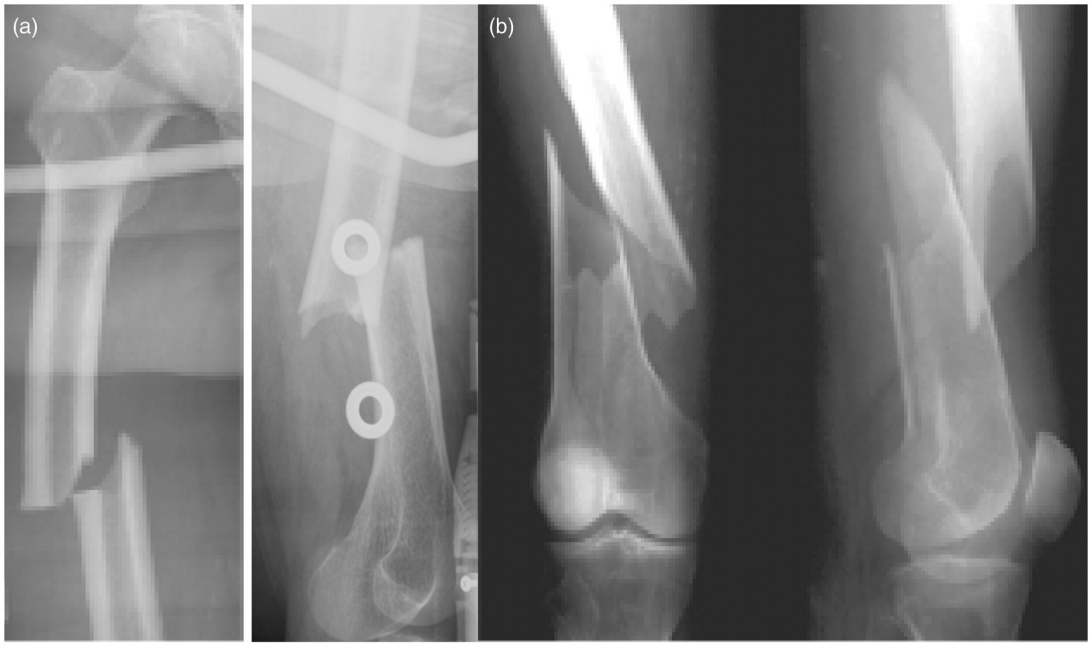


**Figure 1.** Radiographs showing atypical and typical femoral fractures. (a) Radiographs (anteroposterior and lateral) demonstrating the characteristic appearance of an atypical femoral fracture: a transverse or oblique (<30°) fracture line in an area of cortical thickening with a contralateral uni-cortical beak. (b) Radiograph demonstrating a typical osteoporotic spiral fracture involving the diaphyseal femur after a mechanical fall.

on long-term alendronate (ranging from 5 to 13 years) who developed bilateral subtrochanteric femur fractures consistent with the atypical fracture pattern as previously described [Capeci and Tejwani, 2009]. One patient presented with simultaneous bilateral fractures, two patients had sequential fractures, and four patients had contralateral stress fractures noted at the time of the initial fracture. All fractures were treated with reamed intramedullary nailing, bisphosphonates were ceased and fracture union was subsequently established at an average of 4 months.

Recently, a systematic literature review summarized data from case reports and case series on atypical femur fractures reported in women from 2005 to 2010 [Giusti *et al.* 2010]. A total of 31 publications and one unpublished case series reported a total of 141 atypical femur fractures occurring in women on bisphosphonate therapy. Alendronate was the bisphosphonate most commonly used (85%) with duration of therapy $71.5 \pm 40$ months. The majority of patients reported prodromal thigh pain (64%) and a number of patients were receiving glucocorticoids (32.6%) or proton-pump inhibitors (53.8%) at the time of the fracture. Interestingly, patients treated with bisphosphonates for less than 5 years (52%) were more likely to be of Asian origin (60% *versus* 14.5%, $p < 0.001$) or to have a history of femoral shaft fracture (11.8% *versus* 0%, $p = 0.042$) before starting treatment compared with those treated for more than 5 years. This possibly indicates that ethnicity and, perhaps, underlying but undiagnosed skeletal disorders may play a role in the development of these fractures.

Case studies have drawn considerable attention to the occurrence of unusual insufficiency fractures amongst bisphosphonate users but the data are inherently limited by the potential for observer bias, the lack of a control group and the absence of uniform reporting or a standard definition of atypical femur fractures amongst the different reports. However, questions raised by these preliminary reports have prompted further research on this particular subset of femur fracture and its proposed preponderance amongst patients on long-term bisphosphonates.

## Retrospective studies on subtrochanteric femur fractures

Several retrospective studies have examined patients with low-energy subtrochanteric femur

fractures, seeking to identify differences in patients with 'typical' osteoporotic *versus* atypical femur fractures.

In a retrospective review of patients admitted with subtrochanteric fractures to one of two hospitals in Singapore over a 10-month period, nine of the 13 women were on long-term alendronate for a mean duration of 4.2 years whereas four were not [Goh *et al.* 2007]. The patients on alendronate were younger (mean age 66.9 years *versus* 80.3 years) and were noted to be more 'socially active' than those not on alendronate. The majority demonstrated a simple transverse or short oblique fracture occurring at the metaphyseal–diaphyseal junction (8/9) in association with cortical hypertrophy at the lateral aspect of the femur (6/9) and involving the contralateral femur (3/9). Five patients with atypical femur fractures reported prodromal pain in the affected hip in the months prior to the fall, and importantly, the four patients who did not fall at the time of the fracture recalled experiencing a sharp pain or hearing a snapping sound at the moment of fracture.

As an extension to their initial study, the same group later reported a larger cohort of 17 patients, with a mean age of 66 years, who sustained low-energy subtrochanteric fractures within a 20-month period [Kwek *et al.* 2008]. These patients were all on alendronate therapy for an average of 4.8 years, 16 demonstrated the atypical fracture pattern as described, 13 had prodromal thigh pain, seven patients had no trauma, and three patients had bilateral femoral fractures. Interestingly, the majority of patients had a prior history of osteoporotic fracture (8/17) but only 40% of patients with pretreatment bone mineral densities had femoral neck osteoporosis (5/12).

