

# Atypical Fractures of the Femur Related to Prolonged Treatment with Bisphosphonates for Osteoporosis

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**ABSTRACT:** **Background:** Bisphosphonates reduce the overall risk of fractures among patients with osteoporosis, and this beneficial effect is long-lasting. However, since bisphosphonates inhibit bone remodeling, they may enhance the formation and propagation of micro-cracks over time and patients may therefore be prone to atypical fatigue fractures, mainly in the subtrochanteric region and femoral shaft.

**Objectives:** To present two cases of subtrochanteric fractures related to bisphosphonate treatment, and review the current literature.

**Conclusions:** Despite the overall beneficial effect of bisphosphonates, further research is required to prevent this significant complication.

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**KEY WORDS:** bisphosphonates, subtrochanteric fracture, atypical fracture, osteoporosis, femur

## For Editorial see page 110

The potential role of bisphosphonates gained much interest in the late 1960s. This unique class of drugs exhibited a specific affinity for bone cells. Clinical trials were promising as they reported a significant decrease in the incidence of fractures of the spine and hip, along with a concomitant reduction in health care costs [1,2]. Today bisphosphonates are considered a first-line therapy and are a mainstay of primary and secondary prevention of fragility fracture [2,3]. Nevertheless, with the growing and prolonged use of these agents, several case series and case reports have raised concern regarding their long-term use and the associated increased risk of atypical subtrochanteric fracture of the femur [1].

We describe two patients who sustained bisphosphonate-related atypical subtrochanteric fractures, and review the current literature on the pathological, radiological and clinical features of these fractures and their management.

\*The first two authors contributed equally to this study

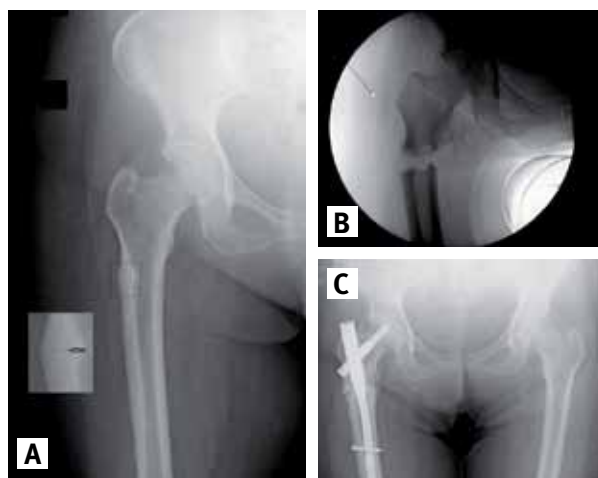
## PATIENT 1

A 68 year old woman visited our outpatient clinic complaining of pain in her right hip. Her prior medical history included non-insulin-dependent diabetes mellitus, asthma, hyperlipidemia and depression. The patient had been taking risedronate for 7 years prior to her visit.

Plain radiographs of the hip demonstrated a thickening of her lateral femoral cortex at the subtrochanteric region, and a subtrochanteric stress fracture was diagnosed [Figure 1A]. She was offered prophylactic fixation, which she refused. Instead, she preferred to ambulate with a walker in order to decrease weight-bearing of her right thigh. Treatment with risedronate was discontinued.

Fifteen months later she was admitted after a minor trauma with the diagnosis of a displaced right-side transverse subtrochanteric fracture [Figure 1B]. Treatment comprised closed reduction and internal fixation with proximal femoral nailing anti-rotation (Synthes™, Switzerland) [Figure 1C].

