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Commentary

Guilt by association? Examining the role of bisphosphonate therapy in the development of atypical femur fractures☆

> "Circumstantial evidence is a very tricky thing! It may seem to point very straight to one thing, but if you shift your own point of view a little, you may find it pointing in an equally uncompromising manner to something entirely different."
> *Sherlock Holmes, The Boscombe Valley Mystery (Sir Arthur Conan Doyle, 1859–1930)*

A highly prevalent condition, osteoporosis imposes substantial health and economic costs due to the dire effects of fragility fractures on mortality and morbidity [1]. There is no doubt, however, that since the introduction of bisphosphonate therapy, a substantial number of osteoporotic fractures have been prevented [2].

Numerous clinical trials have established that bisphosphonates effectively reduce bone turnover, increase bone mineral density and reduce vertebral and non-vertebral fracture risk [3–6]. Bisphosphonates are generally well-tolerated and are considered to have an excellent safety profile even at higher doses [7]. Since 2005, however, there have been increasing concerns regarding the potential risk of what is now known as "atypical femur fractures". These fractures, occurring at times in association with long-term bisphosphonate therapy, are characterized by features specific from 'typical' osteoporotic femur fractures including prodromal thigh pain, circumferential cortical thickening and the development of cortical stress lesions that may precede a complete transverse or oblique fracture of the subtrochanteric femur [8]. Whilst observational and retrospective studies have linked these atypical femur fractures with the use of oral bisphosphonates [9–11], the association remains circumstantial and so far has not been confirmed by large-scale epidemiologic studies [12,14]. Moreover, questions remain regarding the causation and biomechanical evolution of these fractures and the validity of atypical fractures as an entity separate from other low-energy or osteoporotic fractures.

A recent systematic literature review analyzed data from a total of 141 atypical femur fractures that had occurred in female bisphosphonate users [9]. In this review, alendronate was the bisphosphonate most commonly used, the mean duration of therapy was 71.5 ± 40 months, the majority of patients reported prodromal thigh pain, and a significant number of subjects were receiving concomitant glucocorticoids or proton pump inhibitors at the time of the fracture. Interestingly, patients treated with bisphosphonates for less than 5 years were more likely to be of Asian origin or to have a pre-treatment history of femoral shaft fracture as compared to those treated for more than 5 years. Whilst this report identified relevant demographic features and potential risk factors for atypical femur fractures, significant questions remain due to the lack of a control group, missing data, potential observer bias in the absence of a blinded case evaluation and the absence of a standard definition of atypical fractures.

More recently, a 5-year retrospective study of non-hip femur fractures found strong evidence in support of an association between oral bisphosphonate use and the occurrence of atypical fractures [11]. In this study, 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. However, the association reported in this and similar retrospective studies [15,16] may have been confounded by selection bias as patients with atypical fractures are expected to have sufficiently severe osteoporosis as to require bisphosphonate therapy.

Attempts to elucidate the precise incidence of atypical fractures or to confirm their association with bisphosphonate therapy on an epidemiological or observational scale have proved elusive. In 2009, a registry-based cross-sectional study of 11944 patients failed to demonstrate a greater frequency of subtrochanteric femur fractures in patients receiving alendronate [12]. In 2010, this same group demonstrated a significantly higher risk of hip, subtrochanteric and diaphyseal fractures amongst alendronate users compared to matched controls but this increased risk was not dose or duration-dependent suggesting underlying osteoporosis to be the cause [13]. A secondary analysis of three large randomized bisphosphonate trials including 14195 patients concluded that subtrochanteric femoral fractures were very rare and statistically not associated with bisphosphonate use [14]. However, apart from being underpowered these studies did not assess individual fracture radiographs, a *conditio sine qua non* for the identification of the atypical fracture pattern.