Another study reviewed all low-energy subtrochanteric and mid-shaft femur fractures admitted to a trauma centre in New York over a 5-year period [Neviaser *et al*. 2008]. Of the 70 fractures, 59 occurred in women and 11 in men; 50 were subtrochanteric and 20 were mid-shaft fractures. Amongst the 25 patients who had been receiving alendronate prior to the fracture (25 of 70, 36%), 19 (76%) were identified by three orthopaedic specialists as displaying the atypical fracture pattern as previously described [Lenart *et al.* 2008] whilst only one patient who was not on alendronate displayed this pattern (1/45, 2.2%). The authors reported that alendronate use was a significant risk factor for the fracture pattern [odds ratio (OR) 139.33, 95% confidence interval (CI) 19.0−934.4, $p < 0.001$] and that the pattern was 98% specific to alendronate users. Furthermore, the average duration of alendronate use in those with the atypical 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 ($p = 0.002$).

More recently, a 5-year retrospective study of 152 non-hip femoral fractures identified 20 atypical femur fractures following detailed review of individual radiographs [Girgis *et al.* 2010]. Of the 20 patients with atypical femur fractures, 17 had been receiving alendronate ($n = 15$) or risedronate ($n = 2$) for a mean duration of 5.1 years and 3 years respectively. Of the 132 patients whose radiographs did not fulfill the criteria for atypical fracture, two (1.5%) were taking alendronate, and one was taking risedronate (0.8%), with mean treatment durations of 3.5 years and 1 year respectively. It was therefore calculated that oral bisphosphonate use imparted a 37-fold increased risk of atypical *versus* typical osteoporotic fracture, with the atypical fracture pattern being 96% specific to oral bisphosphonate use. Consistent with other reports, the investigators described an additional set of risk factors associated with the development of atypical femur fractures which included a history of low-energy fracture, the use of glucocorticoid therapy for more than 6 months, active rheumatoid arthritis and a level of serum 25-hydroxyvitamin D of less than 40 nmol/L (16 ng/mL). On the basis of the fractures identified and using data from the Australian Bureau of statistics, the authors estimated that the annual incidence of atypical femur fractures in 2006 was 0.23 per 10,000 amongst the general population living within the institution's catchment area and 1.6 per 10,000 in people over 65 years of age [Girgis and Seibel, 2011a]. Using wholesale data on the purchase of oral bisphosphonates by pharmacies within the institution's catchment area, they estimated an annual incidence of atypical femur fractures of 10 per 10,000 in patients taking alendronate and three per 10,000 in patients taking risedronate within this population from 2003 to 2008. Although this study provided incidence estimates of atypical femur fractures identified on the basis of radiograph analysis, these estimates are limited as they were based on a small number of fracture cases.

Another retrospective study evaluated 100 patients with low-energy femoral shaft fractures before and after bisphosphonates became available for use [Isaacs *et al.* 2010]. A total of 21 patients who presented with low-energy femoral shaft fractures between 1995 and 1997 were compared with 79 patients who presented between 2007 and 2009 with low-energy fractures at the same location. The 41 patients who displayed atypical femur fractures had been receiving bisphosphonate therapy (mean duration 7.1 years) with a considerable proportion reporting prodromal thigh pain [29 of 41 (71%)] and displaying bilateral insufficiency fractures [18 of 41 (44%)]. None of the patients who presented with femoral shaft fractures in the era prior to bisphosphonate use demonstrated the atypical fracture pattern.

In another study, 12 out of 20 patients who were admitted to a single centre with low-energy subtrochanteric fractures between 2001 and 2007 were receiving alendronate [Das De *et al.* 2010]. The atypical pattern was found in 11 patients, six had bilateral fractures, the mean duration of bisphosphonate use was 4.6 years and only one of five patients who received a bone mineral density scan at the time of the fracture displayed osteoporosis (the others displayed osteopaenia). However, it was the identification of a precursor femur lesion in patients with atypical femur fractures that was a particularly notable feature of this study. The lesion, described as 'an ellipsoid thickening' in the lateral cortex was noted in nine femurs in patients on long-term alendronate. Five progressed to complete fracture, two were prophylactically fixed prior to the development of a complete fracture, one regressed following the cessation of alendronate therapy and one was followed for a year before the patient died of unrelated causes. For examples of the radiographical appearance of such cortical stress lesions, see Figure 2.

A study examining 55 patients over the age of 60 who were admitted for femoral shaft fractures between 2003 and 2007 identified seven patients with prior alendronate therapy [Ng *et al.* 2011]. Of these, five demonstrated the atypical fracture pattern whilst the remaining two had transverse or oblique fractures but without cortical hypertrophy. Importantly, none of the patients had received bone mineral density scans prior to the commencement of alendronate and the majority of patients had no clear indication for bisphosphonate therapy.

Although these retrospective studies confirm the patterns described in smaller case series and assist in the differentiation of atypical femur fractures from the larger group of osteoporotic subtrochanteric fractures, the potential for selection bias remains in that patients with atypical fractures may have sufficiently severe osteoporosis to require longer-term bisphosphonate therapy. Furthermore, these studies are observational and although they support an association between bisphosphonate use and atypical femur fractures, they are not equipped to address the important question of causality.

### Case–control studies on femur fractures

As subtrochanteric and femoral shaft fractures are generally infrequent amongst patients with osteoporosis, two recent case–control studies have included osteoporotic hip fractures in the analysis of subtrochanteric, diaphyseal and atypical femur fractures.

