Dynamic Chiropractic

SENIOR HEALTH

Long-Term Bisphosphonate Use and Increased Fracture Risk

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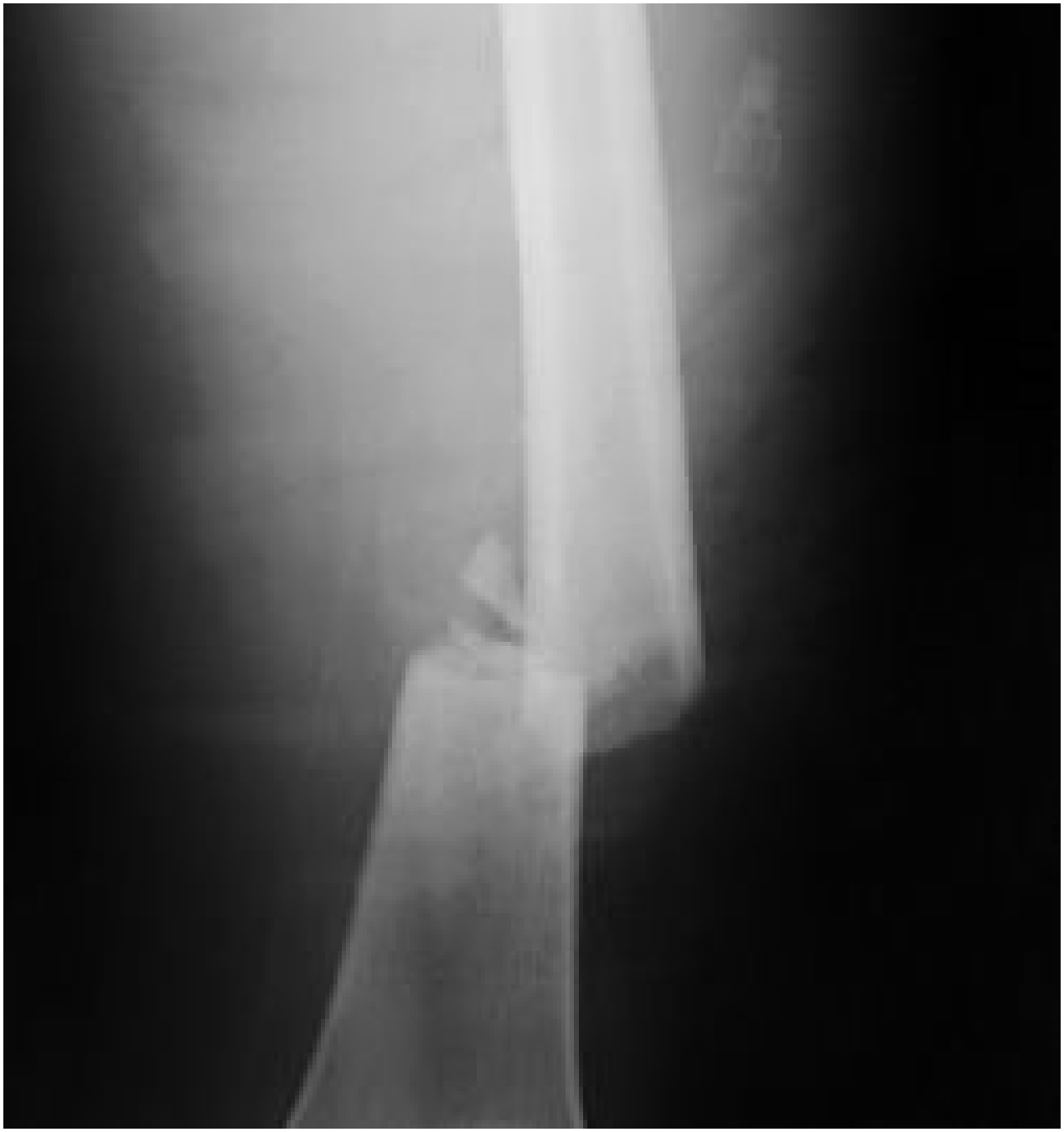
There has been a flurry of reports recently on the association of atypical femoral fractures with long-term treatment with bisphosphonates. Several studies have reported the occurrence of specific and rare types of femur fractures in individuals (mostly women) who had been taking bisphosphonates, specifically alendronate (Fosamax), for approximately 4-8 years.[1-9] It should be noted that the fractures occurred with no apparent trauma. These fractures were *not* from falls. In fact, in most cases, individuals were performing low-energy exercise, sometimes just walking down a flight of stairs.[10-11]