**Figure 1.** Patient 1. **[A]** Subtrochanteric stress fracture (arrow) demonstrated by plain anteroposterior radiograph image. Notice the localized periosteal reaction of the lateral cortex. **[B]** Fluoroscopic image of a displaced right-side transverse, non-comminuted subtrochanteric fracture. **[C]** Anteroposterior radiograph taken 6 months after closed reduction and internal fixation with proximal femoral nailing anti-rotation (Synthes®)



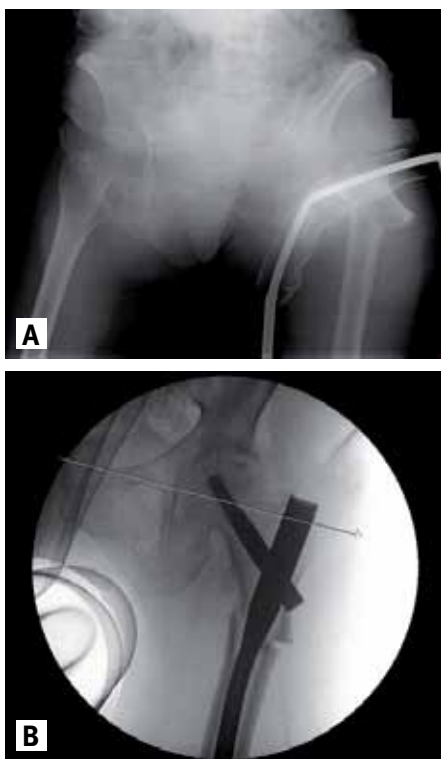
She started ambulation the day after surgery and is currently walking without assistance.

**PATIENT 2**

A 73 year old woman was admitted following a subtrochanteric fracture in her left thigh. She reported severe pain in her left thigh that occurred spontaneously without any predisposing trauma. Subsequently, she collapsed and fell on the affected side. Her orthopedic history revealed an osteoporotic fracture of L2 vertebra 6 months earlier, as well as bilateral hip pain for several months prior to the fall. Her osteoporosis drug regimen included vitamin D, as well as raloxifene for 6 years followed by alendronate for 4 years up to one year prior to this fracture. In the past year she was treated with intravenous zoledronic acid.

Plain radiographs demonstrated a displaced left subtrochanteric transverse fracture [Figure 2A]. On the day of her arrival at the hospital she underwent closed reduction and internal fixation with proximal femoral nailing anti-rotation (Synthes™) [Figure 2B]. Since she complained of pain in her contralateral thigh plain, radiographs as well as a computed tomography scan and elective bone scan were performed. Her skeletal radiographic workup was negative.

**Figure 2.** Patient 2. **[A]** Anteroposterior radiograph of the patient’s hip with displaced left subtrochanteric fracture. **[B]** Intraoperative fluoroscopic image taken after closed reduction and internal fixation with proximal femoral nailing anti-rotation (Synthes™)



The patient started ambulation the day after surgery and is currently walking with a walker. At her last follow-up, 5 months after the surgery, the fracture had united.

**EPIDEMIOLOGY**

Fractures located in the subtrochanteric region or femoral shaft (diaphysis) account for approximately 8% of all hip/femoral diaphyseal fractures [1]. Subtrochanteric fractures share features of typical osteoporosis-related fractures; these fractures are more common in women than men, although their incidence increases with age in both males and females [4]. Interestingly, whereas the incidence of hip fractures declined with the widespread use of bisphosphonates, the incidence of subtrochanteric and femoral shaft fractures did not lessen and has even increased. However, the correlation between bisphosphonate intake and these fractures has not been determined [1].

Prospective randomized clinical trials on aledronate and zoledronate for osteoporotic patients showed significantly improved bone mineral density and decreased fracture risk in the lumbar vertebrae and proximal femur [5]. Furthermore, the investigators of the HORIZON recurrent trial noted significantly lower associated mortality rates with zoledronate treatment [6]. However, several case series and multiple individual case reports suggest that subtrochanteric and femoral shaft fractures may occur after long-term treatment with bisphosphonates. One systematic review that examined 310 subtrochanteric and femoral shaft fractures noticed that 291 (93.8%) of these patients had been treated with bisphosphonates for various durations [1]. These studies indicated that certain common radiological and clinical features are suggestive of a fracture distinct from the common osteoporosis-related subtrochanteric or femoral shaft fracture.

