Atypical Diaphyseal Femur Fractures in Patients With Prolonged Administration of Bisphosphonate Medication for Osteoporosis

Joel A. Horning, MD; John Czajka, MD; Richard L. Uhl, MD

Some patients treated with bisphosphonates for a long period develop weakening of bones, especially in the subtrochanteric and diaphyseal regions of the femur. Cessation of the medication when patients develop pain in these regions may help prevent subsequent fracture.

Bisphosphonates have become widely used for the prevention of osteoporosis associated fractures since their approval in the United States in 1995 by the Food and Drug Administration. They have been shown to decrease the incidence of vertebral and femoral neck fractures in postmenopausal osteoporotic women. While bisphosphonates have a relatively safe side effect profile, osteonecrosis of the jaw has been widely publicized as a side effect from long-term use of bisphosphonates.

Recently, reports of subtrochanteric and diaphyseal femur fractures associated with long-term bisphosphonate use have been published. These fractures are atypical in that they are associated with minimal trauma and are transverse or short oblique in nature. Their occurrence may be associated with concomitant use of other antiresorptive agents, corticosteroids, and proton pump inhibitors. Although complete fractures are rare, patients may report thigh pain and have characteristic radiographic changes that can be identified prior to fracture (Figure 1). Recognizing these prodromal symptoms and stopping the medication may prevent these fractures.

**MECHANISM OF ACTION**

Bisphosphonate drugs act to inhibit bone resorption. Bisphosphonates have a pyrophosphate-like backbone that binds to calcium in bone. Because there is no enzyme that can breakdown this backbone, these medications have a half-life >10 years.

Bisphosphonates are subclassified into nonnitrogen-containing and nitrogen-containing based on their side chain composition. Nonnitrogen-containing bisphosphonates are metabolized into adenosine triphosphate analogues absorbed by osteoclasts. These analogues build up within the osteoclasts and become cytotoxic, leading to decreased cell function and the induction of apoptosis. Nitrogen-containing compounds act by inhibiting farnesyl diphosphate synthetase in the mevalonate pathway, which is important maintenance of the cell membrane. This inhibition causes disruption of the ruffled border and also leads to apoptosis.

Through their action on the osteoclast, bisphosphonates decrease bone resorption and in turn increase bone mineral density, resulting in increased bone strength and decreased risk of fracture during the first 5 years of administration.

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**Figure 1:** A 71-year-old woman presented with right thigh pain. She was on bisphosphonate medication for 10 years prior to this visit. The bisphosphonate medication was stopped, but 6 months later the patient continued to have right thigh pain. Note the thickening and scalloping of the lateral cortex in the diaphyseal region of the femur. A recent MRI showed bone edema in this area.
However, while the ultimate strength of the bone improves, its toughness decreases by as much as 20% due to the accumulation of microdamage and lack of effective remodeling within the bone.\textsuperscript{15-17} The decrease in toughness may lead to failure in areas with high tensile forces, such as the subtrochanteric and diaphyseal regions of the femur.

**Radiographic Appearance**

Radiographs of bisphosphonate associated femur fractures have an uncharacteristic appearance (Figure 2). Subtrochanteric or diaphyseal femur fractures result from higher energy mechanisms with associated comminution or a twisting mechanism resulting in a long spiral oblique. A fracture of the subtrochanteric region may have a transverse or short oblique appearance, unless there is inherent weakness within the bone.

In addition to the unusual appearance of the fracture, characteristic changes involving the femoral cortex on both the compression and tension sides of the femur may present (Figure 1). Chan et al\textsuperscript{18} reported on 34 femur fractures in 22 patients receiving long-term (>4 years) alendronate treatment. They demonstrated a medial break in 85% of fractures. All fractures had a skirt of focal thickening directly opposite laterally. Fourteen cases of incomplete fractures revealed the same focal, lateral thickening.\textsuperscript{18} Magnetic resonance imaging (MRI) evaluation of these incomplete fractures demonstrated only focal edema consistent with incomplete fracture.

**Histologic Appearance**

Bisphosphonates act to decrease osteoclast activity and increase bone mineral density and have been proven to decrease nonvertebral fractures. Animal models and postmortem human studies have shown decreased elastic modulus and toughness with accumulation of microdamage.\textsuperscript{19,20} Odvina et al\textsuperscript{21} evaluated 13 patients presenting with long bone fracture while on long-term bisphosphonate treatment for changes in biochemical markers, bone mineral density, and histology. They found normal serum calcium and parathyroid hormone and low bone mineral density in those tested. Transiliac bone biopsies performed in 6 of 13 patients demonstrated severe depression of bone formation and minimal identifiable osteoblasts.\textsuperscript{21}

