Editorial

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Bisphosphonates and atypical femur fractures

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Bisphosphonates, which have been on the market for roughly a decade, have raised safety concerns in the past. Several case series and multiple individual case reports suggest that some subtrochanteric and femoral shaft fractures may occur in patients who have been treated with long-term bisphosphonates. Several unique clinical and radiographic features are emerging. Recent media spotlight in the United States (US), implying that long-term use of alendronate could cause spontaneous femur fractures in some women, has reignited the debate about the safety of bisphosphonates. *The question posed: is the risk of bisphosphonate-associated fractures so great that treatment should be stopped?*

Postmenopausal women with osteoporosis are commonly treated with the bisphosphonate class of medications, one of the most frequently prescribed medications in the US. While alendronate therapy has been shown to decrease the risk of vertebral and femoral neck fractures in postmenopausal osteoporotic patients, recent reports have associated long-term alendronate therapy with low-energy subtrochanteric and diaphyseal femoral fractures in a number of patients. In the past four years reports have been published implying that long-term bisphosphonate therapy could be linked to atraumatic femoral diaphyseal fractures.[1, 2] According to two studies reported recently at the American Association of Orthopedic Surgeons 2010 Annual Meeting, an unusual type of bone fracture has been reported in women who have taken bisphosphonates for osteopenia and osteoporosis for more than four years.[3, 4] The first report was published in 2005. Odvina et al[5] reported on nine patients who sustained atypical fractures, including some with delayed healing, while receiving alendronate therapy. These authors raised the concern that long-term bisphosphonate therapy may lead to over-suppression of bone remodelling, an impaired ability to repair skeletal microfractures, and increased skeletal fragility. There have been other reports of "peculiar" fractures - i.e. low-energy femur fractures that are typically transverse or slightly oblique, diaphyseal, or subtrochanteric, with thickened cortices and a unicortical beak - in patients who have been on long-term bisphosphonate treatment.[1-4, 6]

In a small prospective study, Lane et al[3] obtained bone biopsies from the lateral femurs of 21 postmenopausal women with femoral fractures. Twelve of the women had been on bisphosphonate therapy for an average duration of 8.5 years, and nine had no history of bisphosphonate use. They found that the heterogeneities of the mineral/matrix ratio were significantly reduced in the bisphosphonate group by 28%, and the crystallinity of the bone was significantly reduced by 33% ($p < 0.05$). The authors concluded that this suggested suppression of bone turnover, resulting in a loss of heterogeneity of the tissue properties, which may be a contributing factor to the risk of atypical fractures that we are starting to see. It is believed that long-term alendronate administration may inhibit normal repair of microdamage arising from severe suppression of bone turnover (SSBT), which, in turn, results in accumulation of microdamage. This process would lead to brittle bone and the occurrence of unexpected stress fractures, characteristically at the subtrochanter of femur. The typical presentation of these fractures consist of prodromal pain in the affected leg and/or a discrete cortical thickening on the lateral side of the femur in conventional radiological examination or the presentation with a spontaneous transverse subtrochanteric femur with typical features. The morbidity of atypical femoral fractures, particularly when bilateral, is high. Surgical intervention is generally required and healing may not be achieved for several years. Despite the lack of conclusive evidence of a causal relationship with bisphosphonate therapy, the current consensus is that treatment should be discontinued in patients who develop these fractures. In view of the high frequency of bilateral involvement, imaging of the contralateral femoral shaft with X-rays, MRI, or an isotope bone scan should be performed. MRI and bone scanning havegreater sensitivity than radiography for an incipient stressfracture. If lateral cortical thickening and/or an incipient stress fracture is seen, prophylactic surgical fixation should be considered. Suppressed bone formation in these patients provides a possible rationale for the use of anabolic skeletal agents, such as parathyroid hormone peptides, but at the present time the efficacy of this approach remains to be established. Parathyroid hormone not only has activated bone-formation markersin trials in humans but has also enhanced the healing of fracturesin studies in animals.

The question of whether these fractures are causally linked to bisphosphonate therapy is widely debated but as yet unresolved. Consequences of long-term suppression of bone

turnover include increased mineralization of bone, alterations in the composition of its mineral/matrix composite and increased micro damage, all of which may reduce bone strength. Whilst these lend biological plausibility to a causal association, however, they do not constitute direct evidence. The bilateral fractures seen in many patients corroborate the suspicion that patients with bisphosphonate-associated stress fractures carry some other risk factor in addition to taking the drug. Microfractures,inadequate mineralization, and outdated collagen are some of the candidate causes. However, until further studies can provide definitive evidenceof bisphosphonate-associated fractures, it is premature to attributeatypical fractures to over-suppression of bone turnover alone,while disregarding secondary and patient-related factors. Many experts believe that prolonged suppression of bone remodelling with alendronate may be associated with a new form of insufficiency fracture of the femur. Studies have not shown if the entire class of medications produce a similar result, but patients who have been treated with any bisphosphonate for an extended period of time should be considered at risk.

A wealth of information from well-designed clinical trials clearly shows that, as a class, bisphosphonates are highly effective at limiting the loss of bone mass, deterioration of bone micro architecture, and increased fracture risk that occur with aging. The benefit/risk ratio of bisphosphonate therapy in patients at high risk of fracture remains overwhelmingly positive because of the very low incidence of atypical femoral fractures. Current estimates suggest that alendronate prevents 200 clinical fractures if 4000 women are treated over three years and will cause one femur fracture over the same course of time.[7] A study by Schilcher et al[8] found that the incidence density of a stress fracture for a patient on bisphosphonate was 1/1000 per year (95% CI: 0.3-2), which is acceptable considering that bisphosphonate treatment is likely to reduce the incidence density of any fracture by 15/1000.[9] Nevertheless, limitation of treatment duration to five years in the first instance, with evaluation of the need to continue therapy thereafter, may be appropriate in clinical practice. The Fracture Intervention Trial Long-term Extension (FLEX), in which postmenopausal women who had received alendronate therapy for five years were randomised to continue receiving alendronate for five additional years or switched to placebo, provided clinical evidence that the effect of bisphosphonate therapy was maintained after discontinuation of therapy.[7, 10] Women who are being treated with bisphosphonates should take a drug holiday if they have been on them for five years. Patients in whom bisphosphonate therapy is discontinued should typically follow up with bone mineral density measurements at 1- to 2-year intervals, with some experts advocating periodic measurement of biochemical markers of bone turnover to detect loss of the antiresorptive effect. Additional research is necessary to determine the exact correlation between the use of bisphosphonates and spontaneous or low-energy trauma fractures.

Competing Interests
None declared
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