Bisphosphonates are a class of drugs that prevent bone loss by decreasing bone resorption. They represent a major treatment for osteoporosis and other metabolic bone diseases. Recent reports suggest that a potential complication of long-term bisphosphonate therapy may be atypical insufficiency fractures of the femur. Concern exists about delayed union after fracture stabilization in patients taking bisphosphonates.

This article describes 2 patients on long-term bisphosphonate therapy treated for atypical femur fractures that failed to heal with intramedullary nailing. Both patients' fractures occurred after at least 4.5 years of bisphosphonate use and displayed classic findings of bisphosphonate fractures reported in the literature, including a subtrochanteric location, presentation after minimal trauma, transverse fracture, no comminution, and cortical beaking. The original fractures were treated at other institutions with intramedullary nails. Subsequently, both patients presented with pain and atrophic nonunion of their fractures. Evaluation included a computed tomography scan of the fracture and a metabolic workup. The patients discontinued bisphosphonate therapy. They were treated with nail removal and definitive plating to achieve compression across the fracture site. Both fractures went on to heal after this treatment with no further complications.

The literature currently recommends treating bisphosphonate fractures with an intramedullary nail. Perhaps initial treatment of these fractures should be similar to an atrophic nonunion, involving compression plating to obtain bone-on-bone contact and promote healing. This would address the biologic and mechanical etiologies of the bisphosphonate fracture.
Bisphosphonates, a class of drugs that prevent bone loss by decreasing bone resorption, are a major treatment for osteoporosis and other metabolic bone diseases. Recent reports have noted incidences of atypical femur fractures in patients who have undergone long-term bisphosphonate therapy for osteoporosis.\(^1\)\(^{-}\)\(^6\)\(^{12}\) These fractures have a characteristic presentation that distinguishes them from typical femur fractures. They present with prodromal thigh, groin, or hip pain, and most occur after a low-energy mechanism.\(^1\)\(^{-}\)\(^4\) These fractures are also unique radiographically. They tend to be simple transverse or oblique fractures with cortical thickening laterally around the fracture site and medial beaking.\(^1\)\(^{6}\)\(^{8}\)\(^{9}\)

It has been hypothesized that these are insufficiency fractures as a result of severely suppressed bone turnover and accumulation of skeletal microdamage.\(^1\)\(^{6}\)\(^{8}\)\(^{9}\)

Despite being unique, bisphosphonate fractures are currently treated similarly to hip and femur fractures with an intramedullary nail. This article describes 2 women on long-term bisphosphonate therapy treated for atypical femur fractures that failed to heal with intramedullary nailing.

**Case Reports**

**Patient 1**

A 59-year-old, nonsmoking woman with a history of hypertension, depression, anemia, high cholesterol, previous diagnosis of osteoporosis, and gastroesophageal reflux presented in March 2009 for nonunion of bilateral femur fractures. She had sustained a right subtrochanteric femur fracture in January 2008 from a fall down stairs. This was treated with an intramedullary nail at another hospital, but reported continued pain in her right femur. While traveling abroad in October 2008, the patient heard a pop while walking up stairs and fell, sustaining a left proximal femoral shaft fracture. This fracture was treated with an intramedullary nail at a hospital in mainland China. She was instructed to bear weight as tolerated and told that her fracture had been transverse in nature. Three weeks after nail placement, the patient fell while walking at home and had increased pain in her left femur.

She presented to the authors’ institution reporting continued bilateral femur pain and 2 additional accidental falls that increased her left femur pain. She had been on alendronate for 4.5 years prior to her fractures. She was taking multiple other medications, none that had negative effects on bone metabolism and fracture healing. She reported a 4- to 6-week history of groin and femur pain leading up to her first fracture.

Radiographs of her femurs revealed transverse fractures with cortical beaking. The right femur fracture was not healed, but an intramedullary nail was in place. The left femur had an intramedullary nail in place with the proximal locking screw broken (Figure 1); the fracture had not healed as supported by radiographs and computed tomography (CT) scans, and significant shortening had occurred. She was referred to an endocrinologist for an aggressive metabolic workup that came back negative for all metabolic bone diseases. T scores were not available. The patient discontinued the alendronate.

Due to the >3 cm of shortening, the patient underwent a staged procedure in July 2009. The intramedullary nail was removed, and an Ilizarov frame (Smith & Nephew, Memphis, Tennessee) was placed. After achieving adequate length, open reduction and internal fixation with large combination curved periprosthetic fracture plate (Synthes USA, Paoli, Pennsylvania) was performed. Careful attention to detail ensured that interfragmentary compression was achieved across the nonunion site. A mixture of autogenous bone from the previously resected hypertrophic callus, Allo Matrix demineralized bone matrix (Wright Medical Technology, Arlington, Tennessee), and a vial of bone morphogenic protein 7 bone graft material (OP-1; Stryker Biotech, Kalamazoo, Michigan) were used to produce a bone graft composite, which was placed to fully cover the nonunion defect. The Ilizarov frame was removed.