**Treatment**

When bisphosphonate-associated femur fractures are identified, the treatment is surgery (Figure 3). Difficulties may occur when presented with an incomplete femoral insufficiency fracture or a patient with contralateral radiographic evidence of bisphosphonate-associated changes. Ha et al\textsuperscript{22}...
attempted to elucidate this by reviewing 12 patients with bisphosphonate-associated femoral insufficiency fractures, 8 of which were bilateral. They found no resolution of symptoms or spontaneous healing in any of the insufficiency fractures and recommended prophylactic fixation.22 Other studies have shown delayed union in similar fractures.23,24 Capeci and Tejwani25 have had success treating bisphosphonate-associated fractures with reamed intramedullary nails. Prophylactic fixation of insufficiency fractures has been recommended in patients with a history of long-term bisphosphonate use, persistent thigh pain, lateral cortical thickening on radiographs and MRI, or bone scintigraphic evidence of stress fracture.26

**DISCUSSION**

Bisphosphonates are used for the treatment of osteoporosis. They have been shown to increase bone density and reduce nonvertebral fractures. The majority of bisphosphonate-associated femur fractures have been reported in the literature. This may be confounded by the higher rate of women treated for osteoporosis with long-term bisphosphonates. Despite an increasing number of recent articles in the literature, subtrochanteric and diaphyseal femur fractures associated with long-term bisphosphonate use are rare, occurring at a rate of approximately 0.8 to 2.4 fractures per 10,000 patient treatment years. This incidence is derived from data obtained from 3 large, multicentered trials.27 Only a minority of these patients received bisphosphonates for more than 4.5 years, raising the question of whether the incidence is actually higher.

The patients described in many case reports are postmenopausal women receiving bisphosphonates presenting with fractures after minimal or no trauma including a fall from standing height or following a minimal twisting injury. As a history is obtained, the patient often reports a period of pain prior to fracture. Prodromal symptoms have been reported to last between 2 to 6 months prior to fracture,28 but in the author’s experience, cases have been observed with prodromal pain up to 2 years prior to fracture.

Currently, the length of time of bisphosphonate therapy during which the patient becomes at risk for subtrochanteric/diaphyseal femur fractures is unknown. The majority of reports describe long-term use ranging from 4 to 8 years prior to fracture.25,28 In addition, there appears to be an association between concomitant drug therapy with corticosteroids or proton pump inhibitors and with other anti-osteoporotic agents like hormone replacement therapy.8,10

Two Danish studies sought to evaluate whether the risk of bisphosphonate-associated femur fractures outweighed their protective affects.17 Both studies were derived from the country’s national registries. The first was a cross-sectional study comparing age, duration of bisphosphonate treatment, and trauma between different femur fractures. They found no significant difference between the occurrence of bisphosphonate-associated subtrochanteric fractures and other osteoporosis-related proximal femur fractures. A second cohort study found no significant difference in the hazard ratio for development of a subtrochanteric/diaphyseal fracture while on bisphosphonates. They concluded the risk of a bisphosphonate-associated fracture was no greater than the risk of an osteoporotic fracture. In critiques of the study, authors have cited the treatment group’s small proportion of patients receiving long-term bisphosphonate treatment. They had a mean treatment time of 2.5 years with a range of 6 months to 8 years. Only 178 patients of an 11,944 study population received bisphosphonates for >6 years.21

Medically, it is difficult to reduce the risk of fracture associated with bisphosphonate use. Some have recommended drug holidays of up to 12 months for patients receiving bisphosphonates for >5 years based on findings from the Fracture Intervention Trial Long-term Extension (FLEX).29 Given the drug’s long half-life in bone, the length of the drug holiday may need to be longer to achieve a desired effect of reducing bisphosphonate-associated fractures. No data that we are aware of are yet available defining the time needed to reverse the microdamage that occurs following bisphosphonate use. In addition, while the protective effect of bisphosphonates remains during these holidays,30 data are not available on whether a drug holiday of any duration has a protective effect regarding bisphosphonate-associated femur fractures.

**CONCLUSION**

Bisphosphonate associated subtrochanteric and diaphyseal femur fractures are rare fractures occurring in postmenopausal women treated with long-term bisphosphonate therapy (>4 years). Patients present after minimal trauma or after a prodrome of pain that may be associated with insufficiency fracture. These paradoxical fractures occur secondary to accumulation of microtrauma in the high stress tension side of the diaphyseal femur. The fractures characteristically have lateral cortical thickening, are transverse, and display medial beaking.

When presented with a patient reporting thigh pain while on bisphosphonate therapy, one must be vigilant in evaluating radiographs to prevent pathologic fracture. Although drug holidays have been recommended, they have not been proven to prevent these fractures. Surgical intervention with prophylactic intermedullary nailing may be undertaken for incomplete insufficiency fractures due to their poor healing potential.

**REFERENCES**

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