Bisphosphonates are one of the most common classes of medications prescribed for osteoporosis. Femoral fractures associated with bisphosphonate use are increasingly being reported in the literature. Orthopedic surgeons should be aware of this potential association and related implications for patient treatment. Bisphosphonate-associated fractures are characteristically simple, transverse with beaking, and subtrochanteric. Diagnosis is based on a careful history, physical examination, and focused imaging. In the setting of either a complete or partial fracture, it is recommended that bisphosphonate therapy be halted and calcium and vitamin D brought into the therapeutic range. Orthopedic management of the completed fracture preferably uses a locked intramedullary nail. The recommendations for incomplete fractures are unresolved. [Orthopedics. 2016; 39(6):e1036-e1040.]

**abstract**

Bisphosphonates are widely used for the prevention of osteoporosis-associated fractures. Femoral fractures associated with bisphosphonate use are increasingly being reported in the literature. Orthopedic surgeons should be aware of this potential association and related implications for patient treatment. Bisphosphonate-associated fractures are characteristically simple, transverse with beaking, and subtrochanteric. Diagnosis is based on a careful history, physical examination, and focused imaging. In the setting of either a complete or partial fracture, it is recommended that bisphosphonate therapy be halted and calcium and vitamin D brought into the therapeutic range. Orthopedic management of the completed fracture preferably uses a locked intramedullary nail. The recommendations for incomplete fractures are unresolved. [Orthopedics. 2016; 39(6):e1036-e1040.]

**Pharmacology of Bisphosphonates**

There are 2 categories of bisphosphonates: simple and aminobisphosphonates (Figure 1). Aminobisphosphonates are more potent than simple bisphosphonates in inhibiting osteoclastic resorption of bone. These 2 classes of bisphosphonates also affect osteoclastic resorption of bone in different ways. Simple bisphosphonates act by being metabolized into nonhydrolyzable adenosine triphosphate analogues. These metabolites accumulate within osteoclasts, inhibiting cellular metabolism, leading to apoptosis and cell death. Aminobisphosphonates appear to act primarily by disrupting the mevalonate biosynthetic pathway and inhibiting protein prenylation, which causes loss of the ruffled border and results in apoptosis (Figure 2). The primary target appears to be farnesy1 pyrophosphate synthase.

**Bisphosphonate Use and Femoral Fractures**

Recent case series have implicated bisphosphonate therapy, specifically alendronate, with low-energy fractures of the subtrochanteric region of the femur. The earliest report of fractures associated with alendronate use was by Odvina et al in 2005. They reported a series of 9 spontaneous fractures of the pelvis, femur, and sacrum.

More recent series focused specifically on fractures of the femoral shaft, particularly in the subtrochanteric region. Goh et al reported a series of patients with subtrochanteric fractures after long-term alendronate therapy. They performed a ret-

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Prospective review of patients with subtrochanteric fracture after low-energy trauma and identified 9 women on alendronate therapy for a mean of 4.2 years who had sustained a subtrochanteric fracture following low-energy trauma. The majority of the fractures were classified as AO type A, compared with women who had sustained a subtrochanteric fracture but were not on long-term alendronate therapy. On radiographs, there was a thickening in the lateral femoral cortex in 6 patients, with bilateral cortical thickening in 3 patients.

In another retrospective review, Kwek et al identified 17 patients who sustained subtrochanteric fractures following low-energy trauma. The mean duration of treatment was 4.4 years with alendronate, with 1 patient taking risedronate for 6 years after 4 years of alendronate therapy. As with the previous study, all but one of the fractures were classified as AO type A. Interestingly, there was evidence of stress reactions in the subtrochanteric region after initiation of alendronate therapy on serial radiographs. These stress reactions subsequently progressed into complete fractures in the same position.

Bisphosphonates cause a high level of collagen cross-linking, reducing the toughness of bone. The brittle bone is more susceptible to microdamage and stress fractures. Because the subtrochanteric region of the femur is subjected to large compressive and tensile forces, it is more susceptible to fractures. Fractures associated with bisphosphonate use demonstrate dependable characteristic radiographic appearance, including focal lateral cortical thickening or transverse fracture line. These characteristics can be used to differentiate atypical fractures from osteoporotic fractures.

