

# Atypical femoral fractures in association with bisphosphonate therapy: a case series

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**Abstract** Well-established clinically as frontline therapy in the management of osteoporosis, bisphosphonates have been shown in numerous trials to be highly effective in reducing the risk of both vertebral and hip fractures. More recently, however, in a multitude of exhaustive case reviews, attention has been raised to the small but by now well-established link between prolonged bisphosphonate usage and the risk for atypical subtrochanteric femoral stress fractures. We present herein a trio of illustrative cases highlighting both clinical presentation and characteristic radiological findings thereof, as well as a discussion of the background, management, and natural history of these oftentimes problematic injuries.

**Keywords** Bisphosphonate · Femur · Fracture

## Introduction

As a class, bisphosphonates represent the single most commonly prescribed medication used in the long-term management and medical treatment of osteoporosis. Their primary course of action is to inhibit bone resorption via the induction of osteoclast apoptosis and to enhance secondary mineralization of bone, leading to increased generalized osseous density. Paralleling this, however, is a loss of general bone turnover and, despite a quantitatively harder osseous matrix, the resultant cancellous bone is also inherently more brittle and less resilient to microtrauma [1]. As shown by now in numerous case series, such resultant stress fractures typically and characteristically manifest themselves as focal areas of often bilateral subtle cortical thickening and beaking along the lateral subtrochanteric aspect of the femoral diaphysis. Both bone

scans and MRI have merit in offering considerably greater sensitivity for early detection. Such osseous changes, if unheeded clinically and radiographically, may lead to abrupt and complete cortical disruption, a potentially devastating injury given the propensity for prolonged and delayed healing [2].

## Case series

Our first patient is a 73-year-old female who presented to the emergency room with a displaced fracture of the proximal right femoral diaphysis following minor trauma (Fig. 1). Of clinical note was a prior 10-year history of Fosamax/alendronate and more recently Boniva/Ibandronate therapy for reported osteoporosis. After IM rod placement in the right femur, the initial postoperative course was uneventful. Bisphosphonate therapy was discontinued at the time of admission. Six months later, because of continued pain at the fracture site as well as developing discomfort in the contralateral proximal femur, a bone scan was performed (Fig. 2). Increased activity was observed both at the former fracture site as well as within the lateral diaphyseal cortex of the contralateral femoral shaft. Subsequently obtained radiographs of the right femur demonstrated medial and lateral cortical thickening with lateral cortical beaking and a faintly visible residual fracture line compatible with delayed healing (Fig. 3). Heterotopic calcification was also noted medially. Radiographs of the contralateral left femur demonstrated a characteristic beaking of the lateral diaphyseal cortex and generalized endosteal thickening (Fig. 4). The appearance was felt suggestive of subtrochanteric stress response likely in conjunction with prior long-term bisphosphonate therapy. Prophylactic intramedullary rodding was contemplated but declined, and the patient was begun on Forteo/teriparatide recombinant parathyroid hormone therapy for enhancement of neo-osteogenesis at the fracture zones. Scheduled follow-

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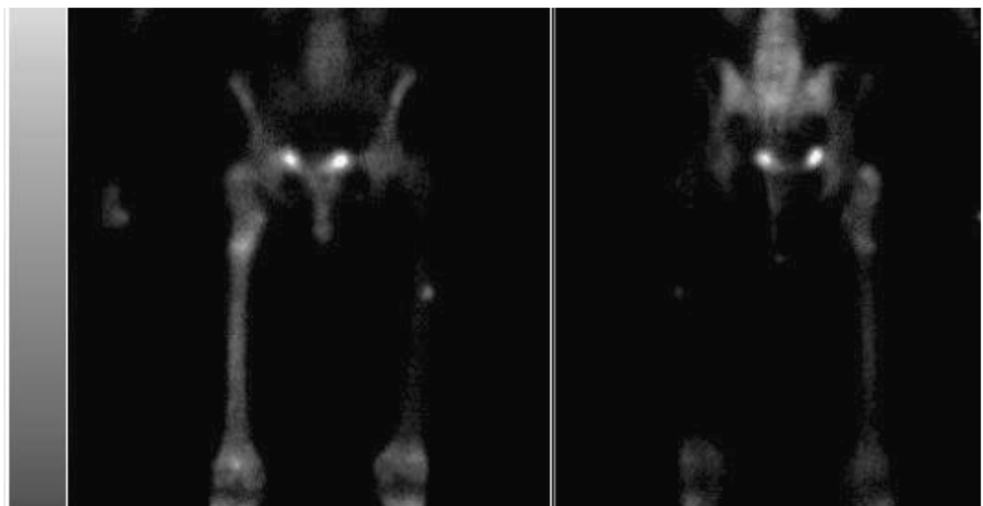


**Fig. 1** AP pelvis radiograph demonstrates a displaced, relatively transverse subtrochanteric fracture of the proximal right femoral diaphysis following minor trauma

up with endocrinology was planned to include potential tetracycline-based bone histomorphometry and bone mineral densitometry.