Recent database studies examining incidence trends in site-specific femur fractures have yielded conflicting results. A study using the National Hospital Discharge Survey and a large medical claims database demonstrated a decline from 1996 to 2006 in the rates of hip fracture, while the rate of subtrochanteric and diaphyseal femur fractures remained stable in spite of the introduction of bisphosphonates during this period [17]. Data from another large database demonstrated a trend towards more frequent subtrochanteric and femur shaft fractures with increasing duration of bisphosphonate use [18]. A third study using data from the Danish Medicines Agency and National Hospital Discharge Register between 1996 and 2006 demonstrated an increased risk of subtrochanteric fracture in patients receiving bisphosphonates but this greater risk was also present prior to the commencement of therapy [19]. This suggested that atypical fractures were due to severe osteoporosis for which bisphosphonates were subsequently indicated. However, two of these studies were limited by the lack of radiograph assessment [17,19] and the third by the lack of a control group to account for the effect of confounders such as age on fracture risk [18].

The evidence-base remains split between a large number of case series and retrospective studies demonstrating an association between atypical femur fractures and bisphosphonate use, and large-scale epidemiologic studies which do not seem to confirm this association. Both approaches have their limitations, and hence the issue remains open for discussion and research.

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In this issue of *Bone*, Giusti et al. present the results of an interesting case–control study in which 63 patients with low-energy subtrochanteric or femoral shaft fractures were age and sex-matched with 126 patients with hip fractures [20]. Apart from the higher prevalence of diabetes amongst patients with subtrochanteric or shaft fractures, the frequency and duration of bisphosphonate use was not significantly different between the two groups. Of note, the investigators identified 10 atypical fractures amongst 906 femur fractures seen at the centre over a period of 11 years. These atypical fractures were more frequently associated with bisphosphonate use than typical subtrochanteric or shaft fractures but 50% of the atypical fractures occurred in patients never exposed to bisphosphonate therapy (5/10). Also, cortical thickening, a widely reported feature of atypical femur fractures was no more prevalent amongst bisphosphonate users as compared to patients who had never been treated with such agents. The authors conclude that atypical fractures occur at a low frequency, were more frequent in bisphosphonate users compared to those with typical subtrochanteric/shaft fractures but also occurred at the same rate in patients never treated with bisphosphonates.

The study has a number of important strengths. The individual adjudication of all 906 femur fractures allowed the investigators to assess atypical fractures as a subset distinct from other subtrochanteric or shaft fractures. Also, this approach avoids the reported 2.3% error rate of the ICD coding system [20]. The presence of a well-defined control group allowed for a differential assessment of patients with common osteoporotic hip fractures and those with less common forms of femur fracture. However, the small number of atypical fractures within the study is a major limitation and impedes further analysis or definitive comparison with other fracture types.

What are the implications of this study for clinical practice? Firstly, the findings provide reassurance that atypical femur fractures are indeed rare events, that bisphosphonate use is not uniform amongst atypical fracture cases and does not appear to increase the risk of subtrochanteric or shaft fractures *per se*, as compared to hip fractures. Secondly, an important question implied by this study is whether there are other unidentified factors that may potentially contribute to atypical femur fractures and whether bisphosphonate use is simply an 'innocent bystander', perhaps reflective of more severe osteoporosis, present in only a subset of cases.

The findings of this study stand in stark contrast to those of a similar case–control study which compared 41 patients with subtrochanteric or femur shaft fractures to 82 patients with intertrochanteric or hip fractures matched for age, sex and body mass index [21]. A significantly greater proportion of long-term bisphosphonate use was found amongst those with subtrochanteric or femur shaft fractures and the atypical fracture pattern was highly associated with bisphosphonate use. In addition to the differences in the study design described by Giusti et al. [20], the contradictory findings of these two case–control studies may also 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.

Is there a pathophysiological basis for linking bisphosphonate use with the development of atypical fractures? In 2005, a case series of 10 insufficiency fractures that occurred in patients receiving long-term bisphosphonate treatment reported 'severely' reduced bone remodeling in transiliac crest biopsies of most patients [22]. However, significantly reduced bone turnover is expected in patients taking bisphosphonates, and histomorphometric analyses of bone taken from the iliac crest may not be indicative of the processes occurring at load-bearing sites such as the subtrochanteric femur. A paper presented at the last ASBMR meeting reported reduced bone matrix heterogeneity at the site of bisphosphonate-related atypical femur fractures [23] but these findings have not been uniform as other studies have demonstrated markedly increased bone resorption in association with atypical femur fractures [9,24].