In one study, the radiographs of all patients with femur fractures admitted to an institution between 1997 and 2007 were reviewed individually in order to identify the atypical fracture pattern (defined as a transverse, or short oblique, non-comminuted subtrochanteric/shaft fracture in an area of thickened cortices with unicortical beaking) [Giusti *et al.* 2011]. Amongst a total of 906 femur fractures and 63 low-energy subtrochanteric/shaft fractures, there were only 10 patients with atypical fractures. The frequency of bisphosphonate use was comparable amongst the 62 patients with subtrochanteric/shaft fractures *versus* 126 patients with hip fractures who were age and gender matched. However, atypical femur fractures were more frequently associated with bisphosphonate use than typical subtrochanteric or shaft fractures (OR 17, 95% CI 2.55−113, $p < 0.005$). Interestingly, cortical thickening was no more prevalent amongst bisphosphonate users compared with patients who had never been treated with such agents and half of the atypical femur fractures occurred in patients never exposed to bisphosphonate therapy (5/10). Therefore, an important question raised by this study was whether other factors potentially contributed to the development of these atypical femur fractures and whether bisphosphonate use is simply an innocent

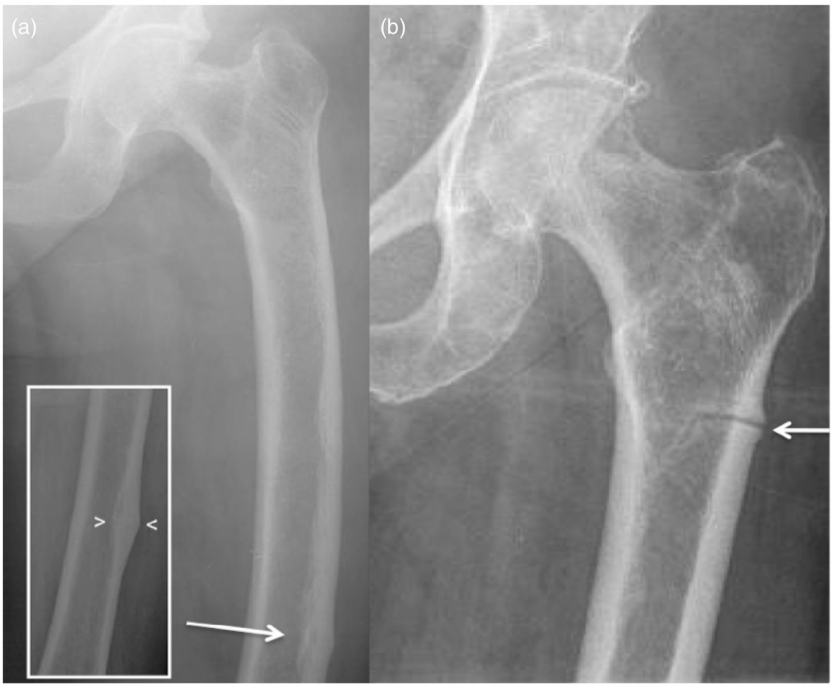


**Figure 2.** Precursor cortical stress lesions in femur. (a) Three years after the development of a complete right-sided femoral shaft fracture, this patient developed left-sided thigh pain and was noted to have an 'ellipsoid thickening' in the lateral femur cortex with bowing of the left femur (arrow). On closer inspection (see insert), a transverse fracture of the cortical femur with a surrounding cortical stress reaction is seen (arrow-heads). The patient had been receiving alendronate for 5 years at the time of this x-ray. (b) These cortical lesions are not specific to bisphosphonate users (arrow). This 85-year-old patient with a 20-year history of rheumatoid arthritis and intermittent high-dose glucocorticoid therapy reported 3 months of thigh pain. The patient denied any prior or current bisphosphonate use. In both cases (a and b), intramedullary nail fixation resulted in relief from the thigh pain and is likely to have prevented the development of a complete transverse fracture.

bystander perhaps reflective of more severe osteoporosis, present in only a subset of cases.

However, the findings of this study stand in stark contrast to those of a similar case–control study comparing the individual radiographs of 41 patients with subtrochanteric or femur shaft fractures with those of 82 patients with intertrochanteric or hip fractures matched for age, sex and body mass index [Lenart *et al.* 2009]. The fracture groups were identified following a retrospective analysis of all patients admitted with femur fractures from 2000 to 2007 at a tertiary centre. A significantly greater proportion of long-term bisphosphonate use was found amongst those with subtrochanteric/femur shaft fractures and duration of bisphosphonate use was also significantly longer in this group ($p = 0.001$). The atypical fracture pattern was highly associated with bisphosphonate use (OR 15.33, 95% CI 3.06 −76.9, $p < 0.001$) and interestingly, duration of therapy amongst subtrochanteric/shaft cases correlated with cortical thickness.

The contradictory findings of these two case–control studies may be explained by potential differences in the populations studied, differences in duration of bisphosphonate use and subjective differences in atypical fracture identification. Regardless of these differences, both studies remain observational and whilst allowing for some elucidation of the relationship between atypical femur fractures and bisphosphonate use, they neither confirm nor refute causality.

### *Post hoc* analysis of bisphosphonate trials

A secondary analysis of three large, randomized bisphosphonate trials, namely the Fracture Intervention Trial (FIT), the FIT long-term (FLEX) trial and the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) Pivotal Fracture Trial (PFT), was performed [Black *et al.* 2010]. Among 14,195 women in these trials, subtrochanteric fractures were not significantly associated with bisphosphonate use and were very rare, occurring at a combined rate of 2.3 per 10,000

patient-years (i.e. 12 fracture events). However, atypical femur fractures were not identified on the basis of individual radiograph review and the observation period was not greater than 4.5 years in the majority of patients. The study was also underpowered for definitive conclusions.

### Population-based registry studies

An emerging number of population-based studies have sought to examine the incidence of subtrochanteric, diaphyseal, and more specifically, atypical femur fractures and their association with bisphosphonate use on a larger scale. A common feature of these studies is the use of hospital discharge registries and medication databases in the analysis of fracture incidence and bisphosphonate use within populations.

In 2009, two Danish registry-based cross-sectional studies were reported [Abrahamsen *et al.* 2009]. The first, a cross-sectional study of 11,944 patients over the age of 60 with femur fractures identified on the basis of International Classification of Diseases, 10th revision (ICD-10) coding, failed to demonstrate a greater frequency of subtrochanteric or diaphyseal femoral fractures *versus* typical hip fractures in patients receiving alendronate (incidence 7% in both groups). They also conducted a cohort study in which 5187 patients exposed to alendronate with a prior history of non-hip fracture were matched with 10,374 untreated patients also with a history of non-hip fracture. After adjustment for various factors, the hazard ratio for subtrochanteric/diaphyseal fracture amongst patients who had alendronate did not indicate a significantly greater risk of fracture than in those not receiving alendronate [hazard ratio (HR) 1.46, 95% CI 0.91−2.35, $p = 0.12$] and the distribution between hip and non-hip fractures was identical in the alendronate cohort and the untreated cohort (14% *versus* 13% respectively, $p = 0.7$). Interestingly, the incidence of hip fractures was significantly greater amongst the alendronate cohort (HR 1.45, 95% CI 1.21–1.74, $p < 0.001$), possibly indicating more severe underlying osteoporosis than in the untreated cohort.

