Citation: IBMS BoneKEy **11**, Article number: 559 (2014) | doi:10.1038/bonekey.2014.54

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CLINICAL CASES

Response to Teriparatide in a patient with bisphosphonate-induced atypical femur fracture

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Bisphosphonates are the first-line and commonly prescribed drugs for the treatment of osteoporosis. They act by decreasing bone resorption, hence altering bone remodeling, which may lead to a low bone turnover state. Atypical femur fracture is one of the rare complications seen following prolonged use of bisphosphonates. We report a 1-year follow-up of our previously published case of atypical femur fracture and its response to Teriparatide, and a brief review of literature.

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Introduction

Bisphosphonates are the first-line and commonly prescribed drugs for the treatment of osteoporosis in view of their proven efficacy, safety and cost effectiveness. They act by decreasing bone resorption, hence altering bone remodeling, which may lead to a low bone turnover state. Atypical femur fracture is one of the rare complications seen following prolonged use of bisphosphonates. We report a 1-year follow-up of our previously published case of atypical femur fracture[1] and its response to Teriparatide.

Patient Characteristics

A 59-year-old postmenopausal woman presented with pain and restricted mobility of the right lower limb of 6 months duration, which aggravated following fall from the standing height. Medical history was largely unremarkable except for postmenopausal osteoporosis diagnosed at another center, for which she was on oral ibandronate 150 mg monthly for the last 18 months. There was no history of previous fracture. Her bone mineral density (BMD) *T*scores at the hip and spine with Hologic DXA scan before ibandronate treatment were -1.8 and -2.8, respectively. Examination revealed tenderness over the right thigh.

Biochemical parameters were as follows: serum albumin corrected calcium: 8.8 mg dl^{-1} (normal: 8.5–10.2), serum phosphorus: 3.2 mg dl^{-1} (normal: 2.5–4.5), alkaline phosphatase: 45 U l^{-1} (normal: 40–125), 25-OH vitamin D: 38 ng dl^{-1} (normal: 30–100), PTH: 42 pg ml^{-1} (normal: 8–50), C-terminal telopeptide: 119 pg ml^{-1} (normal: 299–543). BMD *T* scores at the hip and spine were -1.8 and -2.6, respectively.

Based on the clinical presentation, characteristic radiological findings (**Figure 1**) and the low bone turnover markers in the background of bisphosphonate therapy, a diagnosis of bilateral atypical femur fracture with a complete fracture on the right side and an incomplete one on the left side was made. The patient underwent intramedullary (IM) nailing of both femurs (**Figure 1**). Bisphosphonate therapy was stopped and she was continued on calcium and vitamin D supplements. She was initiated on Teriparatide at a dose of 20 μg daily in view of the underlying low bone turnover state.

On follow-up at 5 months after surgery, she made clinically significant improvement, as evident by reduction in pain and improved mobility. A repeat X ray imaging showed callus, bridging the fracture site (**Figure 2**). Subsequently, after 1 year, almost complete healing of the atypical fractures (**Figure 3**) was noted bilaterally, along with an increase in both formation and resorption markers with an alkaline phosphatase of 85 U l^{-1} and a C-terminal telopeptide level of 441 pg ml^{-1}. She was continued on Teriparatide, calcium and vitamin D and scheduled for a review visit after 6 months. Serial imaging along with biochemical parameters is shown in **Figure 4**.

Discussion

Bisphosphonates are the most widely used treatment for osteoporosis globally and are generally considered safe with minimal adverse events. The common side effects include upper gastrointestinal symptoms, febrile illness, hypocalcemia and a transient worsening of renal function. Atypical femur fractures and osteonecrosis of the jaw are among the rare reported serious adverse effects. Atypical femur fracture is seen

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Received 14 May 2014; accepted 12 June 2014; published online 13 August 2014