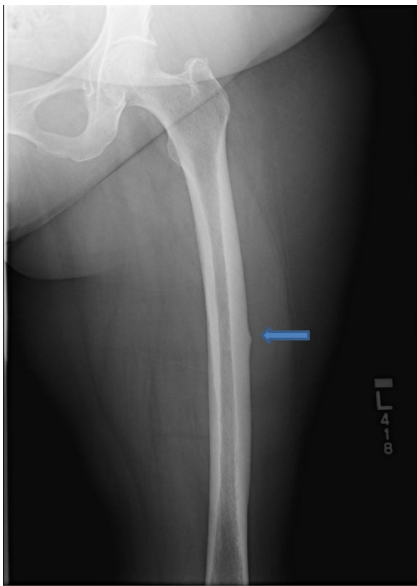
Our second patient, a 51-year-old female, presented with complaints of vague tenderness in the mid thigh region bilaterally and no antecedent trauma. AP radiograph of the left femur demonstrated a subtle area of cortical beaking involving the subtrochanteric lateral femoral diaphyseal cortex with mild associated endosteal thickening (Fig. 5). Images of the contralateral right femur were notable for a similar, slightly more inconspicuous proximal diaphyseal area of lateral subtrochanteric cortical beaking and endosteal thickening without a demonstrable fracture plane (Fig. 6). A concurrently obtained bone scan demonstrated congruent areas of subtly increased uptake within the midleft and proximal right femoral lateral cortices (Fig. 7). Of clinical relevance was a

**Fig. 2** AP and PA coned images obtained following the injection of 20 mCi Tc 99m MDP at time of a bone scan performed 6 months after the initial injury demonstrate a persistent area of abnormal uptake at the site of prior right subtrochanteric fracture. Additionally, there is a secondary area of contralateral increased activity in the lateral cortex of the mid-left femoral diaphysis



**Fig. 3** AP radiograph of the proximal right femur obtained following bone scan demonstrates a locking intramedullary rod, persistent medial and lateral diaphyseal cortical thickening, slight lateral beaking, and a faint residual fracture plane compatible with delayed healing. Heterotopic calcification is observed in the medial soft tissues

preceding 10-year history of alendronate and estrogen use for reported osteoporosis. Intermittent usage of prednisone dose packs for asthma exacerbations was also noted. Laboratory findings were noncontributory. Preceding bone densitometry readings obtained over the last 5 years had demonstrated a steadily increasing average T score within the both the femoral neck and lumbar spine regions, rising from an average of  $-1.8$  in the lumbar region and  $-1.2$  in the right femoral neck to a most recent value of  $-1.3$  and  $-0.4$ , respectively. Bisphosphonate usage was discontinued because of clinical and radiographic suspicion for atypical stress injuries in conjunction with suppressed bone turnover. An attempted tetracycline-labeled iliac crest bone biopsy was technically inadequate. After brief discussion of possible IM



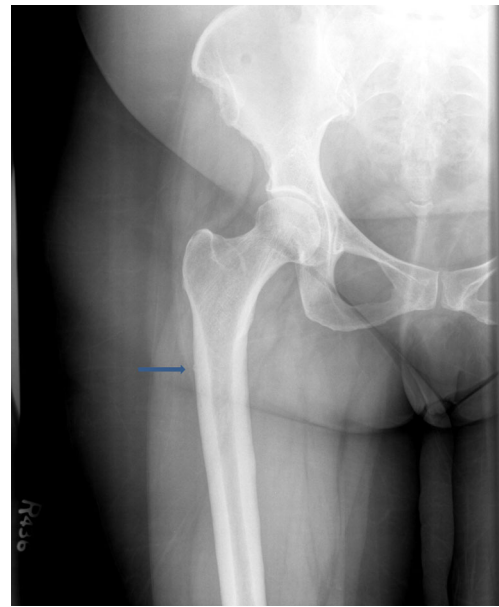
**Fig. 4** AP radiograph of the contralateral proximal left femur obtained at the time of bone scan also demonstrates characteristic lateral cortical diaphyseal primarily endosteal thickening with typical lateral beaking of the cortex indicative of evolving stress response and potential incipient fracture

rod placement, teriparatide therapy was begun in an attempt at initial nonoperative medical management. Symptomatic improvement was noted in early follow up with planned return to the endocrinology clinic and repeat bone scan after 3 months of medical therapy.