The patient was nonweight bearing on discharge. She was advanced to partial weight bearing 7 weeks postoperatively. Her latest radiographs demonstrated a healed left femur fracture (Figure 2). The plate and screws were in place, and no signs of hardware failure existed. Clinically, she was pain free at latest follow-up and did not return to the authors’ institution after 10-month follow-up. Her right femur nonunion healed after discontinuing alendronate and required no further intervention.

**Patient 2**

A 44-year-old, nonsmoking woman presented in August 2009 for nonunion of the left proximal femur. While participating in rehabilitation for right knee...
issues in February 2009, the patient sustained a subtrochanteric stress fracture of the left hip, which was observed by the treating clinician (J.T.W.). In March 2009, she completely fractured through the stress fracture after a fall. This was a classic bisphosphonate transverse fracture in the subtrochanteric region of the femur with cortical beaking. The fracture was stabilized with a short cephalomedullary nail (Gamma; Stryker, Kalamazoo, Michigan) (Figure 3). However, the patient reported continued pain in the left hip that did not subside over the next few months. Computed tomography scan revealed atrophic nonunion of the left subtrochanteric femur in July 2009. The patient was referred to the authors’ institution.

At presentation, she reported pain and some left hip abductor weakness. In addition, she reported right knee pain from gait alterations. A partial list of her medications included gabapentin, ranitidine, calcium plus vitamin D, and risedronate. She had been taking 35 mg of risedronate weekly for the past 5 years. She had undergone a total hysterectomy at age 27 years, making her postmenopausal for >10 years before beginning treatment with a bisphosphonate.

The patient was referred to an endocrinologist to undergo an extensive workup for metabolic bone disease. The workup was negative, and she was taken off of risedronate. T scores were not available. Radiographs showed an atrophic nonunion and progressive varus deformity.

The patient underwent revision of the fixation for her nonunion in November 2009. The cephalomedullary nail was removed, and the defect from the screw was filled with Pro-Dense demineralized bone matrix composite graft (Wright Medical Technology). Compression across the fracture site was achieved with a proximal 12-hole locking plate from the Peri-Loc system (Smith & Nephew, London, United Kingdom). Iliac crest bone marrow was harvested and mixed with AlloMatrix de- mineralized bone matrix (Wright Medical Technology) and bone morphogenic protein 7 bone graft material (OP-1; Stryker Biotech) to make a composite bone graft that was placed along the nonunion site.

No complications occurred following revision. The patient was nonweight bearing on discharge and was advanced to partial weight bearing 1 month postoperatively. At 1-year follow-up, radiographs showed a well-healed subtrochanteric femur fracture with abundant callus formation. Her plate and screws were in place, and no signs of hardware failure existed (Figure 4). Distally, the patient had a lucent line, and she reported no distal left femur pain. The authors recommended using a cane, undergoing a bone scan, and discussing alternative osteoporotic medications with her endocrinologist if the pain did not subside in the following 2 to 3 weeks. She did not return to the authors’ institution after 1-year follow-up.

**Discussion**

Bisphosphonates are a widely prescribed class of drugs used to prevent and treat the loss of bone mass. Bisphosphonates primarily inhibit the activity of osteoclasts and induce their apoptosis, effectively inhibiting bone resorption.\(^3\,5\,8\,13\)

This class of drugs was first reported as a potential treatment for postmenopausal osteoporosis in 1976 and is now used extensively for this purpose.\(^13\) Bisphosphonates have been well studied and proven effective in clinical trials to decrease the occurrence of fractures and increase bone mass in postmenopausal women.\(^3\,5\,6\,8\,13\,15\) Alendronate and risedronate are 2 drugs of this class developed in the 1990s that are prescribed extensively for the treatment of
postmenopausal osteoporosis and were used in the current patients. Common side effects of the drugs include upset stomach and esophageal problems. Osteonecrosis of the jaw and atrial fibrillation have also been reported as adverse events.

Odvina et al described 9 cases of atraumatic nonspinal fractures in patients on long-term bisphosphonate therapy. This included the first reports of atypical femoral fractures in the literature for this group of patients, with 5 cases reported. Several reports have been published since then describing this atypical fracture pattern in the femoral shaft or subtrochanteric femur. Capeci and Tejwani reported 7 patients who sustained bilateral bisphosphonate fractures similar to patient 1 in the current article, and additional recent reports suggest that these fractures tend to be bilateral. This literature collectively established that radiographic findings of simple transverse or oblique fracture type, cortical thickening, and medial beaking were unique to bisphosphonate fractures. They also helped distinguish a pattern of presentation for these cases where a woman on bisphosphonates presents with prodromal pain or a femoral stress fracture and subsequently sustains a fracture after a low-energy mechanism.