Another group studied the site-specific epidemiology of femur fractures among people 50 years of age and older using two databases from the United States, the National Hospital Discharge Survey and a large medical claims database (MarketScan) [Nieves *et al.* 2010]. Over a 10-year period (1996–2006), overall hospital discharge rates for hip fractures amongst women decreased remarkably (from 600/100,000 to 400/100,000 person-years) whilst the discharge rates for subtrochanteric and femoral shaft fractures remained stable despite the introduction of bisphosphonate therapy during this time (each approximately 20/100,000 person-years). Similar trends were found amongst men. Using MarketScan data, the combined incidence of subtrochanteric and femoral shaft fractures was below 25/100,000 person-years, representing an upper limit of the incidence of atypical femur fractures (in the absence of radiograph review).

In contrast, a similar study combined 10-year data (1996–2006) from two Danish registries (the National Hospital Discharge Register and the Danish Medicines Agency) of 103,562 age- and gender-matched patients exposed to bisphosphonates with those of 310,683 patients who were not exposed to bisphosphonates [Vestergaard *et al.* 2011]. After adjustment for glucocorticoid use, hormone therapy, and prior fracture, a greater risk of subtrochanteric fractures was noted amongst patients who had alendronate but this was present predominantly prior to the commencement of alendronate therapy (OR 2.36, 95% CI 2.05−2.72, $p < 0.05$) and after 5 years of treatment, the risk returned to that of controls. Osteoporosis was therefore considered the predominant factor in the development of subtrochanteric fractures in this study.

Another study assessing health utilization databases from two US states identified 104 low-energy subtrochanteric or diaphyseal femur fractures among 33,815 patients [Kim *et al.* 2011]. These fractures were rare with an estimated incidence ratio of 1.46 per 1000 person-years amongst patients receiving bisphosphonates (95% CI 1.11−1.88) and did not occur more frequently amongst those receiving bisphosphonates *versus* those receiving raloxifene/calcitonin (HR 1.03, 95% CI 0.70−1.52). However, this comparison is limited as atypical fractures have also been reported amongst patients using tamoxifen and raloxifene [Giusti *et al.* 2010; Visekruna *et al.* 2008].

In a recent study from Canada that combined data from the Ontario Public Drug Program database and Canadian Institute for Health Information Discharge Abstract Database, a

cohort of 205,466 women aged 68 years or older who had commenced bisphosphonates from 2002 to 2008 was identified [Park-Wyllie *et al.* 2011]. Compared with bisphosphonate use lasting less than 100 days, treatment for 5 years or longer was associated with a greater risk of subtrochanteric or femoral shaft fracture (adjusted OR 2.74, 95% CI 1.25–6.02) and a reduced risk of osteoporotic hip fracture (adjusted OR 0.76, 95% CI 0.63–0.93). After matching each subtrochanteric/shaft fracture with five controls without fractures exposed to bisphosphonates, the investigators estimated that 64% of the subtrochanteric/shaft fractures among women taking bisphosphonates for longer than 5 years were attributable to extended bisphosphonate use (i.e. attributable fraction of the exposed women = 64%).

The main limitation of such population-based studies is the lack of individual radiograph review and the subsequent inability to differentiate atypical femur fractures from the larger group of subtrochanteric/shaft fractures [Girgis and Seibel, 2011b]. This is particularly relevant because atypical femur fractures account for a minority of subtrochanteric and shaft fractures [Girgis *et al.* 2010; Giusti *et al.* 2010].

A large cohort study from a Californian Health Management Organization analyzed radiographic data from 15,000 femur fractures occurring between 2007 and 2009 [Dell *et al.* 2010]. After radiograph analysis, 135 atypical femur fractures were identified. Using pharmacy data, it was observed that the majority of atypical fractures were associated with bisphosphonate use (97%) and longer duration of use. Although this study represents the largest single group of atypical femur fractures, the lack of a control group to account for the effect of confounders such as age on fracture risk is a limitation of this otherwise important contribution.

The most recent cohort study examining 1271 women in Sweden who sustained a femur fracture in 2008 identified 59 atypical fracture cases on the basis of individual radiograph review [Schilcher *et al.* 2011]. These were compared with 263 control patients who had sustained ordinary subtrochanteric or shaft fractures. Data on medications and coexisting conditions were obtained from national registries. A total of 78% of the case patients and 10% of the controls had received bisphosphonates, corresponding to a multivariable-adjusted odds ratio of 33.3 (95% CI 14.3–77.8). The duration of use influenced the risk (OR per 100 daily doses 1.3, 95% CI 1.1–1.6) and following drug withdrawal, the risk diminished by 70% per year since the last use (OR 0.28, 95% CI 0.21–0.38). However, this study provided reassurance in that the absolute risk of an atypical fracture in patients on bisphosphonates was five cases per 10,000 patient-years (95% CI 4–7).

## Proposed pathophysiology

The predominant hypothesis regarding the pathophysiology of atypical femur fracture is that severe suppression of bone turnover leads to the accumulation of bone microdamage and the development of an insufficiency fracture at the point of maximal, weight-bearing stress, namely at the subtrochanteric or diaphyseal femur [Ng *et al.* 2011; Goh *et al* 2007; Odvina *et al.* 2005].