Our third patient, a 70-year-old female, presented with persistent proximal right thigh pain, again without antecedent



**Fig. 5** AP coned radiograph of the mid- and distal left femur demonstrates elliptiform endosteal thickening of the mid-diaphyseal cortex with characteristic lateral beaking

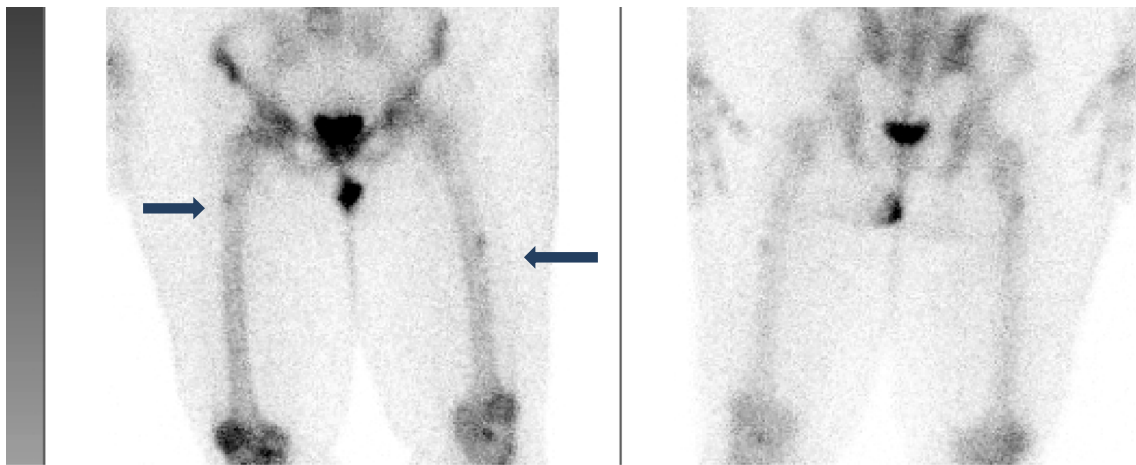


**Fig. 6** AP coned radiograph of the proximal right femur demonstrates a subtle lateral cortical excrescence approximately 3 cm subjacent to the trochanteric plane. Slight endosteal cortical thickening is also observed

trauma. There was likewise a relevant clinical history of preceding 10-year alendronate therapy for reported osteoporosis. AP radiograph performed at the time of presentation was notable for a subtle area of typical lateral femoral subtrochanteric diaphyseal cortical beaking and thickening (Fig. 8). An MRI, performed concurrently because of clinical uncertainty, demonstrated congruent findings of lateral cortical irregularity and mild diffuse subjacent intramedullary edema. No clear fracture plane was identified (Figs. 9, 10, and 11). Teriparatide treatment was begun after discontinuation of bisphosphonates with planned follow up in endocrinology for tetracycline-labeled bone biopsy and repeat bone densitometry.

## Discussion

As a class of medication, bisphosphonates, including commercially available alendronate, risedronate, ibandronate, and zoledronic acid, have shown substantial efficacy in reducing the accrued risk of osteoporotic related insufficiency fractures, occurring in approximately 50 % of women and 25 % of men over the course of a lifetime [3]. Beyond ameliorating the effects of senescent osteoporotic changes, they have also proven clinical utility in mitigating the osteoclastic-driven demineralization of host bone stock in both Paget's disease and osteolytic metastases. Their profile as a medication class is, however, not an entirely innocuous one. Atrial fibrillation, renal insufficiency, and osteonecrosis of the jaw have all been reported, albeit very rarely, as side effects, the latter of which



**Fig. 7** Coned AP and PA images of the pelvis and femoral regions from a bone scan obtained following the injection of 20 mCi Tc 99mMDP demonstrate faint areas of increased uptake involving the proximal right and mid-left lateral femoral diaphyseal cortices

is seen predominantly only in the setting of high-dose intravenous therapy for the treatment of bone metastases [3].