Recently, Shane et al published the findings of the Task Force of the American Society for Bone and Mineral Research that defined the atypical femoral fracture that can occur after bisphosphonates. Major criteria are the location between the lesser trochanter and supracondylar flare, association with minimal or no trauma, transverse or short oblique configuration, lack of comminution, and a medial spike in complete fractures. Additional minor features relevant to the current patients include prodromal symptoms, increased cortical thickness, the use of pharmaceutical agents, including bisphosphonates, and delayed healing. This pattern is consistent with the radiographic and clinical findings of the current patients.

After these reports were published and gained attention in the literature, Black et al performed a secondary analysis of randomized bisphosphonate trials that showed the relative risk for atypical femoral fractures from long-term bisphosphonate use to be low. They recommended that bisphosphonates should still be used in the treatment of osteoporosis. In addition, the Food and Drug Administration published a safety update in 2010 that recognized the existence of bisphosphonate fractures and had the risk added to drug labels, but recommended no changes in treatment patterns. They also acknowledged that the optimal length of treatment is not known, which suggests that atypical bisphosphonate fractures will continue to appear in clinical practice.

Most cases of femoral fracture after bisphosphonate use reported in the literature are fixed with intramedullary nailing. However, no large series in the literature has focused on determining an optimal treatment for bisphosphonate fractures. The current recommendation in the literature is to treat bisphosphonate fractures with an intramedullary nail and partial to full weight bearing postoperatively. Some suggest prophylactic rod placement when a patient on long-term bisphosphonate therapy is diagnosed with a stress fracture.

In the current cases, patients with a history of long-term bisphosphonate use had been previously treated for this atypical femoral fracture with an intramedullary nail. They displayed classic findings of bisphosphonate fractures reported in the literature, including the subtrochanteric location, presentation after minimal trauma, transverse fracture, no comminution, and cortical beaking. Patient 1 sustained bilateral sequential femur fractures during separate falls after a prodrome of groin and femur pain. Patient 2 fractured through a femoral stress fracture after a fall. Both patients presented with pain and atrophic nonunion of their fractures. The patients discontinued bisphosphonate therapy and were treated with bone grafting and compression plating. After this treatment, both patients progressed to fracture healing.

In the patient with bilateral fractures, 1 nonunion healed after discontinuing alendronate without surgical intervention. Reports have noted that the physiologic effects of alendronate continue for at least 5 years after discontinuing use, which is consistent with the fact that alendronate is incorporated into bone matrix and has a long biologic half-life. Other case reports have suggested that bisphosphonate withdrawal enables fracture healing. In 1 report, cortical thickening indicative of a stress fracture regressed after discontinuing alendronate. In addition, Odvina et al reported that 2 of 5 patients with a femoral fracture progressed to fracture healing after the cessation of alendronate. As a whole, 5 of the 9 nonvertebral fractures reported by Odvina et al healed after stopping alendronate. In addition, the choice of a short cephalomedullary Gamma nail may have been a poor decision in this case. In a recent study, Norris et al reported that Gamma nails have high incidences of periprosthetic fractures compared with other short and long nails.

The treatment of these challenging fractures is two-fold. The underlying etiology is from the decreased bone resorption, leading to significant decreases in bone turnover attributable to the bisphosphonates after long-term use. Fractures occur in this setting of altered bone turnover. Healing has been demonstrated with cessation of the medication. However, fracture healing requires consideration of the biology of why it does not heal (the bisphosphonates) and solving the mechanical problem of an intramedullary nail in a fracture that does not have the same capacity to heal. Perhaps initial treatment of these fractures should involve compression plating to obtain bone-on-bone contact and promote healing. When the patients treated with an intramedullary nail failed to heal, they were diagnosed with atrophic nonunion. Therefore, the authors addressed the biologic failure with bone.
grafting and bisphosphonate cessation and addressed the mechanical failure with compression plating.

CONCLUSION

Bisphosphonates are a popular and established treatment for osteoporosis. However, too much of a decrease in bone resorption may lead to long-term disorders of bone metabolism, including postmenopausal osteoporosis. Insufficiency fractures after long-term bisphosphonate use may be difficult to heal. These fractures should be treated similarly to atrophic nonunion, with consideration for bone grafting and compression plating.

REFERENCES


