The purpose of this study was to elaborate on the association between the use of bisphosphonates and low-energy femoral shaft fractures. A retrospective review was performed between January 2000 and January 2010 to identify patients older than 65 years who sustained femoral shaft diaphyseal fractures (Orthopaedic Trauma Association classification 32 A [extra-articular], B [partial articular/unicondylar], or C [complete articular/bicondylar]) using ICD-9 code 821.01. After exclusion criteria were applied, 77 patients remained for analysis. A total of 66 patients had no history of bisphosphonate therapy, and 11 patients had received bisphosphonate therapy for >2 years prior to admission. All 11 patients in the bisphosphonate group had sustained a low-energy fall from a standing height or lower. In 9 of 11 (82%) patients in the bisphosphonate group, radiographs resembled transverse shaft fractures with lateral cortical beaking that have been observed in patients on chronic bisphosphonate therapy.

Our series echoes the findings of other authors, who found that bisphosphonate use is associated with lateral cortical beaking and low-energy, transverse fractures of the femoral shaft. Further research is needed to determine if specific medications and length of treatment are important risk factors.
Osteoporosis is defined by the World Health Organization as a reduction in bone mass 2.5 standard deviations below the mean for a healthy young adult.\(^1,2\) It manifests by deterioration of bone microarchitecture, resulting in increased bone fragility and fracture risk.\(^1\) Osteoporosis affects >28 million Americans and 75 million people worldwide.\(^2\) It is the most common underlying etiology of hip and vertebral fractures in elderly patients, resulting in significant morbidity and mortality.\(^1\) The cost of treating osteoporotic fractures in the United States was estimated at $22.5 billion in 2004 and is expected to increase sharply by 2025.\(^3\) Because of the immense resources required for treatment and the sheer magnitude of the disease, medications were developed to increase bone density and public health initiatives were undertaken to reduce the incidence of falls.

Bisphosphonates have become the most clinically important class of antiresorptive medications used to treat osteoporosis.\(^2\) The US Food and Drug Administration approved alendronate, risedronate, ibandronate, and zoledronic acid for use in the treatment of osteoporosis.\(^3\) Bisphosphonates inhibit the formation of GTPase, leading to loss of osteoclast regulation, including loss of control of cell morphology, disruption of integrin signaling, altered membrane-protein trafficking, loss of membrane ruffling and cytoskeleton disruption, and induction of apoptosis.\(^2,3\)

Several randomized, controlled trials have demonstrated the ability of bisphosphonates to increase bone mineral density and decrease the incidence of hip and vertebral fractures.\(^4-6\) Although bisphosphonate therapy has been successful in reducing the number of hip and vertebral fractures, a troubling association with low-energy transverse femur fractures exists in this population.\(^7,14\) The purpose of this study was to further elaborate on the association between the chronic use of bisphosphonates and low-energy femoral shaft fractures at our institution.

**MATERIALS AND METHODS**

After obtaining Institutional Review Board approval, a retrospective review was performed of all records between January 2000 and January 2010 to identify patients older than 65 years who sustained a femoral shaft diaphyseal fracture (Orthopaedic Trauma Association [OTA] classification 32 A [extra-articular], B [partial articular/unicondylar], or C [complete articular/bicondylar]) using ICD-9 code 821.01. Admission history and physical examination, mechanism of injury, radiographs, demographic data, and medication lists were reviewed for these patients. Patients with no history of bisphosphonate use were excluded, as were patients with periprosthetic and pathologic fractures. Low-energy fractures were identified as those caused by a fall from standing height or lower.

**RESULTS**

Ninety-nine patients (77 women, 12 men) were identified from the medical record search. Twenty patients with periprosthetic fractures and 2 patients with distal femur fractures (33A-1 [simple transverse]) were excluded after review of radiographs, leaving 77 patients for review. Sixty-six patients (59 women, 7 men; average age, 78 years [range, 66-100 years]), had no history of bisphosphonate therapy. Eleven patients (14% of remaining cohort) (10 women, 1 man; average age, 75.5 years [range, 67-94 years]) had received bisphosphonate therapy for >2 years prior to injury. The exact length of treatment with bisphosphonates was unavailable due to lack of detailed outpatient records. Alendronate was used in 7 patients, risedronate in 3 patients, and ibandronate in 1 patient. No patients in this study were treated with zolendronic acid.