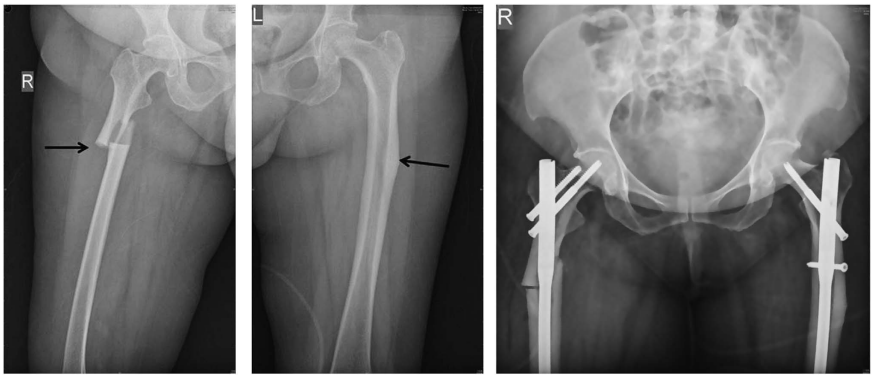

Figure 1 Images showing bilateral atypical femur fractures before and after intramedullary nailing.

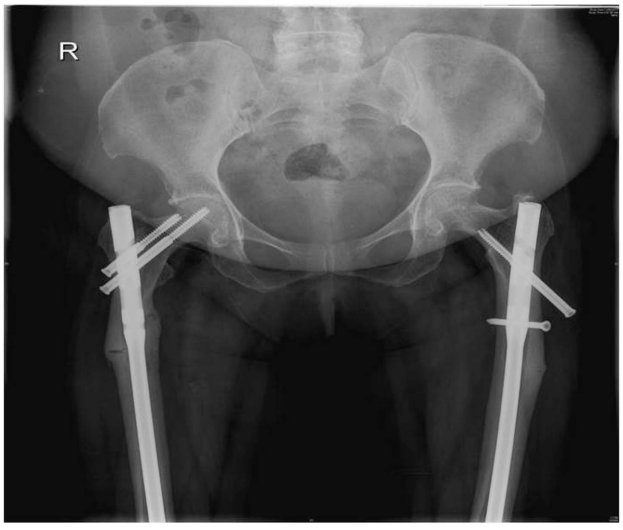

Figure 2 Bilateral atypical femur fracture following intramedullary nailing and Teriparatide treatment at 5-month follow-up. A callus bridging the fracture site.

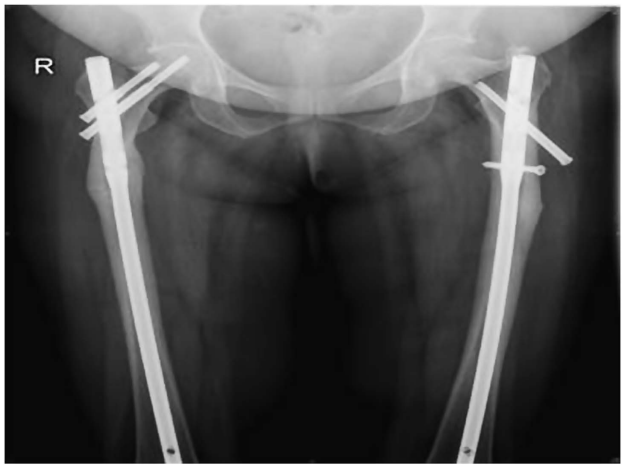

Figure 3 Bilateral atypical femur fracture following intramedullary nailing and Teriparatide treatment at 1-year follow-up showing almost complete healing at the fracture site.

at doses used to treat osteoporosis. A complication such as osteonecrosis of the jaw is more commonly seen at higher doses used for indications like malignancy even though it has also been reported in doses used for treating osteoporosis.[2] It highlights the importance of recognizing this complication in view of the widespread use of bisphosphonates.

