

# Low-Energy Femoral Shaft Fractures Associated With Alendronate Use

Andrew S. Neviaser, MD, Joseph M. Lane, MD, Brett A. Lenart, BS,  
Folorunsho Edobor-Osula, MD, MPH, and Dean G. Lorch, MD

**Objective:** Increasing evidence suggests long-term alendronate use may overly suppress bone metabolism, limiting repair of microdamage and creating risk for insufficiency fractures. The purpose of this study is to demonstrate an association between alendronate use and a specific pattern of low-energy femoral shaft fracture.

**Design, Setting, and Patients:** A retrospective review was performed of patients with femoral shaft fractures admitted to a Level 1 trauma center between January 2002 and March 2007. Seventy low-energy fractures were identified.

**Main Outcome Measure:** The medical records were reviewed, and the incidence and duration of alendronate use were recorded. The incidence of a specific femoral shaft fracture in those patients taking alendronate compared with those not being treated was determined.

**Results:** There were 59 females and 11 males. The average age was 74.7 years. Twenty-five (36%) were being treated with alendronate. None of the patients had used or were using other bisphosphonates. Nineteen (76%) of these 25 patients demonstrated a simple, transverse fracture with a unicortical break in an area of cortical hypertrophy. This fracture pattern was seen in only 1 patient (2%) not being treated with alendronate. Alendronate use was a significant risk factor for the fracture pattern (odds ratio [OR] 139.33, 95% CI [19.0–939.4],  $P < 0.0001$ ). This pattern was 98% specific to alendronate users. The average duration of alendronate use in those with the pattern was significantly longer than those who did not exhibit the pattern but were taking alendronate, 6.9 years versus 2.5 years of use, respectively ( $P = 0.002$ ). Only 1 patient with the fracture pattern had been taking alendronate for less than 4 years.

**Conclusions:** Low-energy fractures of the femoral shaft with a simple, transverse pattern and hypertrophy of the diaphyseal cortex are associated with alendronate use. This may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair resulting from its prolonged use.

**Key Words:** alendronate, osteoporosis, insufficiency fractures, subtrochanteric fracture, femur fractures, bisphosphonates

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## INTRODUCTION

Alendronate has been widely and successfully used to treat osteoclast-mediated metabolic bone diseases, such as osteoporosis. It has been proved effective in improving all clinical measures of osteoporosis, including increasing bone-mineral density, reducing laboratory markers of bone turnover, and reducing the number of fractures in the spine and long bones.<sup>1,2</sup> Alendronate targets osteoclasts by binding to the inorganic component of bone. Bound alendronate is released during resorption and endocytosed by osteoclasts. Once inside the cell, alendronate inhibits the mevalonate pathway for cholesterol synthesis and induces osteoclast apoptosis.<sup>3</sup> Bone resorption and remodeling rates are diminished as a result of osteoclast death. The sequelae of long-term alendronate use on bone metabolism, however, remain unclear. Studies in experimental animals treated with alendronate demonstrate reduced bony repair and accumulation of microdamage, leading to reduced bone toughness.<sup>4,5</sup> Odvina and Goh have each reported on patients sustaining low-energy fractures after prolonged therapy.<sup>6,7</sup> They warn that prolonged treatment with alendronate may lead to adynamic, fragile bone. We have empirically recognized a number of patients, treated with alendronate, who have sustained fractures of the proximal femoral shaft after minimal or no trauma. These fractures are characterized by a simple, transverse pattern, beaking of the cortex on one side, and hypertrophy of the diaphyseal cortex (Fig. 1). We retrospectively reviewed all low-energy subtrochanteric and midshaft femur fractures admitted to our Level 1 trauma center in the last 5 years. We hypothesized that this specific femoral shaft fracture is associated with long-term alendronate use.