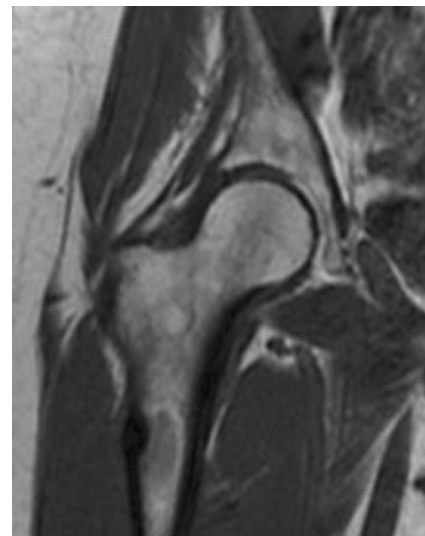
Increasingly in the literature, there has been growing recognition of the association between long-term bisphosphonate therapy and a small but real risk for atypical femoral subtrochanteric stress fractures. The first report, published by Odvina et al., appeared in 2005 as a case series detailing the fracture findings and outcome in a group of nine women all of whom had been treated with bisphosphonates for a year or more [4]. Larger cohort studies performed thereafter have, however, repeatedly demonstrated the relative minute actual risk of injury. In 2010, Abrahamsen et al. published data comparing the incidence of subtrochanteric femoral fractures between 1996 and 2005 in over 39,000 patients treated with alendronate versus that in 158,000 controls; the fracture

incidence was slightly more than doubled by the use of bisphosphonates though remained vanishingly rare at 31 versus 13 per 10,000 patient/year [5]. In the following year, Kim et al. published their data examining the rate of atypical femoral fractures in a cohort of over 33,000 patients on bisphosphonates, finding an incidence of only 104 overall cases, translating to an occurrence rate of 1.46 per 1,000 patients treated per year [6].

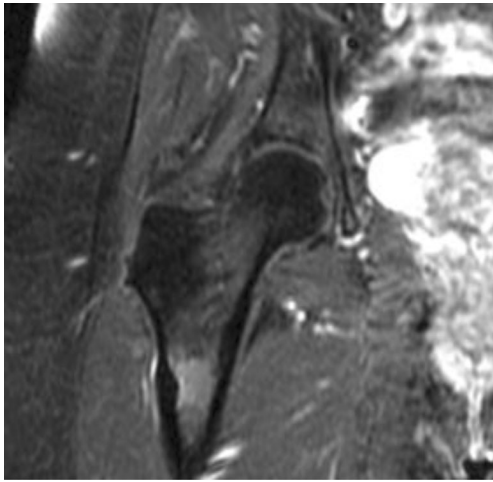
In 2010, a task force appointed by the American Society for Bone and Mineral Research established a set of common defining features to better standardize the reporting of atypical femoral fractures. In addition to subtrochanteric location, five main characteristics were identified: mild or no inciting trauma, little to no comminution of the fracture plane, and a transversely oriented fracture plane originating at the lateral



**Fig. 8** AP radiograph of the right hip demonstrates a focal area of lateral cortical beaking and associated mild endosteal thickening involving the proximal subtrochanteric diaphysis

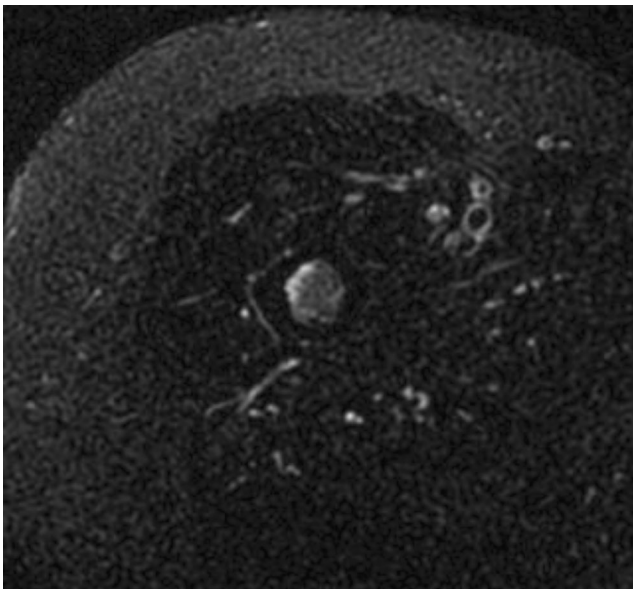


**Fig. 9** Coronal T1-weighted image through the right hip redemonstrates lateral subtrochanteric diaphyseal cortical thickening and slight intramedullary diminished fatty marrow signal intensity compatible with edema