National registry cohort analysis studies add support to the association between long-term bisphosphonate usage and atypical subtrochanteric fracture [1,7]. The National Institute of Arthritis, Musculoskeletal and Skin Diseases found an increased incidence of subtrochanteric fractures with widespread bisphosphonate use, despite decreasing overall hip fracture rates [1]. Similarly, Park-Wyllie et al. [8] contended that women treated with bisphosphonates for more than 5 years bear a significantly increased risk of subtrochanteric or femoral shaft fracture. However, these women had lower overall risk for osteoporotic fractures when compared with non-bisphosphonate users.

Other studies that attempted to clarify the association between bisphosphonate use and atypical fracture could not support such an association. Black and fellow researchers [9] performed post-hoc analysis of the FIT, FLEX, and HORIZON trials but could not find a significant increase in bisphosphonate-related subtrochanteric fractures when com-

pared with placebo. One of the difficulties in interpreting the outcome of these studies [7-9] is the lack of specific radiological or clinical criteria for the diagnosis of atypical fracture.

Recently, Schilcher et al. [10], using strict radiographic criteria of atypical subtrochanteric fractures, conducted a nationwide cohort analysis of the Swedish National Registry. They concluded that the absolute risk of atypical fracture associated with bisphosphonates for the individual patient with a high risk of osteoporotic fractures is small when compared with the beneficial effects of the drug.

In summary, the data suggest that atypical femoral fractures are distinct and rare, but their incidence may increase with duration of bisphosphonate use. Notably, the use of bisphosphonates has yet to be proven as a distinctive cause of these atypical femoral fractures [1].

### BASIC SCIENCE STUDIES

Bisphosphonates are an analogue of pyrophosphate with a highly specific affinity to bone (specifically, hydroxyapatite). They reduce bone mineral dissolution and resorption [11] and localize their action via osteoclast acid activation and subsequent inhibition of bone resorption without osteoclast destruction [12]. Two subclasses of bisphosphonates are in use: nitrogen containing (N-BP) and non-nitrogen containing (n-BP). While the N-BP subclass (alendronate, ibandronate, pamidronate, risedronate, zoledronate) directly inhibits osteoclasts, the n-BP subclass (etidronate, tiludronate) indirectly affects bone resorption through its metabolites, which were found to form toxic ATP analogues, inducing osteoclast apoptosis [13].

Through these pathways, bisphosphonates prevent the loss of bone and alter the cancellous micro-architecture. Bisphosphonate treatment reduces bone turnover and increases overall mineralization but leaves mineral particle shape, thickness and orientation unaffected. In addition, it also narrows the bone mineralization density distribution and increases bone strength and stiffness [14]. Consequently, bisphosphonates decrease fracture risk by suppressing bone resorption and increasing bone stiffness. Yet, by reducing remodeling, they increase micro-damage accumulation due to ineffective repair of cracks [15]. The American Society for Bone and Mineral Research led a taskforce [1] that articulated several key questions regarding this complication and proposed several possible pathogenic mechanisms associated with atypical femur fractures [Table 1].

During therapy, bisphosphonates are incorporated into newly formed bone and may persist there for years [16]. Thus, even in the face of increased bone mass, prolonged reduction of remodeling could have an added negative effect

N-BP = nitrogen-containing bisphosphonate

n-BP = non-nitrogen-containing bisphosphonate

**Table 1.** Possible pathogenic mechanisms associated with atypical femur fractures

- Alterations to the normal pattern of collagen cross-linking either by changes to maturity of cross-links formed by enzymatic processes, or by advanced glycation end-product accumulation
- Microdamage accumulation
- Increased mineralization
- Reduced mineralization heterogeneity
- Variations in bone turnover rates
- Reduced vascularity and anti-angiogenic effects

Adopted from Shane et al. [1]

beyond the treatment period and could eventually increase the long-term risk of atypical fractures.