## PATIENTS AND METHODS

After approval from the internal review board, a retrospective review was undertaken of all low-energy subtrochanteric and midshaft femur fractures admitted to a Level 1 trauma center between January 2002 and March 2007. Potential patients were identified through ICD-9 codes 820.2 through 821.01, inclusive. All AO Type 32, as well as Type 31 A3, fractures that involved or extended distally to the lesser trochanter, were eligible for inclusion. Low-energy fractures were

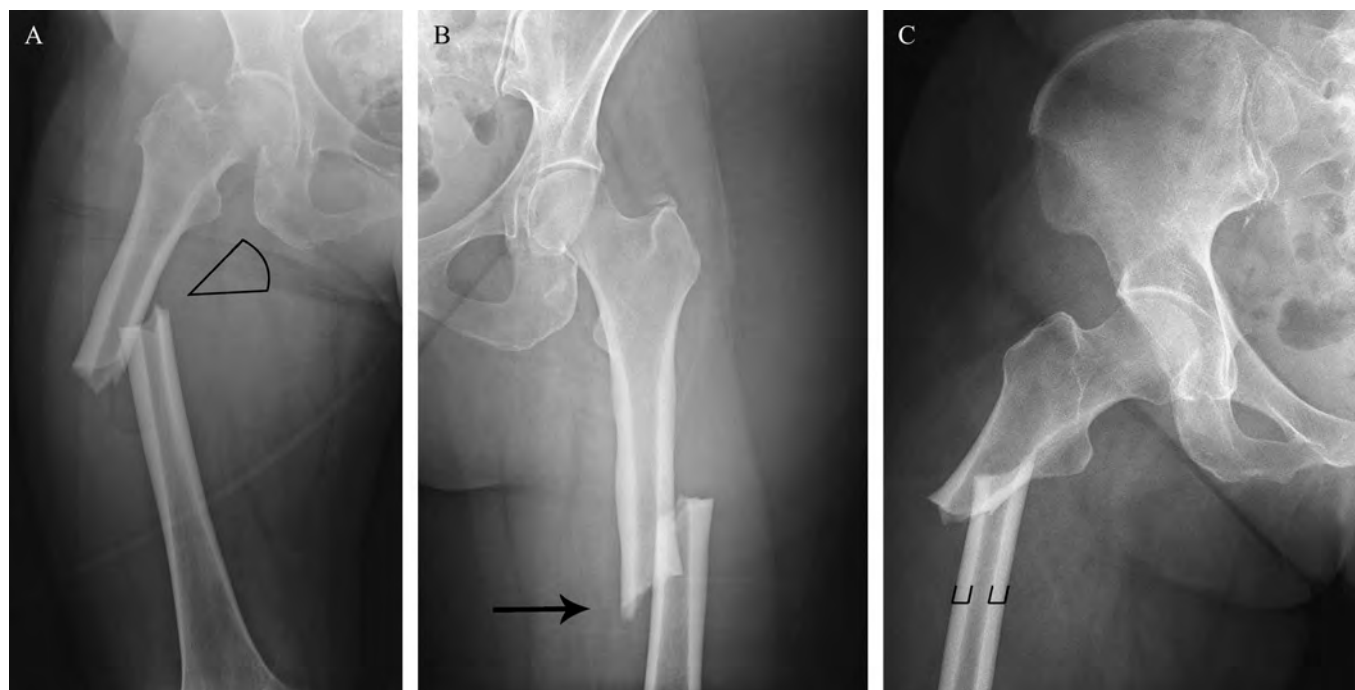
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From the Hospital for Special Surgery, New York, New York and Weill Medical College of Cornell University, New York, New York.

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Reprints: Joseph M. Lane, MD, Osteoporosis and Metabolic Bone Disease Service, 535 E. 70<sup>th</sup> Street, New York, New York, 10021 (e-mail: lanej@hss.edu).

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**FIGURE 1.** Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

defined as those caused by the equivalent to a fall from a standing height or less, as documented in the medical record. Fractures caused by higher-energy trauma (motor vehicle accidents, falls from greater heights, blunt trauma, etc) or by bone tumors, either metastatic or primary, were excluded. Fractures at or beyond the distal third of the femoral shaft (AO Type 33) and pertrochanteric (Type 31 A1–2) were also excluded. Seventy low-energy fractures below the lesser trochanter and above the distal one third of the diaphysis were identified. The medical records were reviewed, and the incidence and duration of alendronate use were recorded. Confirmation of alendronate use and duration was obtained via phone contact with patients or their primary medical doctor. Two experienced attending orthopaedic surgeons and 1 orthopaedic resident independently reviewed the injury radiographs of these patients on 2 separate occasions. Each observer was blinded to patient characteristics, including alendronate use. The reviewers were asked to identify fractures that had a simple, transverse, or short oblique pattern in areas of thickened cortices with a unicortical beak. There was no communication among reviewers. The radiographs were shown in a computer-based slide presentation to each reviewer separately. The order of the radiographs was random and changed between the 2 sessions. Fleiss's and Cohen's kappa coefficients for interobserver and intraobserver agreement, respectively, were calculated by comparing the proportion of agreement in relation to the agreement as a result of chance. Kappa values of less than 0.40 indicate poor agreement, whereas values greater than 0.81 indicate near-perfect agreement. Risk estimates for association of bisphosphonate

use and the fracture pattern were represented as odds ratios (OR) with 95% confidence intervals (CI)