Intriguing similarities have been described between atypical femur fractures and fractures classically seen in patients with adult-onset hypophosphatasia, a congenital disorder arising from mutations within the gene encoding for the tissue-nonspecific isoenzyme of alkaline phosphatase [Whyte, 2009]. In this condition, the extracellular accumulation of inorganic pyrophosphate within bone inhibits hydroxyapatite growth and dissolution, thereby blocking skeletal mineralization and, importantly, arresting bone turnover. Clinically, patients present in adulthood with chronic pseudo-fractures that affect the lateral aspect of the subtrochanteric femur, occur in association with cortical thickening and prodromal pain [see Figure 3(a)]. Similarly, particular forms of osteopetrosis, such as carbonic anhydrase II deficiency and pycnodystosis due to cathepsin K gene mutations, are characterized by osteoclast dysfunction and subsequent excess bone formation with femur cortical thickening and fractures that bear a striking resemblance to atypical fractures [see Figure 3(b)] [Clifton-Bligh, 2011; Yates *et al.* 2011]. Whilst these similarities support the hypothesis of bisphosphonate-related suppression of bone turnover in atypical femur fractures, this observation also raises other questions such as the role of genetics and the possibility of mineralization defects in the development of atypical femur fractures.

A closer examination of the atypical fracture pattern may lead to a better understanding of the biomechanical evolution of these fractures. The

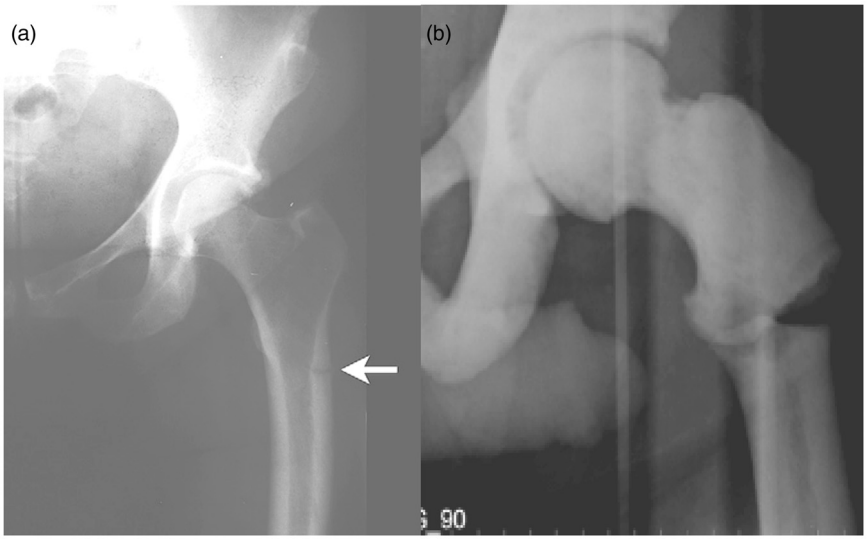


**Figure 3.** Genetic conditions which may mimic atypical fractures. (a) A 48-year-old woman with adult-onset hypophosphatasia developed subtrochanteric pseudo-fractures that presented with thigh pain [Whyte, 2009]. (Reproduced with permission from John Wiley and Sons, license date 27 April 2011, license number 2657010333028.) (b) A 56-year-old man with known autosomal-dominant osteopetrosis sustained a left subtrochanteric fracture of the hip after experiencing pain and spontaneously collapsing to the floor while walking [Birmingham and McHale, 2008]. The transverse nature of these fractures, the associated cortical thickening and the location of the fracture within the subtrochanteric femur in these genetic conditions all bear similarities to atypical fractures. These resemblances suggest a genetic component and may help explain the development of atypical fractures. (Reproduced with permission from Springer, license date 27 April 2011, license number 2657011247210).

precursor lesion appears to be an incomplete stress fracture in the lateral cortex of the subtrochanteric femur that clinically corresponds with prodromal thigh pain (see Figure 2) [Das De *et al.* 2010]. Following detailed examination of 44 atypical femur fractures, it was recently postulated that this lesion represents a focal point where maximal tensile stress couples with the accumulation of microdamage sufficiently severe to result in the development of an insufficiency fracture [Koh *et al.* 2011]. The accompanying cortical thickening may represent a localized stress reaction and could potentially contribute to the spontaneous extension of the fracture through the width of the femur to result in a complete transverse fracture. Although this represents one interpretation of objective radiographic features, further characterization of these features by advanced imaging modalities is an essential component in understanding the sequential evolution of these fractures.

If bisphosphonates do result in severe suppression of bone turnover, then the existing evidence base is limited by the lack of a standard definition for this proposed condition and small studies that do not uniformly support this possibility. In one study, bone histomorphometry reported severely reduced bone remodeling in trans-iliac crest biopsies of five patients with atypical femur [Odvina *et al.* 2010]. A recent abstract reported reduced bone matrix heterogeneity at the site of a number of bisphosphonate-related atypical femur fractures, possibly leading to more brittle bone [Boskey *et al.* 2010]. In contrast, however, a case report described an imbalance in bone turnover with increased bone resorption and reduced bone formation at the iliac crest and femoral cortex in a patient with bilateral atypical fractures [Somford *et al.* 2009]. Larger studies in patients with atypical fractures examining clear histomorphometric parameters to define severe suppression of bone turnover and standard biopsy procedures are needed to address this question.

The general effects of long-term bisphosphonate therapy on bone turnover have been studied extensively in animal models and also in humans. Bone biopsies obtained from patients

who had received alendronate for 5 years followed by a further 5 years of alendronate or placebo demonstrated new bone formation and the absence of qualitative defects in skeletal histology amongst those on long-term therapy [Recker *et al.* 2004**]**. In addition, bone biopsies obtained after 5 years of risedronate or placebo amongst 74 participants of an extension arm of a randomized trial showed the presence of double tetracycline labeling, similar reduction in bone-forming measures but the absence of qualitative defects amongst those on risedronate compared with placebo [Ste-Marie *et al.* 2004]. Studies assessing bone turnover markers in patients treated with bisphosphonates have shown sustained but not progressive decreases in these markers, even with up to 10 years of bisphosphonate therapy [Black *et al.* 2006; Harris *et al.* 1999].

