

Bisphosphonates and low-impact femoral fractures: Current evidence on alendronate-fracture risk

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Several recent medical articles have described multiple cases of unusual low-impact subtrochanteric stress fractures or completed fractures of the femur in patients who have been on the bisphosphonate alendronate for several years for osteoporosis or osteopenia. Some patients have experienced such fractures in both femurs. The fractures are often preceded by pain in the affected thigh, may have a typical x-ray appearance, and many have delayed healing. It has been hypothesized that in some patients, long-term alendronate causes oversuppression of bone turnover, resulting in bones that are brittle despite improved bone density. In patients with atypical or low-impact fractures of the femoral shaft, consider the possible connection with alendronate use. Some bone specialists now recommend stopping alendronate in most patients after 5 years.

Schneider JP. Bisphosphonates and low-impact femoral fractures: Current evidence on alendronate-fracture risk. *Geriatrics*. 2009;64(1):18-23.

Key words: atypical fracture, femoral shaft, low-impact fracture, oversuppression, subtrochanteric

Drugs discussed: alendronate, ibandronate, pamidronate, risedronate, teriparatide, zoledronic acid

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Disclosure: As she was the patient in a related 2006 *Geriatrics* case report, the author discloses that she has a personal interest in understanding the possible causative role of alendronate and atypical femoral fractures. She states that she has no financial interests in any pharmaceutical product used to treat osteoporosis.

A 66-year old, previously healthy woman developed a spontaneous stress fracture of her right foot, which eventually healed. Nine months later she took a step in her bedroom and collapsed to the floor. An x-ray revealed a nontraumatic fracture of her right femur. She underwent surgery with placement of an intramedullary rod. Her physician told her she had most likely had a stress fracture, which became a completed fracture. A bone scan done shortly after her surgery revealed a stress fracture of her left femur. Some months later she underwent prophylactic rodding of the left femur. The patient had been on alendronate for 7 years.

A 65-year woman visiting Europe stepped off the bottom step of a van and collapsed. An x-ray revealed a nontraumatic fracture of her left femur. She had been experiencing a dull ache in her left femur for some months. The patient underwent placement of an intramedullary rod. One year later she developed a dull ache in her right femur. A bone scan showed a stress fracture in the right femur. A bone specialist recommended prophylactic rodding of the right femur, which was done. The patient had been on alendronate for 9 years.

A 59-year-old-woman took a step, her right leg gave out, and she fell to the ground as she heard her leg break. Her femur was fractured. The orthopedic surgeon on call told her, "We don't usually see this type of fracture without trauma." For the preceding year she'd experienced pain in her right thigh, which was severe enough to cause limping. An x-ray had been negative, and her primary care physician thought she had fibromyalgia. She had been on alendronate for more than 5 years.

These unpublished case reports, and several other similar ones, were sent to the author following publication of a 2006 report in *Geriatrics*¹ of a 59-year-old, previously healthy woman who, while riding on a subway train, suffered a comminuted spiral fracture of the right femur when the train jolted (see figure, page 20). The patient had been experiencing pain in her right thigh for 3 months. A bone scan a week before the fracture showed a stress fracture of the right femur. The patient had been taking alendronate, 70 mg/week, for approximately 7 years for osteopenia, as well as calcium plus hormone replacement therapy. Despite pro-

longed use of an electrical bone stimulator, and cessation of alendronate use, the fracture did not unite. After 9 months, the patient had a second surgical procedure to replace the original rod with a larger one. After a delay, the bone finally united. The author suggested a possible causal relationship between long-term alendronate and the femoral fracture.

Fragility fractures of the proximal femur are rare. However, in the past 3 years, multiple additional cases like those above have been published and the evidence continues to grow that in a small subpopulation of patients, long-term alendronate use may be related to low-impact, nontraumatic, or “atypical” fractures of the femur, often with delayed healing. This paper reviews the older evidence for a connection between bisphosphonates and bone fragility, and summarizes recent reports and recommendations.

Femoral fractures and alendronate

Bisphosphonates are considered first-line treatment for postmenopausal osteoporosis. They are prescribed for millions of geriatric patients. Bisphosphonates—alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva), and zoledronic acid (Zometa, Reclast)—inhibit bone resorption by decreasing the activity of osteoclasts. Extensive studies have shown that therapy with bisphosphonates improves bone density and decreases fracture risk.²⁻⁶ When discontinued after 5 years, the physiologic effect of alendronate continues for at least 5 years, with no increase in morphometric vertebral fracture risk or in the risk of nonvertebral fractures compared with patients who continued to take alendronate for the full 10 years.⁷ This result is consistent with the fact that alendronate is incorporated into bone matrix and has a biological half-life of more than 10 years.

Bone turnover is a natural part of maintaining bone health. When bone turnover is inhibited by bisphosphonates, microdamage that occurs regularly in bone but is normally repaired might accumulate after long-term use. There have long been concerns about the long-term safety of bisphosphonates because of their potential to cause oversuppression of bone turnover.⁸⁻¹³ The first report suggestive of the clinical relevance of these hypothetical concerns was published in 2005 by Odvina et al,¹⁴ describing 8 postmenopausal women and a man who sustained unusual nontraumatic nonspinal fractures while on alendronate therapy for 3-8 years. All 9 continued taking alendronate after the fracture. Six of the 9 patients had delayed or absent fracture healing for 3 months to 2 years during continued alendronate therapy. All 9 patients underwent iliac crest biopsy of trabecular bone. All the specimens showed markedly suppressed bone formation. The authors concluded that long-term alendronate therapy may result in severe suppression of bone turnover, with increased susceptibility to nonspinal fractures along with delayed healing.

In 2007 a group from Singapore published a retrospective review of patients admitted with a low-energy subtrochanteric fracture (defined as one in the region of the femur that extended from the lesser trochanter to the junction of the proximal and middle third of the femoral shaft.)¹⁵ Of 13 women identified, 9 were on long-term alendronate therapy (mean 4.2 years, range 2.5-5). Their average age was 67 years, versus 80 years in the non-alendronate group. Four of the 9 patients in the alendronate group reported that the fracture had occurred in the absence of a fall. Five patients reported experiencing prodromal

pain in the fractured limb, starting 2-6 months before the injury; none of the patients in the non-alendronate group had prodromal symptoms. In 6 patients in the alendronate group, cortical hypertrophy was identified on the lateral side of the subtrochanteric region of the femur, and 3 of these also had cortical hypertrophy on the contralateral femur.

Long-term alendronate therapy may suppress bone turnover.

The Singapore group recently elaborated on its findings with a retrospective review of postmenopausal patients with subtrochanteric insufficiency fractures admitted to their hospital over a 20-month period.¹⁶ They found 17 patients, whose mean age was 66 years, and all had been taking alendronate, for a mean of 4.4 years (range 2.2-8), except for one patient who was on risedronate for 6 years after 4 years of alendronate. All fractures were low-energy, typically sustained after tripping. Seven of the patients reported experiencing acute pain before they fell, suggesting that the fracture preceded the fall. Thirteen of the 17 patients (76%) had experienced prodromal pain in the affected thigh ranging from 1 week to 2 years before the fracture. Often these patients had been treated for referred pain from a spinal origin, without improvement. Three patients had sustained prior contralateral femoral fractures 2-4 years earlier but had been continued on their bisphosphonate; the patient who was switched to risedronate was one of these. Five other patients had stress reactions seen on plain x-rays in the contralateral femurs; a bone scan of one of these patients showed abnormal uptake in that femur. Pointing to