Neviaser et al performed a retrospective review of low-energy subtrochanteric and midshaft femoral fractures. They identified 70 patients, 25 of whom were being treated with alendronate for a mean duration of 6.2 years. Twenty of the 70 fractures were simple transverse or short oblique pattern in areas of thickened cortices with unicortical beak. Nineteen of the patients were treated with alendronate, and 1 was not treated. Alendronate use was a significantly associated with having the fracture pattern (odds ratio [OR], 139.33; \( P < .0001 \)).

In a follow-up retrospective case-control study, Lenart et al identified 41 patients with low-energy subtrochanteric and femoral fractures and 82 patients with low-energy intertrochanteric/femoral neck fractures as controls. Fifteen of the 41 patients with subtrochanteric/femoral fractures had a history of bisphosphonate use, compared with 9 of the 82 intertrochanteric/femoral neck controls (OR, 4.4; \( P = .002 \)). The classic simple transverse or oblique fracture with beaking of the cortex was observed in 10 of the 41 subtrochanteric/shaft fractures. This was highly associated with bisphosphonate use because 10 of the 15 subtrochanteric/shaft cases who were on a bisphosphonate were identified to have this pattern (OR, 15.33; \( P < .001 \)). Only 3 of the 26 subtrochanteric/shaft cases who were not on bisphosphonates were found to have the simple with thick cortices pattern. This was the first study to elucidate the effect of the duration of bisphosphonate use on the fracture pattern. They found the mean duration of use to be 7.3±1.8 years in the subtrochanteric/shaft cases with the fracture pattern, compared with 2.8±1.3 years in those without the pattern (\( P < .001 \)), thus suggesting that prolonged bisphosphonate use is associated with low-energy subtrochanteric/shaft fractures.

In a retrospective study, Schilcher and Aspenberg identified more than 3000
patients on bisphosphonate therapy. They found 8 patients with stress fractures of the shaft. Mean duration of treatment was 5.8 years. Two patients had bilateral fractures.

In one of the largest reviews of its kind, Abrahamsen et al used a cross-sectional study of 11,944 patients in the Danish National Hospital Discharge Register with low-energy subtrochanteric, diaphyseal femoral, and hip fractures. The patients were older than 60 years and treated with alendronate for at least 6 months. In this study, 7% of patients with atypical fractures were found to be alendronate exposed, and the same was found for typical hip fractures. The subtrochanteric and diaphyseal fractures displayed an age, trauma mechanism, and sex pattern similar to that of classic osteoporosis-related hip fractures. They also conducted a register-based matched-cohort analysis of femoral fracture patients to test the hypothesis that the increase in risk of these atypical femoral fractures in patients treated with alendronate exceeded the increase in risk of atypical femoral fracture related to osteoporosis. All patients who began alendronate treatment and stayed on therapy for at least 6 months (n=5187), as well as 2 matched control subjects, were used (n=10,374). The hazard ratio for subtrochanteric or diaphyseal fractures with alendronate was 1.46 (range, 0.91-2.35; P=.12) compared with 1.45 (1.21-1.74; P<.001) for hip fractures after adjusting for comorbidity and comediations. The results show that patients with these atypical femoral fractures were no more likely to be on alendronate treatment than patients with hip fractures, but oral glucocorticoid use was reported to be more prevalent. They concluded that the subtrochanteric fractures were a result of osteoporosis rather than a consequence of long-term bisphosphonate use. Capeci and Tejwani reported 7 patients who had sustained bilateral subtrochanteric or diaphyseal femoral fractures while on alendronate therapy for greater than 5 years. All 7 patients were women and had been on alendronate therapy for an average of 8.6 years. Radiographically, all fractures demonstrated a medial fracture spike and cortical thickening. All subtrochanteric fractures were fixed with antegrade interlocked femoral nailing with reaming and healed uneventfully at 4 months. Alendronate therapy was discontinued at the time of the second fracture fixation in the patients with sequential fractures and at the time of injury in the 1 patient with simultaneous fractures. The patient with bilateral simultaneous diaphyseal fractures was treated with simultaneous retrograde interlocked femoral nailing with reaming and had radiographic evidence of union of both fractures at 3 months.