All 11 patients in the bisphosphonate group had sustained a low-energy fall from a standing height or lower. In the nonbisphosphonate group, 63 patients had a fall from standing and 3 were involved in motor vehicle accidents. In 9 (82%) patients in the bisphosphonate group, the radiographs resembled simple, transverse shaft fractures with lateral cortical thickening that have been observed in patients on chronic bisphosphonate therapy (Figure). None of the radiographs of patients in the nonbisphosphonate group demonstrated lateral cortical thickening. The fracture patterns in the nonbisphosphonate group varied; 3 of 66 (5%) were simple and transverse in nature. The remaining fractures in the nonbisphosphonate group were either comminuted (18/66 [27%]) or spiral (45/66 [68%]).

**DISCUSSION**

Alendronate, approved for use in 1995, was the first bisphosphonate available in the United States for the treatment of osteoporosis. Bisphosphonate use is now widespread and has become the standard of care in the treatment of osteoporosis. Now that patients have been on bisphosphonate therapy for many years, the orthopedic and medical literature has begun to identify an association between long-term
biphosphonate use and transverse, low-energy femoral fractures. These fragility fractures have been attributed to the inhibition of osteoclasts and, therefore, the inhibition of bone remodeling. Radiographs of the affected femur often demonstrate cortical beaking/thickening at the fracture site, representing failure to effectively remodel microdamage. Our series of patients adds to the growing body of literature highlighting the association between bisphosphonate use and low-energy femur fractures with associated lateral cortical thickening on radiographs.

Goh et al9 reported a series of 13 patients who sustained low-energy subtrochanteric fractures. Nine of the 13 patients had been treated with bisphosphonates for an average of 4.2 years. The authors noted cortical hypertrophy on the tension side of the subtrochanteric region of the femur on radiographs. Neviaser et al13 reported a series of low-energy femur fractures in patients taking alendronate. Seventy-six percent of the patients on alendronate demonstrated a simple, transverse fracture with a unicortical beak in an area of cortical hypertrophy; however, this fracture pattern was seen in 1 patient who was not being treated with alendronate. Capeci and Tejwani7 reported on a series of 7 patients with bilateral diaphyseal or subtrochanteric femur fractures. All patients underwent bisphosphonate therapy for >5 years, and all demonstrated the expected radiographic findings of a medial spike and lateral cortical thickening.

A weakness of the current study is the inability to determine the exact length of bisphosphonate therapy in our case series. Review of medical records was able to demonstrate that all patients included in the series had been on bisphosphonate therapy for at least 2 years, but the exact year in which the therapy was initiated was unable to be obtained in all patients. Although other series have shown a mean duration of therapy of 4.2 to 8.6 years,7,9 our current series has shown that patients are at risk for low-energy transverse femur fractures after only 2 years of continuous bisphosphonate use. However, the relatively small number of patients in this series does not allow us to make any conclusions in regard to specific bisphosphonates and their association with this fracture pattern.

Although bisphosphonate therapy has been shown to decrease the incidence of lumbar and femoral neck fractures, our series corroborates the worrisome evidence found by other authors that bisphosphonate use is associated with low-energy, transverse fractures of the femoral shaft. In a patient population at risk for low-energy fractures, prolonged pharmacologic therapy with bisphosphonates may place these patients at an additional risk for fractures of the diaphyseal femur. Future research should determine if patients on chronic bisphosphonate therapy should undergo screening radiographs for signs of impending femur fracture. More research is also needed to determine if 1 bisphosphonate has a higher rate of low-energy femur fracture than others.

REFERENCES