Bisphosphonates such as alendronate, risendronate and ibandronate are inhibitors of bone resorption. Extensive studies have shown that therapy with bisphosphonates improves bone density and decreases fracture risk. These drugs, especially the oldest one, alendronate, are used by large numbers of postmenopausal women, as well as smaller numbers of men with osteoporosis. In 2008, bisphosphonate sales exceeded $3.5 billion, according to data from IMS Health.

Impact on Bone Quality

Since bisphosphonates accumulate in bone tissue and suppress bone turnover, it appears that at least initially, the bone increases in density. Increased bone density, however, does not necessarily equate with good bone *quality*. Bone remodeling and turnover is a natural part of maintaining bone health. By decreasing osteoclast activity and bone resorption, the osteoblast activity is also affected; therefore, bone formation is also decreased. The microdamage that occurs regularly in bone and is normally repaired accumulates over time and is apparently not repaired because the normal process of bone resorption and formation has been altered by treatment with bisphosphonates. After long-term use, the quality of the bone is not maintained.



There have long been concerns about the potential oversuppression of bone turnover with long-term use of bisphosphonates and therefore their long-term safety. The concern is even greater when bisphosphonate is taken concurrently with another agent that may inhibit bone turnover, such as estrogen. The current patient package insert for Fosamax (alendronate) states, "The long-term effects of combined Fosamax and HRT on fracture occurrence and fracture have not been studied." The drug company admits that long-term effects of bisphosphonates are not known. We are now just beginning to realize that long-term treatment with bisphosphonates may actually damage the quality of bone because it suppresses the normal repair and maintenance process. Bisphosphonates are stored in bone for up to 10 years after their consumption is stopped; although their metabolic effects are of shorter duration, we don't know how long they are metabolically active. The research just hasn't kept up with the pace of production and use of the drug. Obviously, it's a matter of economics.

Recent Research Findings

Two preliminary studies presented at the 2010 annual meeting of the American Academy of Orthopedic Surgeons (AAOS) suggest that long-term suppression of bone remodeling by bisphosphonates may alter material properties of bone, potentially affect the bone's mechanical integrity and could contribute to the risk for atypical fractures. Researchers at Columbia University Medical Center evaluated the bone structure of 111 postmenopausal women with primary osteoporosis; 61 had been taking bisphosphonates for at least four years and 50 controls were taking calcium and vitamin D supplements. Bisphosphonates improved structural integrity early in the course of treatment; however, those gains were diminished with long-term treatment, according to an AAOS press release.

"In the early treatment period, patients using bisphosphonates experienced improvements in all parameters, including decreased buckling ratio and increased cross-sectional area," Melvin Rosenwasser, MD, orthopedic surgeon at Columbia University Medical Center, stated in the release. "However, after 4 years of use, these trends reversed, revealing an association between prolonged therapy and declining cortical bone structural integrity."

The second unrelated prospective, pilot study evaluated the bone composition of 21 postmenopausal women who were treated for femoral fractures; 12 had a history of bisphosphonate treatment for an average 8.5 years and nine had no history of treatment. Researchers at the Hospital for Special Surgery in New York City analyzed microarchitecture and material properties of the bone, using samples removed from each patient's femur during surgical placement of a femoral nail. The researchers reported no differences between the groups in bone microarchitecture. However, material properties of the bone displayed reduced bone tissue heterogeneity in bisphosphonate-treated patients. This may be associated with reduced strength and may potentially contribute to the presentation of atypical fractures, according to the release.[12]

Recently, Odvina[13] and colleagues reported on nine patients (eight postmenopausal women and one man) who sustained unusual spontaneous nonspinal fractures while on alendronate therapy (10 mg/day or 70 mg/week) for 3-8 years. Three of the eight women were also on HRT. The present case report above fits into this category of patient. All nine patients continued taking alendronate after the fractures. Six of the nine patients had delayed or absent fracture healing for three months to two years during alendronate therapy. All of the patients had iliac crest biopsies of trabecular bone. The biopsy specimens underwent histomorphometric analysis using tetracycline labeling to study bone metabolic activity. All patients showed markedly suppressed bone formation, with reduced or absent osteoblastic surface in most patients. Matrix synthesis was markedly diminished.