Black et al examined the incidence of fracture of the subtrochanteric or diaphyseal femur in 3 large randomized trials (ie, Fracture Intervention Trial [FIT], FIT Long-Term Extension [FLEX], and HORIZON Pivotal Fracture Trial). Two of these trials (FIT, FLEX) studied the use of oral alendronate, and the other trial (HORIZON) studied zoledronic acid infusions. The trials used similar protocol-specific procedures for original collection and classification of fractures. The authors reviewed 284 records for hip or femoral fractures among 14,195 women across the trials. A total of 12 fractures in 10 patients were identified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient-years. As compared with placebo, the relative risk was 1.03 (95% confidence interval [CI], 0.06-16.46) for alendronate use in the FIT trial, 1.33 (95% CI, 0.12-14.67) in the FLEX trial, and 1.50 (95% CI, 0.25-9.00) for zoledronic acid use in the HORIZON trial. The authors concluded that the occurrence of subtrochanteric or diaphyseal femoral fractures was rare and that no significant increase in risk is associated with bisphosphonate use. This study was limited because the event was rare, and future case-control studies were recommended.

According to a 2010 Task Force report, an atypical femoral fracture was defined as an atraumatic or low-trauma fracture located in the subtrochanteric region or the femoral shaft. High-trauma fractures, femoral neck fractures, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors, and periprosthetic fractures were excluded from the diagnosis of atypical femoral fractures. Other major features of atypical femoral fractures included transverse or short oblique configuration and noncommninated incomplete fractures involving only the lateral cortex (whereas complete fractures extend through both cortices and may have a medial spike). Minor features include localized periosteal reaction or beaking of the lateral cortex, generalized cortical thickening of the femoral shaft, a history of prodromal pain, bilateral fractures and symptoms, and delayed healing in association with certain medication and medical conditions. All major features are needed to define a fracture as atypical, whereas minor features may not be present in some cases. Recently, the American Society for Bone and Mineral Research published an updated version of a previous 2013 report that included revised criteria for atypical femoral fractures. According to the new definition, 4 of the 5 major criteria (vs all the criteria) should be present to define an atypical femoral fracture (Table).

### Diagnosis and Management of Atypical Femoral Fractures

A large segment of patients on long-term bisphosphonates who sustain a low-energy femoral fracture report pain or a dull ache for weeks or months in the affected limb prior to the time of fracture. The pain is localized to the anterolateral thigh or groin. There is no neurovascular compromise. The fracture is usually preceded by a low-energy impact such as twisting or falling from a standing height or lower. Some patients have no reported
incidence of a fall. Patients are unable to bear weight following the fracture. Radiographs demonstrate a simple transverse fracture (Figure 3). There is usually a transverse fracture line extending from the lateral tension side of the cortex and lateral cortical thickening adjacent to the fracture. The majority of fractures are AO type A (simple, transverse), with some reported cases of AO type B (comminution in the form of a medial or lateral wedge fragment). Typically, there is a unicortical break with a diaphyseal cortical hypertrophy of the proximal femoral shaft. The usual combined cortical thickness divided by the diameter is less than 25%, but these patients have a cortical width that is over 35%. There may also be cortical thickening of the contralateral femur.

Close monitoring of patients on long-term alendronate and other bisphosphonates is necessary, especially if a stress reaction is noted. The initial component of care is to recognize the potential association of prolonged bisphosphonate treatment with subtrochanteric/proximal diaphyseal femoral stress fractures. Patients with thigh pain and long-term bisphosphonate use should initially have a radiograph obtained. If there is thickened cortex even without obvious fracture, the patient should then undergo either bone scan or magnetic resonance imaging (MRI) to rule out a stress fracture. Routine radiographs may be performed of the contralateral femur to investigate for a contralateral stress reaction after a low-energy fracture in a patient who is taking a bisphosphonate. Advanced imaging, including bone scan or MRI, can be considered if clinical suspicion is elevated with normal radiographs of the contralateral femur.