Wang and Bhattacharyya[3] studied the incidence rates for non-hip femur fractures before and after 1995 when the oral bisphosphonates were widely used. An increasing trend in the incidence of subtrochanteric fractures with an age-adjusted rate of 20 vs 29 per 100 000 ($P = 0.002$) during 1984–1995 and 1996–2007 was noted, respectively. In another study conducted by Schilcher *et al.*,[4] the age-adjusted relative risk of atypical fracture ($n = 59$) was 47.3 (95% CI, 25.6–87.3). However, the absolute risk was 5 cases per 10 000 patient-years (95% CI, 4–7). After drug withdrawal, the risk reduced by about 70% per year (odds ratio, 0.28; 95% CI, 0.21–0.38). It was thus found that even though the relative risk of atypical femoral fracture (AFF) was high among bisphosphonate users, the absolute risk was small. Various studies have quoted a prevalence of $\sim$4–6 per 100 000 person years of use.[5]

The American Society of Bone Mineral Research (ASBMR) task force recently reviewed the literature on 310 cases of AFFs and found that in these patients the median duration of bisphosphonate therapy was 7 years. Two-thirds of these subjects had prodromal groin or thigh pain. Bilateral fractures or radiographic abnormalities were observed in 28% of subjects and in about 26% of them delayed healing was seen. A concomitant glucocorticoid and proton pump inhibitor use was seen in 34% and 39% of the patients, respectively.[5,6] Based on these findings, ASBMR formulated a provisional case definition of AFFs, which includes the major and minor features. All major features are required to designate a fracture as atypical, whereas minor features are not required but have been associated with atypical fractures. High trauma fractures, fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors and periprosthetic fractures should be excluded.[5]

AFFs are the stress or insufficiency fractures seen following prolonged bisphosphonate therapy. Bisphosphonates reduce bone remodeling and 'freeze' the skeleton, which may lead to accumulation of microcracks over time, resulting in fatigue fractures (stress fractures).[7] Bisphosphonate therapy-induced decreased bone remodeling affects bone quality through the following mechanisms: (1) an alteration in microdamage physiology in the form of accumulation of microcracks over time

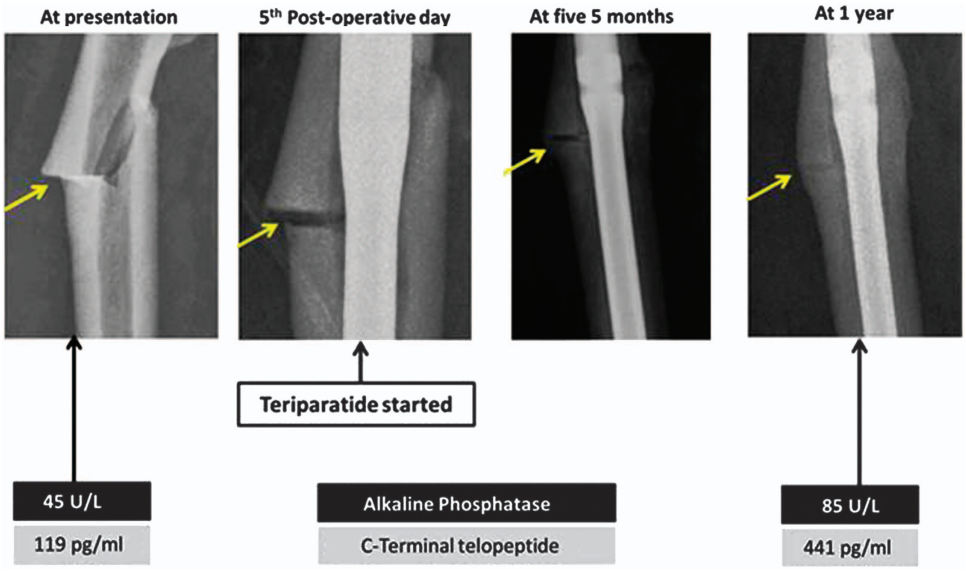

Figure 4 Sequential imaging of the right complete atypical femur fracture and bone turnover markers. (**a**) Complete transverse fracture with thickened cortex and low bone turnover markers at presentation. (**b**) Intramedullary nailing. (**c**) A callus bridging the fracture site at 5-month follow-up. (**d**) Almost complete healing at the fracture site with increase in bone turnover markers at 1-year follow-up.