Data from randomized clinical trials do not provide evidence for long-term over-suppression of bone turnover during bisphosphonate therapy. Thus, bone biopsies taken from patients who had received 10 years of alendronate and 5 years of risedronate therapy demonstrated intact double tetracycline labeling, indicative of ongoing bone formation, and there were no qualitative defects in skeletal histology as compared to 5 years of alendronate therapy or placebo, respectively [25,26]. Moreover, studies assessing bone turnover markers in bisphosphonate-treated patients reveal a sustained but not progressive decrease in bone turnover even with up to 10 years of bisphosphonate therapy [27,28].

Findings from animal studies have shed some light on the issue but are difficult to extrapolate to the human situation. Studies in female beagle dogs receiving risedronate or alendronate in excess of the equivalent human clinical doses demonstrated increased cortical microdamage and suppression of cortical remodeling at non-weight bearing sites [29] but no increase in microcrack frequency or morphologic changes at the femoral neck [30]. When doses of risedronate or alendronate equivalent to the clinical dosing regimen were given for 1 year in the same animal model, a dose-dependent reduction in bone turnover and increase in micro-crack surface density was offset by the effect of increased bone volume in the preservation of the mechanical properties of bone [31]. Therefore, while suppression of bone turnover is one of the mechanisms to which bisphosphonates owe their efficacy, severe suppression as characterized by the accumulation of microdamage or changes to the structural integrity of bone which predispose to fracture has not consistently been found in association with long-term bisphosphonate therapy. The possibility remains, however, that a subset of patients may be particularly susceptible to the effects of bisphosphonate therapy, perhaps relating to ethnicity, underlying osteoclast dysfunction or morphological features affecting femur loading.

In conclusion, the role of bisphosphonates in the development of atypical femur fractures has proven a difficult and elusive area of research. The low frequency and the requirement for individual radiograph assessment to identify these fractures, the lack of a standard definition for 'fracture atypia' and the difficulty in distinguishing the role of osteoporosis from other factors in the development of atypical fractures have been particular challenges. Bearing this in mind, the evidence remains split between circumstantial observations of an association and epidemiologic data which do not validate such an association. In recognizing these challenges, both the American Society of Bone and Mineral Research (ASBMR) and a working group established by the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF) have published separate statements seeking to summarize the existing data, define atypical fractures and guide further research [32,33]. As stated by these societies and many other authors, further research should include long-term, prospective observational studies examining the development of subtrochanteric fractures, specific data on bone biopsies and fracture healing in bisphosphonate-treated patients, and further analyses of clinical, biomechanical and genetic factors pertinent to the development of atypical fracture. We also believe that examining the significance of cortical thickening, an unexplained feature of atypical fractures, may provide valuable insights into their pathomechanism. Whilst cortical thickening appears to predate the commencement of bisphosphonate therapy in patients with atypical fractures and is more prevalent in younger patients [20], investigators are at odds regarding the effect of bisphosphonates on progressive cortical thickening in patients with atypical fractures [20,21]. Whether cortical thickening represents a pre-existing defect in bone metabolism susceptible to the effect of bisphosphonates or rather a localized stress reaction in response to the accumulation of cortical micro-damage and stress fracture remains speculative.

Until further research eventuates, it is 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 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.

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Christian M. Girgis
Garvan Institute of Medical Research,
The University of New South Wales, Sydney, Australia
The University of Sydney, Sydney, Australia
E-mail address: cgirgis@usyd.edu.au.

Markus J. Seibel
Bone Research Program, ANZAC Research Institute,
The University of Sydney, Sydney, Australia
Corresponding author at: Bone Research Program, ANZAC Research Institute, 1A Hospital Road, Concord, Sydney, NSW 2139, Australia.
E-mail address: markus.seibel@sydney.edu.au.

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