Findings from animal studies have shed some light on the issue but are difficult to extrapolate to the human situation. In female beagle dogs receiving risedronate at doses 5–20 times the clinical human dose, examination of the femoral neck did not reveal an increase in micro-crack frequency or morphology [Forwood *et al.* 1995]. However, a similar study using very high doses of alendronate or risedronate *versus* placebo in female beagle dogs for 1 year demonstrated increased cortical microdamage, suppression of cortical remodeling and reduced bone toughness in non-weight-bearing bone, namely the ninth rib [Mashiba *et al.* 2000]. Another study in which equivalent clinical doses of risedronate or alendronate was given for 1 year to the same animal model demonstrated dose-dependent reduction in bone turnover and increase in micro-crack surface density, but this was offset by the effect of increased bone volume in the preservation of the mechanical properties of bone [Allen *et al.* 2006]. Relevant to the question at hand, a study examining fracture toughness of the mid-shaft femur in aged osteopaenic rats treated for 4 months with high doses of ibandronate or risedronate did not demonstrate significant differences between these rats and those receiving placebo [Shahnazari *et al.* 2010].

Therefore, while the reduction of bone turnover is the mechanism by which bisphosphonates affect bone strength and fracture risk, severe suppression as characterized by the accumulation of microdamage or changes to the structural integrity of bone that predispose to fracture have not been found in association with long-term bisphosphonate therapy in humans. The possibility remains that a subset of patients may be particularly susceptible to the effects of bisphosphonate therapy, perhaps relating to ethnicity, genetics, underlying osteoclast dysfunction or morphological features that affect femur loading.

## Implications for clinical practice

Following detailed analysis of the emerging evidence base on atypical femur fractures, the implications this issue poses to the continued use of bisphosphonates in the management of osteoporosis should be considered. Where do we, as clinicians, stand on the issue of atypical femur fractures and their relation to bisphosphonate use?

Firstly, on balance, the cumulative body of evidence supports an association between long-term bisphosphonate therapy and the development of atypical femur fractures. Although subject to publication bias, this association rests on the basis of numerous case series, retrospective analyses and a large database study which all involve the direct and individual assessment of radiographs in the identification of atypical fractures. However, as the nature of this association is unclear and causality has not been established, the potential for risk amongst bisphosphonate users to suffer an atypical femur fracture clearly pales in comparison to the large body of hard evidence supporting a significant reduction in the overall risk of fracture in men and women with osteoporosis.

Secondly, by all accounts, atypical femur fractures are remarkably rare both in absolute terms and relative to the incidence of osteoporotic hip fractures [Park-Wyllie *et al.* 2011; Abrahamsen *et al.* 2009]. Even on the assumption of a causal link, it is very likely that for each atypical femur fracture to potentially result from prolonged bisphosphonate therapy, many more osteoporotic fractures would be prevented by the use of such drugs. A sense of perspective on the issue should guide practice.

However, on the basis of circumstantial evidence, the possibility of insufficiency fractures should be considered amongst patients who report unexplained thigh or groin pain in the context of prolonged bisphosphonate therapy, concomitant glucocorticoid therapy or a history of rheumatoid arthritis, diabetes mellitus or proton-pump

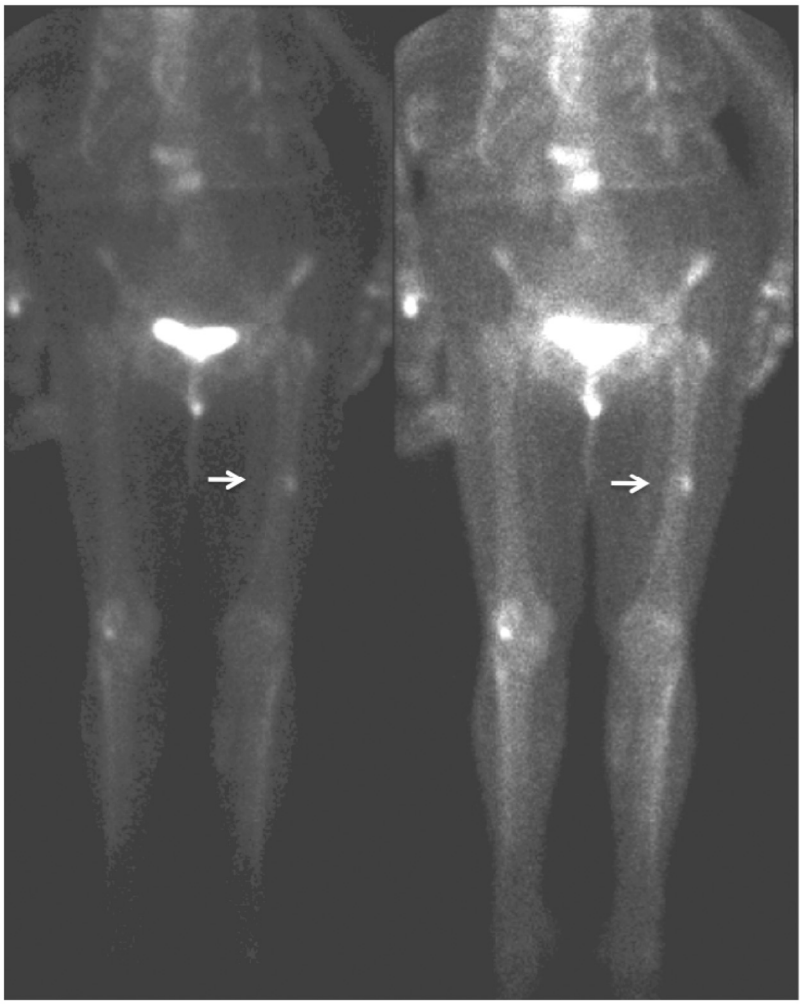

**Figure 4.** Atypical fracture on technetium-labeled whole-body bone scintigraphy. A 65-year-old woman who had been taking alendronate for 7 years reported a 6-month history of left thigh pain. A whole-body technetium-labeled bone scan demonstrated a focal area of intense uptake in the femoral shaft on both early and delayed images (arrows). This represented a cortical stress lesion for which she later underwent intramedullary nail fixation.

inhibitor use. Prompt evaluation of such patients with imaging of the affected femur to assess for cortical stress fractures with x-ray (see Figure 2) or bone scan (see Figure 4) and the measurement of markers of bone turnover in such individuals is often helpful. In the event that such a precursor lesion is found, the decision to cease bisphosphonate therapy, to commence teriparatide or consider prophylactic femoral rod insertion to prevent the development of a complete fracture may be undertaken, but is based on purely empirical grounds.