due to inefficient bone remodeling, thereby propagating the fracture line; (2) reduction in heterogeneity of mineral and organic matrix due to alteration in both the collagen cross links and mineral content; and (3) accumulation of advanced glycosylation end products in view of reduced turnover. Bisphosphonate use has been shown to delay remodeling of hard callus, which may lead to formation of woven bone callus instead of ordered lamellar bone callus. Delayed healing has been reported in ~26% of atypical femur fractures.[7] Biomechanical factors such as bowing of femur and different hip axis length, as observed among different populations (for example, oriental Asians), have been associated with an increased risk of AFFs.[8]

Natural history shows that AFFs evolve over time. AFFs initially present with a 'cortical bump' (early periosteal thickening) followed by transverse 'cortical lucency' (fracture), which later leads to a complete fracture. Most of these fractures are preceded by pain, which warrants a high degree of clinical suspicion for an early diagnosis and management.

An X ray is the most useful imaging modality in this condition. However, computed tomography, magnetic resonance imaging and radionuclide bone scan may show a cortical fracture or lucency, associated new-bone formation, focal bone and marrow hyperemia, which will aid in the diagnosis of incomplete femoral fractures. In addition, bone turnover markers provide essential information on the degree of suppression of bone remodeling. However, published literature in this regard is limited. Bisphosphonates should be discontinued after diagnosis and it is prudent to maintain adequate calcium and vitamin D supplementation. IM nailing is the preferred method of fixation. It is also important to assess the contralateral femur, especially in patients who have a history of thigh pain, in view of a higher frequency of bilateral involvement. It has been shown that the incidence of subsequent atypical femur fractures was significantly higher among subjects who continued bisphosphonates (>3 years) than among those who discontinued the drug following the index fracture (41% vs 19%).[8]

Teriparatide (a recombinant PTH), being an anabolic agent, may be beneficial in these cases. PTH along with calcium and vitamin D has been shown to improve bone turnover and micro architecture, thus enhancing fracture healing. Healing stress fractures requires directed remodeling along the fracture line, in contrast to the endochondral ossification and callus formation needed for other complete fractures. As the major focus of PTH in bone is on the remodeling process, PTH treatment could provide the stimulus needed to increase the number and quality of fresh osteoclasts and osteoblasts to form the basic multicellular unit at stress fracture sites.[9] In a study by Chiang *et al.*,[10] Teriparatide treatment in 5 of the 14 patients with atypical fracture was associated with more than twofold increase in bone remodeling markers and fracture healing. Of the remaining patients ($n=9$) who were managed either conservatively or surgically, seven had poor fracture healing with persistent pain, one sustained an atypical fracture on the other side and one had delayed fracture union after 1 year. However, in the absence of randomized controlled studies, it remains uncertain whether PTH accelerates healing of AFFs.

Reconstruction nail fixation has been recommended for both complete and incomplete fractures as it is shown to improve fracture healing in these fractures. In subjects with minimal pain and no definite fracture line on imaging, a trial of conservative therapy with offloading and calcium and vitamin D supplementation may be considered. However, if there is no symptomatic and radiographic improvement after 2 to 3 months of conservative therapy, prophylactic nail fixation must be considered, as most of these fractures progress to complete fractures.

The number needed to treat with bisphosphonates for 3 years to prevent osteoporotic fractures is 91 for preventing one hip fracture and 14 for preventing one radiological vertebral fracture, whereas the number needed to harm, that is, the number of bisphosphonate users needed for one case of atypical fracture to occur, is 2000 per year of use or 700 for 3 years. The benefits far outweigh the risk.[4]

Conclusion

Bisphosphonate use may be associated with atypical subtrochanteric fractures. Non-comminuted, bilateral, transverse or oblique femoral fractures distal to lesser trochanter are the diagnostic hallmarks. The risk–benefit ratio still remains favorable for use of bisphosphonates to prevent fractures. Discontinuation of bisphosphonates, calcium and vitamin D supplementation, and surgery are the recommended treatment. The use of anabolic agents like Teriparatide may offer a promising mode of treatment for these atypical shaft fractures.

Conflict of Interest

The authors declare no conflict of interest.

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