## RESULTS

There were 59 females and 11 males. Baseline characteristics are described in Table 1. The average age was 74.7 years. Of the patients, 25 (36%) were being treated with alendronate. We were able to contact 15 patients and 3 primary care physicians to confirm alendronate use in 18 of the 25 patients (72%) being treated. We confirmed the duration of use in 16 of these patients (64%). All patients who were contacted confirmed the record to be accurate. None of the patients had used or were using other bisphosphonates. None of the males were being treated with alendronate.

A total of 31 patients (44%) had a diagnosis of osteoporosis. Of the 25 patients being treated with alendronate, 21 had been diagnosed with osteoporosis (84%). The 4 patients who had not been documented as having osteoporosis in the medical record did not have any other condition typically treated with alendronate. Ten patients had a diagnosis of osteoporosis but had not been treated with alendronate or any other antiresorptive medications. Breakdown of all described subgroups is summarized in Figure 2.

Fifty of the fractures were subtrochanteric, and 20 were located in the femoral shaft. Further classification is provided in Figure 3. The reviewers identified 20 patients with a simple, transverse, or short oblique pattern in areas of thickened cortices with a unicortical beak, represented in Figure 1. Nineteen of the 25 (76%) patients taking alendronate exhibited

**TABLE 1.** Baseline Characteristics for Patients With Low-Energy Femoral Shaft Fractures (Differences Between Means for Patients Receiving Alendronate Treatment, Those Receiving Alendronate With Characteristic x-ray Pattern, and Those not Receiving Alendronate Treatment Were Calculated Using the Student's *t*-test)

	Age	Race	History of Osteoporosis (%)
All	74.4	68 W, 2 A	44.3
Female	76.5	57 W, 2 A	50.8
Male	63.5	11 W	9.1
Alendronate	69.4*	23 W, 2 A	84.0
Female	69.4	23 W, 2 A	84.0
Male	—	—	—
Nonalendronate	77.1	45 W	22.2
Female	81.4	34 W	26.4
Male	63.5	11 W	9.1
Alendronate + x-ray	69.5†	17 W, 2 A	84.2
Alendronate - x-ray	69.4	6 W	83.3

W, white; A, Asian; + x-ray, patients with characteristic x-ray pattern; - x-ray, patients without characteristic x-ray pattern.

\**P* = 0.058 for age of bisphosphonate versus nonbisphosphonate.

†*P* = 0.065 for age of bisphosphonate + x-ray vs nonbisphosphonate.

this fracture pattern. One patient of the 45 not taking alendronate (2.2%) was identified as having the fracture pattern. This patient was diagnosed with multiple myeloma several years after her fracture but had no lesions on her injury radiographs. Thus, 19 of 20 patients identified as having the fracture pattern were taking alendronate (95%). Alendronate use was a significant risk factor for having the fracture pattern in question (OR 139.33, 95% CI [19.0–939.4], *P* < 0.0001). This pattern was 98% specific to alendronate users. Identification of the fracture was consistent. The interobserver kappa coefficient was 0.93. Intraobserver kappa values ranged from 0.87 to 1.0.

The duration of alendronate use was established in 16 patients and averaged 6.2 years (range 1–10 years). Ten of these patients demonstrated the fracture pattern. Six did not. Of the 6 patients who were taking alendronate but did not

exhibit the pattern, the average duration of alendronate use was 2.5 years. This was significantly shorter compared with the 10 patients who had the fracture pattern (average 6.9 years of use, *P* = 0.002). There were no differences in age, race, body mass index (BMI), or osteoporosis history between these groups or among the entire study population.