In the setting of either a complete or partial fracture, bisphosphonate therapy should be halted and calcium and vitamin D brought into therapeutic range (9.5 mg and 32 ng/mL, respectively). The dose of calcium, usually in the form of citrate, should be over 800 mg/d. Both vitamin D2 and vitamin D3 are effective, but the latter is more physiological. Dosing depends upon the 25(OH) vitamin D level: less than 20 ng/mL requires 5000 units vitamin D3

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Major</td>
<td>The fracture is associated without trauma or minimal trauma, as in a fall from a standing height or lower</td>
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<td></td>
<td>The fracture is noncomminuted or minimally comminuted</td>
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<td></td>
<td>Complete fractures extend through both cortices and may be associated with a medial spike, whereas incomplete fractures involve only the lateral cortex</td>
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<td></td>
<td>The fracture line originates at the lateral cortex and is substantially transverse in orientation but may be short oblique as it progresses medially across the femur</td>
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<td></td>
<td>Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (flaring or beaking)</td>
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<tr>
<td>Minor</td>
<td>Unilateral or bilateral prodromal symptoms, such as dull or aching pain in the groin or thigh</td>
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<tr>
<td></td>
<td>Generalized increase in cortical thickness of the femoral diaphysis</td>
</tr>
<tr>
<td></td>
<td>Delayed fracture healing</td>
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<tr>
<td></td>
<td>Bilateral incomplete or complete femoral diaphyseal fractures</td>
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<tr>
<td></td>
<td>Localized periosteal reaction of the lateral cortex</td>
</tr>
<tr>
<td></td>
<td>Prodromal symptoms, such as a dull or aching pain in the groin or thigh</td>
</tr>
<tr>
<td></td>
<td>Comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatemia)</td>
</tr>
<tr>
<td></td>
<td>Use of pharmaceutical agents (eg, bisphosphonates, glucocorticosteroids, proton pump inhibitors)</td>
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</tbody>
</table>

Figure 3: The majority of fractures associated with bisphosphonate use are AO type A (simple, transverse) fractures (arrow).
per day; 20 to 32 ng/mL requires 2000 units vitamin D3 per day; and greater than 32 ng/mL requires 1000 units vitamin D3 per day. Strongly consider the use of an anabolic agent such as parathyroid hormone (PTH) (1-34) to reverse the bone metabolism. Parathyroid hormone (1-34) increases both bone formation and resorption and is highly effective in the treatment of osteoporosis. Parathyroid hormone increases cortical and trabecular bone volume as compared with no change with bisphosphonates. Animal fractures studies demonstrate that PTH (1-34) increased the rate of union and the biomechanical character of the callus. Currently there are no randomized clinical trials of PTH in the treatment of diaphyseal fractures.

Orthopedic management of the completed fracture preferably uses a locked intramedullary nail. Plates, especially locking plates, preclude enchondral repair and may have a higher failure rate. Due to the narrowed canal and brittle nature of the bone, intramedullary reaming is necessary. Overreaming may be needed (2-3 mm) to match the patient’s femoral arc with that of the intramedullary nail. The nail uses endochondral repair, in which remodeling has a limited role. Conversely, if a rigid locking plate is used, repair goes predominantly through remodeling, and the previously encased bisphosphonates inhibit this process. Both methods have been successful; however, intramedullary nailing appears to have a more predictable success rate.

The recommendations for the incomplete fractures are unresolved. Due to the lack of evidence, the management of bisphosphonate-associated incomplete fractures remains an orthopedic dilemma. In addition to stopping bisphosphonates and supplementing calcium and vitamin D, an anabolic agent such as teriparatide may promote the healing of these fractures. To date, no studies have investigated the role of teriparatide in this context. Painful fracture treated with nonweight bearing and resorption of the bisphosphonate may progress to complete fracture within several months. Some surgeons recommend prophylactic full-length intramedullary nailing in this setting. 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. Evaluation of the contralateral limb in these patients cannot be overemphasized, regardless of symptoms. For patients with complete or incomplete stress fractures, antiresorptive drugs should be discontinued, vitamin D and calcium should be initiated, and teriparatide therapy may be beneficial in terms of time to recovery.

**Conclusion**

Bisphosphonate-associated atypical femoral fractures are mostly simple transverse or short oblique and classified as AO type A. In the setting of either a complete or partial fracture, bisphosphonate use should be halted and calcium and vitamin D brought into therapeutic range. Orthopedic management of the completed fracture preferably uses a locked intramedullary nail. The recommendations for the incomplete fractures are unresolved. Painful fracture treated with nonweight bearing and cessation of bisphosphonate alone have progressed to complete fracture within several months. Additional studies, including prospective trials, are needed to better define the pathophysiology and treatment.

**References**