**Fig. 10** Coronal fat-saturated T2-weighted image through the right hip demonstrate increased marrow signal intensity in the proximal diaphysis and lateral cortical thickening with slight beaking felt to be consistent with clinically suspected atypical stress injury

cortex with focal cortical thickening at the fracture site. Minor characteristics included delayed fracture healing, prodromal symptoms of vague local pain, and generalized lateral cortical thickening [7]. Incidence has not been confined to the femur, with varying secondary sites of weight-bearing osseous involvement noted including the anterior tibial cortex, pelvis, fibula, and metatarsals [8]. Bone scans and MRI have proven clinical utility in the detection of more radiographically subtle areas of injury, demonstrating increased uptake and marrow edema with associated lateral cortical thickening. Tomosynthesis has been used as well in some centers in an attempt to better elucidate early frank cortical disruption and fracture versus more indolent stress response. Prodromal pain



**Fig. 11** Axial fat-saturated T2-weighted correlative image slice through the proximal right femoral diaphysis again demonstrates lateral cortical beaking, endosteal thickening, and subjacent marrow edema

is fairly common occurring in up to 71 % of patients. Fracture bilaterality can be seen in up to 44 % of patients [9]. Delayed healing can likewise be seen in up to 26 % of published cases as was noted in the retrospective FDA adverse event reporting system review published in 2013 by Edwards et al. [10]. The duration until complete osseous union has also been shown to be dependent upon the length of usage with full healing averaging 4.8 versus 9.3 months in patients who had been on bisphosphonates for less than and greater than 3 years respectively in one series [3].

The seemingly paradoxical induction of atypical stress fractures by bisphosphonates appears to be multifactorial in etiology. Bisphosphonates increase osteoclastic apoptosis, acting to reduce bone turnover as mediated by osteoclastic function and also increase secondary mineralization of bone resulting in harder, though more brittle matrix that is more susceptible to and less able to repair the effects of long-term microdamage. There is also evidence that bisphosphonate use may adversely affect the maturation of collagen within the osseous cancellous matrix [11, 12]. The *in vivo* effects of reduced bone remodeling can be quantitated by the use of tetracycline labeling and subsequent iliac crest bone biopsy [12]. As would be expected given the increased secondary mineralization engendered in the host osseous matrix, nearly two thirds of patients who have been treated with bisphosphonates and present with atypical stress fractures are not frankly osteoporotic and actually have mean femoral bone density T-scores within only the osteopenic or normal range [3]. There is evolving evidence that other medication usage including corticosteroids and proton pump inhibitors may have a compounding effect on stress fracture induction [8, 12].

Because of the propensity for delayed union in atypical femoral stress fractures, there has been increasing clinical interest in proactively treating incipient or complete cortical injuries with a variety of supplemental measures including the recombinant parathyroid hormone teriparatide/Forsteo and low-intensity pulsed ultrasound. In addition, given the increased patient morbidity inherent in cases of delayed union, some centers advocate prophylactic fixation of detected stress injuries when found at radiological screening even in the absence of a frank fracture plane [3]. Given the low incidence of atypical fractures and the clinically proven efficacy of bisphosphonates in decreasing osteoporotic insufficiency fractures in the femoral neck and spine, there have been no collective statements issued regarding their withdrawal as a medication class. There is, however, an emerging clinical recognition and consensus that a drug holiday after 3–5 years of use is advisable in asymptomatic patients who have demonstrated an improved T score of  $-2.0$  or higher and have had no typical antecedent osteoporotic insufficiency fractures [12].

Insufficiency fractures in conjunction with senile-, medication-, or metabolic-related osteoporosis differ in

appearance and location, typically manifesting as more superiorly positioned purely endosteal bands of linear trabecular sclerosis in the subcapital femoral neck region. These often, though not uniformly, show a more lateralized position in contradistinction to the medial endosteal proximal femoral predilection displayed by activity induced stress fractures in young adults [13, 14]. Osteomalacic insufficiency fractures, otherwise known as Looser zones, also show a medial predilection in the proximal femur and, unlike bisphosphonate related injuries, demonstrate no associated cortical thickening and may be multiple in number [14].

Screening and early detection of incipient atypical femoral stress fractures in the bisphosphonate-treated osteoporotic patient population falls firmly into the bailiwick of both the treating clinician and the consulting radiologist. As such, it behooves us as imaging specialists to be both cognizant of and attentive to the oftentimes subtle manifestations of these potentially problematic injuries.

**Conflict of interest** The authors declare that they have no conflicts of interest.

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