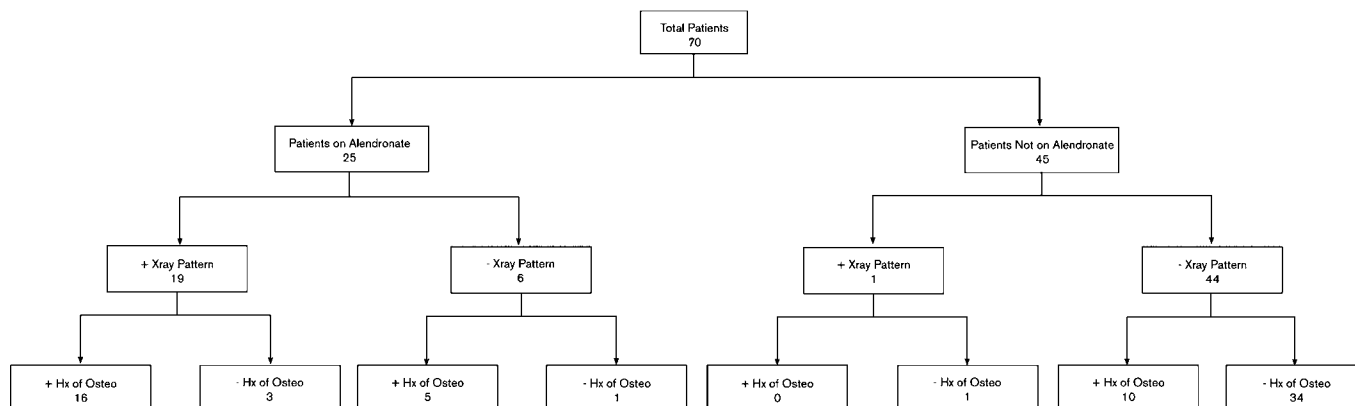
The fracture pattern was not present in the 10 untreated patients with osteoporosis. No significant difference was found in the mean BMI of those taking and those not taking alendronate. The patients taking alendronate were, on average, younger than those not taking the drug by 8.9 years, but this difference was not significant.

## DISCUSSION

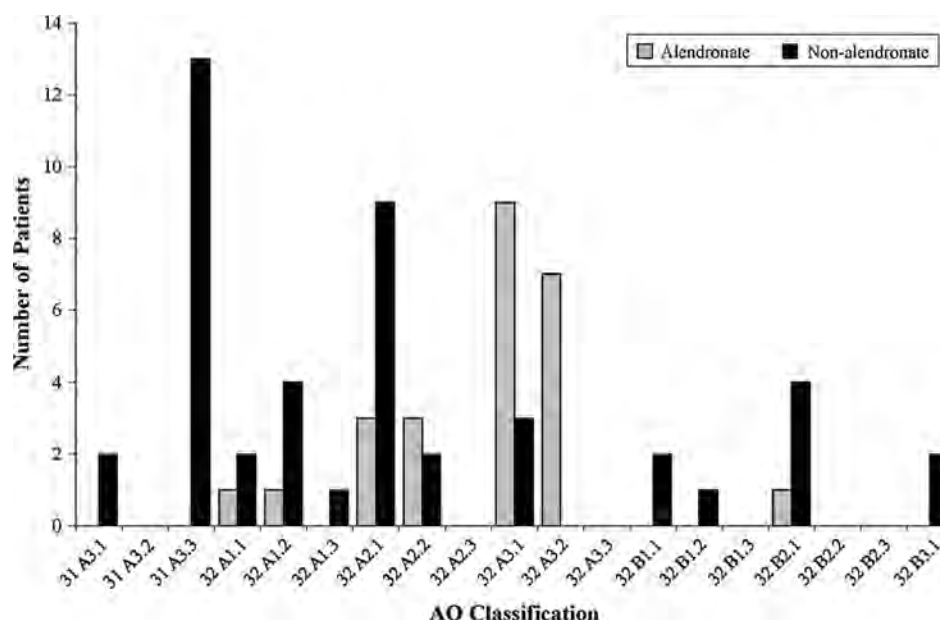
The treatment of osteoporosis remains a highly successful intervention for reducing fractures in the elderly. Alendronate was the first oral bisphosphonate available in the United States and remains the most common antiresorptive medication used in treating this disease. The Fracture Intervention Trial, a multicenter randomized control study, demonstrated that alendronate reduced the risk of clinically significant fractures by more than 50% compared to placebo.<sup>1</sup>

We identify a fracture that is specific to patients being treated with alendronate and tends to occur after use of more than 4 years. Fractures associated with alendronate were AO type 32 A3 (simple, transverse). A unicortical beak was typically present, and the diaphyseal cortex was hypertrophied. Although we have not established a causal relationship, the association is sufficiently strong to consider alendronate's effect on bony metabolism when treating these patients.