### DIAGNOSIS

The prototype patient presenting with a complete atypical fracture of the femur is an elderly woman treated with bisphosphonates after sustaining a minimal trauma. The clinical presentation of incomplete atypical femoral fracture resembles that of a stress fracture. Nearly 70% of patients with a confirmed femoral stress fracture report prodromal pain for a period of weeks prior to the actual diagnosis [1]. Many of these patients have either simultaneous or sequential bilateral symptoms [17].

Comorbid conditions with known bone quality sequelae such as diabetes mellitus, and patients treated with glucocorticosteroids may also predispose to atypical femoral fractures [1,18,19].

### IMAGING

Radiographs of the femur acquired in anteroposterior and lateral projections usually suffice to demonstrate the characteristic findings in complete or incomplete fractures [20,21]. More sophisticated imaging modalities – such as bone scintigraphy, magnetic resonance imaging, or CT – are used for detecting early or subtle prefracture features [1,19,22]. Radiological characteristics of these atypical fractures follow a sequential occurrence: in the prefracture phase there is a focal cortical thickening from periosteal new bone apposition, mainly in the lateral cortex [22] [Figure 1B]. The associated focal or diffused cortical thickening, especially of the lateral cortex, produces an appearance of cortical ‘beaking’ or ‘flaring’ adjacent to a discrete transverse fracture line [19].

As the occult fracture evolves and propagates medially, obvious displacement ultimately occurs, forming a complete fracture. Subsequently, an oblique component may be observed as a prominent medial ‘spike’. Especially in the prefracture phase, these findings may be quite subtle and, thus, non-diagnostic. In patients with a high index of suspicion

for an occult fracture, more advanced diagnostic imaging modalities may be useful.

Unilateral or bilateral increased uptake in bone scintigraphy may demonstrate the presence of an evolving stress or insufficiency fracture [1]. MRI can detect the reactive hyperemia and periosteal new bone formation of an evolving stress or insufficiency fracture [23]. CT is capable of detecting subtle reactive periosteal new bone formation and the small, discrete radiolucency of the evolving fracture and its focal intracortical bone resorption [1].

### DIAGNOSTIC CRITERIA

The American Society for Bone and Mineral Research Taskforce [1] defined major and minor diagnostic features for complete and incomplete atypical fractures of the femur [Table 2]. All major features must be present in order to diagnose an atypical fracture and distinguish it from more common hip fractures. Minor features may or may not be present in individual patients. Of note, association with bisphosphonate therapy was included as a minor feature.

### PREVENTION, TREATMENT AND MANAGEMENT

Before initiating bisphosphonate treatment, one should consider the benefits and risks. Osteoporotic patients with normal or only moderately reduced femoral neck or total hip bone mineral density have a low risk for an osteoporotic fracture and should not be treated with bisphosphonates but should be started perhaps with alternative drugs such as raloxifene [1].

The literature indicates that for patients with a stable bone mineral density and without a history of a recent fracture, ceasing bisphosphonate treatment should be considered [24].

There is limited evidence regarding the efficacy of bisphosphonates (alendronate or zoledronic acid) in preventing femoral fractures beyond the standard 3 to 5 years of treatment. Recently, an article published in the *New England Journal of Medicine* analyzed the FLEX and HORIZON studies and concluded that for patients with a femoral neck T-score of less than -2.5 and no history of vertebral fracture or for those with a T-score of lower than -2 and a prior vertebral fracture, bisphosphonates reduce the risk of additional vertebral fractures. However, continuation of treatment beyond 3–5 years is not indicated for patients with an estimated femoral neck T-score higher than -2 [24].

Bearing in mind that the median duration of bisphosphonate treatment for patients with atypical fractures was 7 years [1,17], more accurate criteria should be followed rather than widespread prophylactic long-term treatment. In addition, it is important to instruct physicians and patients about the prodromal symptoms of thigh or groin pain reported in more than half the patients with atypical fracture [1].