A discussion on the sustained efficacy and appropriate duration of bisphosphonate therapy in patients with osteoporosis is a complex area and beyond the scope of this review. For an in-depth discussion on this issue, we refer readers to a recent review [Seeman, 2009]. It suffices to say that in the absence of definitive evidence, a reasonable approach should include case-by-case analysis of the patient's on-drug fracture history, the presence of relevant risk factors for osteoporosis and objective trends in bone density and turnover in the decision for a drug holiday.

## Conclusion

Despite our better understanding of the phenomenon of atypical femur fractures over the past 6 years, a cloud of uncertainty continues to intrigue investigators in this field. Observations of the

atypical fracture pattern indicate a profoundly pathological condition with dire biomechanical consequences. However, the underlying cause and subsequent mechanisms resulting in the development of these fractures remain elusive. Further research is needed to address the precise role of bisphosphonate therapy, genetic factors and other potential predisposing factors in the development of these fractures. This may include long-term, prospective observational studies examining the development of subtrochanteric fractures, specific data on bone biopsies and fracture healing in patients treated with bisphosphonates, and further analyses of clinical, biomechanical and genetic factors pertinent to the development of atypical femur fractures. Whether this phenomenon represents "a new breed" of femoral fracture, the body of evidence supports the emergence, or at least recognition, of atypical fractures since 2005. However, fractures with striking similarities have been long seen in sufferers of rare genetic conditions, suggesting an underlying genetic role in the development of atypical fractures.

Until further research eventuates, it is also unclear whether bisphosphonate therapy is a prime culprit, one of several compounding causes, or merely an innocent bystander indicative of severe osteoporosis, in the development of atypical femur fractures. Whilst physicians should remain vigilant of the possibility of cortical insufficiency and atypical femur fractures in patients on long-term bisphosphonate therapy and accordingly investigate such patients who report unexplained thigh or groin pain, the established efficacy of bisphosphonates in the prevention of common fragility fractures in patients with osteoporosis should be borne in mind.

## Funding

Markus Seibel has received funding from Merck Sharp and Dohme, Novartis, Amgen and Sanofi-Aventis.

## Conflicts of interest statement

Markus Seibel is a member of the advisory boards for Merck Sharp and Dohme, Novartis, Amgen and Sanofi-Aventis.

## References

Abrahamsen, B., Eiken, P. and Eastell, R. (2009) Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: A register-based national cohort study. *J Bone Miner Res* 24: 1095–1102.

Allen, M.R., Iwata, K., Phipps, R. and Burr, D.B. (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: 872–879.

Birmingham, P. and McHale, K.A. (2008) Treatment of subtrochanteric and ipsilateral femoral neck fractures in an adult with osteopetrosis. *Clin Orthop Relat Res* 466: 2002–2008.

Black, D.M., Schwartz, A.V., Ensrud, K.E., Cauley, J.A., Levis, S., Quandt, S.A. *et al.* (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: 2927–2938.

Black, D.M., Kelly, M., Genant, H., Palermo, L., Eastell, R., Bucci-Rechtweg, C. *et al.* (2010) Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med* 362: 1761–1771.

Boskey, A., Lane, J.M., Rebolledo, B., Gladnick, B., Meredith, D. and Donnelly, E. (2010) Reduced matrix heterogeneity with bisphosphonate treatment in postmenopausal women with proximal femoral fractures. American Society of Bone and Mineral Research Meeting October 15–19, 2010, Toronto, abstract 1140.

Capeci, C.M. and Tejwani, N.C. (2009) Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg Am* 91: 2556–2561.

Clifton-Bligh, R. (2011) Lecture on osteopetrosis. Endocrine seminar. Royal North Shore Hospital, Sydney, Australia, March 2011.

Cranney, A., Tugwell, P., Adachi, J., Weaver, B., Zytaruk, N., Papaioannou, A. *et al.* (2002a) Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev* 23: 517–523.

Cranney, A., Wells, G., Willan, A., Griffith, L., Zytaruk, N., Robinson, V. *et al.* (2002b) Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 23: 508–516.

Das De, S., Setiobudi, T., Shen, L. and Das De, S. (2010) A rational approach to management of alendronate-related subtrochanteric fractures. *J Bone Joint Surg Br* 92: 679–686.

Dell, R., Greene, D., Ott, S., Silverman, S., Eisemon, E., Funahashi, T. and Adams, A.A. (2010) Retrospective analysis of atypical femur fractures in a large California HMO from the years 2007 to 2009. American Society of Bone and Mineral Research Meeting October 15–19, 2010, Toronto, abstract 1201.

Dunstan, C.R., Felsenberg, D. and Seibel, M.J. (2007) Therapy insight: The risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. *Nat Clin Pract Oncol* 4: 42–55.

Forwood, M.R., Burr, D.B., Takano, Y., Eastman, D.F., Smith, P.N. and Schwardt, J.D. (1995) Risedronate treatment does not increase microdamage in the canine femoral neck. *Bone* 16: 643–650.

Girgis, C.M., Sher, D. and Seibel, M.J. (2010) Atypical femoral fractures and bisphosphonate use. *N Engl J Med* 362: 1848–1849.

Girgis, C.M. and Seibel, M.J. (2011a) Population and treatment-based incidence estimates of atypical fractures. *Med J Aust* 194: 666.

Girgis, C.M. and Seibel, M.J. (2011b) Bisphosphonate use and femoral fractures in older women. *JAMA* 305: 2068.

Giusti, A., Hamdy, N.A.T., Dekkers, O.M., Ramautar, S.R., Dijkstra, S. and Papapoulos, S.E. (2011) Atypical fractures and bisphosphonate therapy: A cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. *Bone* 48: 966–971.

Giusti, A., Hamdy, N.A.T. and Papapoulos, S.E. (2010) Atypical fractures of the femur and bisphosphonate therapy: A systematic review of case/case series studies. *Bone* 47: 169–180.

Goh, S.K., Yang, K.Y., Koh, J.S.B., Wong, M.K., Chua, S.Y., Chua, D.T.C. and Howe, T.S. (2007) Subtrochanteric insufficiency fractures in patients on alendronate therapy: A Caution. *J Bone Joint Surg Br* 3: 349–353.