The clinical utility of recognizing this fracture is recognition of the underlying pathophysiology that led to the fracture. The proximal femoral shaft is an area subject to high stress and would not be expected to fracture from minimal trauma without underlying metabolic bone pathology, such as osteoporosis. The fracture pattern was not seen in the 11 untreated patients with osteoporosis, suggesting that osteoporosis alone is not sufficient to cause this specific failure of the femoral shaft. Further investigation is needed to



**FIGURE 2.** Subgroup breakdown of patients in the analysis. + x-ray pattern, patients with presence of the x-ray pattern; - x-ray pattern, patients without presence of the x-ray pattern; + Hx of osteo, patients with a history of osteoporosis; - Hx of osteo, patients without a history of osteoporosis.



**FIGURE 3.** Classification of femoral shaft fractures. All 70 fractures were classified based on the Muller AO classification. Gray bars represent patients taking alendronate; black bars represent patients not taking alendronate. 32A3.1 and 32A3.2 represent simple, transverse subtrochanteric and midshaft fractures, respectively. 31A3.3 represents intertrochanteric fractures that extend into the subtrochanteric region.

determine if alendronate is indeed the cause of this fracture. However, reports of insufficiency fractures in patients taking alendronate and studies in experimental animals suggest that adynamic metabolism from impaired resorption may be the underlying pathophysiology that leads to these fractures.<sup>4-9</sup>

In 2005 Odvina et al reported on 9 patients who had sustained spontaneous, nontraumatic, nonpathologic fractures while receiving prolonged alendronate therapy (longer than 3 years).<sup>7</sup> All 9 were engaged in normal activities of daily living, such as walking, standing, or turning around, at the time of fracture. Fracture sites included the pubic ramus, femoral shaft, ischium, rib, and sacrum. Six of these patients displayed either delayed healing or histomorphometric evidence of severely suppressed bone turnover. The bone surface was virtually devoid of cellular elements, bone formation rate was reduced, and matrix formation was severely impaired. The authors raised the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nontraumatic, nonpathologic fractures. Studies in experimental animals treated with alendronate have demonstrated reduced repair and accumulation of microdamage in bone, as well as impaired fracture healing.<sup>4,5,8,9</sup>

Goh et al recently reported on 13 subtrochanteric insufficiency fractures over a 10-month period, 9 of which were in patients being treated with alendronate.<sup>6</sup> Eight of the 9 fractures had a pattern similar to what we describe and were associated with the cortical hypertrophy. The patients taking alendronate were younger and more active than those not being treated. They also reported prodromal thigh pain in 5 patients.

We have expanded on this case series by demonstrating a statistically significant association between alendronate use

and this type of low-energy femur fracture. The simple transverse pattern, cortical hypertrophy, and prodrome of pain suggest that this injury may result from propagation of a stress fracture, which patients with suppressed microdamage repair are unable to heal. Minimal trauma is then required to produce a complete fracture. Optimal treatment will likely need to address the depressed bone metabolism. Further investigation is needed to validate the role of osteobiologics and anabolic osteoporosis agents in these patients, both of which would theoretically appear to be important components of treatment.

Alendronate is an appropriate and highly successful first-line therapy for postmenopausal osteoporosis. This study was done to highlight a potential consequence of long-term therapy that may not be unique to alendronate. The potential for suppression of repair exists for all bisphosphonate drugs and may only be apparent with alendronate because it has been available for the longest time and is the most widely used.

This study carries all the shortcomings of a retrospective review. Using the medical record as the gold standard for determining alendronate incidence and use, as well as fracture mechanism, holds some inherent inaccuracy. This inaccuracy was minimized by contacting those patients taking alendronate. The uniform agreement between these patients and the record demonstrates that the record is accurate.

In conclusion, we describe a fracture pattern of the femoral shaft that is specific for patients being treated with alendronate. This fracture is characterized by (1) a simple, transverse pattern; (2) beaking of the cortex on one side; (3) hypertrophied diaphyseal cortices; and (4) resulting from minimal or no trauma. These fractures may be a consequence of alendronate use and its impact on bony metabolism, although further investigation is necessary.

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