**Table 2.** Major and minor features of atypical fractures

Major features
<ul style="list-style-type: none"> <li>• Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare</li> <li>• Not associated with trauma or minimal trauma, as in a fall from a standing height or less</li> <li>• Transverse or short oblique configuration</li> <li>• Non-comminuted</li> <li>• Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex</li> </ul>
Minor features
<ul style="list-style-type: none"> <li>• Localized periosteal reaction of the lateral cortex</li> <li>• Generalized increase in cortical thickness of the diaphysis</li> <li>• Prodromal symptoms such as a dull or aching pain in the groin or thigh</li> <li>• Bilateral fractures and symptoms</li> <li>• Delayed healing</li> <li>• Comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatemia)</li> <li>• Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticosteroids, proton pump inhibitors)</li> </ul>

Adopted from Shane et al. [1]

The literature is scarce regarding the treatment of atypical femoral fracture associated with prolonged bisphosphonate treatment. Complete fractures warrant prompt surgical treatment with full-length intramedullary nailing. Plates, especially locking plates, preclude enchondral repair and may have a higher failure rate [17]. Treatment of incomplete fracture is somewhat more controversial. Some surgeons recommend prophylactic full-length intramedullary nailing in this setting as well [17,25]. If the patient has minimal pain, conservative treatment may also suffice, with partial weight-bearing. If no clinical improvement occurs within 3 months, prophylactic fixation by intramedullary nailing may be warranted [1]. The evaluation of the contralateral limb in these patients cannot be overemphasized, regardless of symptoms [1,17]. For patients with complete or incomplete stress fractures, antiresorptive drugs should be discontinued, vitamin D and calcium should be initiated [1], and teriparatide therapy may be beneficial in terms of time to recovery [1].

### SUMMARY

Although the widespread use of bisphosphonates has decreased dramatically in the last few years, the incidence of fragility fractures among patients with osteoporosis has been related to a new and distinct type of atypical femoral fractures occurring distal to the lesser trochanter. Their main features include occurrence after minimal or no trauma, association with a medial spike, transverse or short oblique configuration, localized periosteal reaction of the lateral cortex, and presentation of prodromal symptoms such as a dull or aching pain in the groin or thigh. Atypical fractures may be diagnosed by plain radiographs, but bone scintigraphy, MRI and CT may be helpful to avoid misdiagnosis. Excessive and long-term bisphos-

phonate treatment should be avoided in order to decrease the risk of these atypical fractures in the relevant patients. Clearly, for a complete fracture, surgical reduction and fixation with intramedullary nailing are indicated. However, for newly incomplete stress fractures, the treatment is controversial and both surgical and conservative methods may be considered.

Further research is needed to gain more knowledge regarding the screening for early diagnosis and management of this emerging phenomenon related to the widespread use of bisphosphonate treatment.

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#### Capsule

### Transcranial amelioration of inflammation and cell death after brain injury

Traumatic brain injury (TBI) is increasingly appreciated to be highly prevalent and deleterious to neurological function. At present, no effective treatment options are available, and little is known about the complex cellular response to TBI during its acute phase. To gain insights into TBI pathogenesis, Roth et al. developed a novel murine closed-skull brain injury model that mirrors some pathological features associated with mild TBI in humans and used long-term intravital microscopy to study the dynamics of the injury response from its inception. The authors demonstrated that acute brain injury induces vascular damage, meningeal cell death, and the generation of reactive oxygen species (ROS) that ultimately breach the glial limitans and promote spread

of the injury into the parenchyma. In response, the brain elicits a neuroprotective, purinergic receptor-dependent inflammatory response characterized by meningeal neutrophil swarming and microglial reconstitution of the damaged glial limitans. They also showed that the skull bone is permeable to small molecular-weight compounds and uses this delivery route to modulate inflammation and therapeutically ameliorate brain injury through transcranial administration of the ROS scavenger, glutathione. These results shed light on the acute cellular response to TBI and provide a means to locally deliver therapeutic compounds to the site of injury.

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