Harris, S.T., Watts, N.B., Genant, H.K., McKeever, C.D., Hangartner, T., Keller, M. *et al.* (1999) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: A randomized controlled trial. Vertebral Efficacy With Risedronate Therapy Study Group. *JAMA* 282: 1344–1352.

Ing-Lorenzini, K., Desmeules, J., Plachta, O., Suva, D., Dayer, P. and Peter, R. (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.

Isaacs, J.D., Shidiak, L., Harris, I.A. and Szomor, Z.L. (2010) Femoral insufficiency fractures associated with prolonged bisphosphonate therapy. *Clin Orthop Relat Res* 468: 3384–3392.

Kim, S.Y., Schneeweiss, S., Katz, J.N., Levin, R. and Solomon, D.H. (2011) Oral bisphosphonates and risk of subtrochanteric or diaphyseal femur fractures in a population-based cohort. *J Bone Miner Research* 26: 993–1001.

Koh, J.S.B., Goh, S.K., Png, M.A., Ng, A.C.M. and Howe, T.S. (2011) Distribution of atypical fractures and cortical stress lesions in the femur: Implications on pathophysiology. *Singapore Med J* 52: 77–79.

Kwek, E.B., Goh, S.K., Koh, J.S., Png, M.A. and Howe, T.S. (2008) An emerging pattern of subtrochanteric stress fractures: A long-term complication of alendronate therapy?. *Injury* 39: 224–231.

Lee, P., van der Wall, H. and Seibel, M.J. (2007) Looking beyond low bone mineral density: Multiple insufficiency fractures in a woman with postmenopausal osteoporosis on alendronate therapy. *J Endocrinol Invest* 30: 590–597.

Lenart, B.A., Lorich, D.G. and Lane, J.M. (2008) Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med* 358: 1304–1306.

Lenart, B.A., Neviaser, A.S., Lyman, S., Chang, C.C., Edobor-Osula, F., Steele, B. *et al.* (2009) Association of low-energy femoral fractures with prolonged bisphosphonate use: A case control study. *Osteoporos Int* 20: 1353–1362.

Mashiba, T., Hirano, T., Turner, C.H., Forwood, M., Johnston, C.C. and Burr, D.B. (2000) Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res* 15: 613–620.

Neviaser, A.S., Lane, J.M., Lenart, B.A., Edobor-Osula, F. and Lorich, D.G. (2008) Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma* 22: 346–350.

Ng, Y.H., Gino, P.D., Lingaraj, K. and Das De, S. (2011) Femoral shaft fractures in the elderly: Role of prior bisphosphonate therapy. *Injury* 42: 702–706.

Nieves, J.W., Bilezikian, J.P., Lane, J.M., Einhorn, T.A., Wang, Y., Steinbuch, M. *et al.* (2010) Fragility fractures of the hip and femur: incidence and patient characteristics. *Osteoporosis Int* 21: 399–408.

Odvina, C.V., Levy, S., Rao, S., Zerwekh, J.E. and Rao, D.S. (2010) Unusual mid-shaft fractures during long-term bisphosphonate therapy. *Clinical Endocrinology* 72: 161–168.

Odvina, C.V., Zerwekh, J.E., Rao, D.S., Maalouf, N., Gottschalk, F.A. and Pak, C.Y. (2005) Severely suppressed bone turnover: A potential complication of alendronate therapy. *J Clin Endocrinol Metab* 90: 1294–1301.

Park-Wyllie LY, Mamdani MM, Juurlink DN, Hawker GA, Gunraj N, Austin PC. *et al.* (2011) Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA* 305(8): 783–789.

Recker, R., Ensrud, K., Diem, S., Cheng, E., Bare, S., Masarachia, P. *et al.* (2004) Normal bone histomorphometry and 3D microarchitecture after 10 years alendronate treatment of postmenopausal women. *J Bone Miner Res* 19(Suppl 1): S45.

Rizzoli, R., Akesson, K., Bouxsein, M., Kanis, J.A., Napoli, N., Papapoulos, S. *et al.* (2011) 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. *Osteoporosis Int* 22: 373–390.

Schilcher, J., Michaëlsson, K. and Aspenber, P. (2011) Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med* 364: 1728–1737.

Seeman, E. (2009) To stop or not to stop, that is the question. *Osteoporos Int* 20: 187–195.

Shahnazari, M., Yao, W., Dai, W., Wang, B., Ionova-Martin, S.S., Ritchie, R.O. *et al.* (2010) Higher doses of bisphosphonates further improve bone mass, architecture, and strength but not the tissue material properties in aged rats. *Bone* 46: 1267–1274.

Shane, E., Burr, D., Ebeling, P.R., Abrahamsen, B., Adler, R.A., Brown, T.D. *et al.* (2010) Atypical subtrochanteric and diaphyseal femoral fractures: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 25: 2267–2294.

Siris, E.S., Pasquale, M.K., Wang, Y. and Watts, N.B. (2011) Estimating bisphosphonate use and fracture reduction among US women aged 45 years and older, 2001–2008. *J Bone Miner Res* 26: 3–11.

Somford, M.P., Draijer, F., Thomassen, B.J., Chavassieux, P.M., Boivin, G. and Papapoulos, S.E. (2009) Bilateral fractures of the femoral diaphysis in a patient with rheumatoid arthritis on long term treatment with alendronate. *J Bone Miner Res* 24: 1736–1740.

Ste-Marie, L.G., Sod, E., Johnson, T. and Chines, A. (2004) Five years of treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis. *Calcif Tissue Int* 75: 469–476.

Vestergaard, P., Schwartz, F., Rejnmark, L. and Mosekilde, L. (2011) Risk of femoral shaft and subtrochanteric fractures among users of bisphosphonates and raloxifene. *Osteoporosis Int* 22: 993–1001.

Visekruna, M., Wilson, D. and McKiernan, F.E. (2008) Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab* 93: 2948–2952.

Whyte, M.P. (2009) Atypical femoral fractures, bisphosphonates, and adult hypophosphatasia. *J Bone Miner Res* 24: 1132–1134.

Yates, C.J., Bartlett, M.J. and Ebeling, P.R. (2011) An atypical subtrochanteric femoral fracture from pycnodysostosis: A lesson from nature. *J Bone Miner Research* 26: 1377–1379.