Yes, the numbers are small, but the reports and studies are now demonstrating that bisphosphonates should not be used long term, and it is highly questionable whether patients with osteopenia should be prescribed the drug at all. It has been popular to give bisphosphonates to perimenopausal and menopausal women who have T-scores of between -1 and -2.5, indicating osteopenia. The idea was to head off the bone loss by suppressing bone resorption, but unfortunately, this also indirectly suppresses the normal process of bone remodeling and formation.

Take-Home Points

Present conclusions are that during long-term alendronate therapy, severe suppression of bone turnover may occur, resulting in increased susceptibility to nonspinal fractures along with delayed healing. Current evidence suggests that bisphosphonates should be stopped after five years. Patients who remain at a high risk of fractures or who have had fractures despite bisphosphonate therapy could be considered for treatment with intermittent PTH (parathyroid hormone). In

otherwise healthy perimenopausal women who merely have osteopenia, the best therapeutic option is probably *not* bisphosphonates.

Studies have shown the efficacy of bisphosphonates in the first five years of therapy in improving bone density and diminishing the risk of fractures. After that, however, until additional studies are done that clarify the risks of nontraumatic fractures, the delayed healing of bone fractures associated with long-term treatment with bisphosphonates, and which risk factors, if any, can help predict which patients are at increased risk for these adverse affects, it is reasonable to suggest patients stop the drug, continue weight-bearing exercise, take calcium supplements and have their bone density monitored with DEXA.

Weight-bearing exercise is essential for the prevention and treatment of osteoporosis and unfortunately, it is often overlooked or underemphasized. Muscle strength is an accurate predictor of bone strength. Weight-bearing exercise has been shown to be the most effective way to strengthen bone and protect against osteoporosis-related fractures.[14-15] Medication is *not* the best way to prevent osteoporosis; nutrition and exercise are key for bone health (and overall health).

References

1. Somford MP, Draijer FW, Thomassen BJ, et al. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. *J Bone Miner Res*, 2009 Oct;24(10):1736-40.
2. Cermak K, Shumelinsky F, Alexiou J, et al. Case reports: subtrochanteric femoral stress fractures after prolonged alendronate therapy. *Clin Orthop Relat Res*, 2009 Dec 18. [Epub ahead of print]
3. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg* (U.S.), 2009 Nov;91(11):2556-61.
4. Goddard MS, Reid KR, Johnston JC, Khanuja HS. Atraumatic bilateral femur fracture in long-term bisphosphonate use. *Orthopedics*, 2009 Aug;32(8).
5. Ing-Lorenzini K, Desmeules J, Plachta O, et al. Low-energy femoral fractures associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital. *Drug Saf*, 2009;32(9):775-85.
6. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med*, 2008 Mar 20;358(12):1304-6.
7. Sayed-Noor AS, Sjödén GO. Case reports: two femoral insufficiency fractures after long-term alendronate therapy. *Clin Orthop Relat Res*, 2009 Jul;467(7):1921-6. Epub 2009 Feb 6.
8. Neviaser AS, Lane JM, Lenart BA, et al. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma*, 2008 May-Jun;22(5):346-50.
9. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? *Injury,* 2008 Feb;39(2):224-31. Epub 2008 Jan 28.
10. Somford MP, Geurts GF, den Teuling JW, et al. Long-term alendronate use not without consequences? *Int J Rheumatol*, 2009;2009:253432. Epub 2010 Jan 27.
11. ABC News: "Fosamax: Is Long Term Use of Bone Strengthening Drug Linked to Fractures?"
12. AAOS 2010 Annual Meeting; podium presentations. www3.aaos.org/education/anmeet/anmt2010/podium/podium.cfm?Pevent=241
13. Odvina CV, Zerwekh JE, Sudhaker Rao D, Maalouf N, Gottschalk FA, Pak CYC. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metabolism,* 2005;90(3):1294-1301.
14. Rubin C, Turner AS, Muller R, et al. Quantity and quality of trabecular bone in the femur are enhanced by a strongly anabolic, noninvasive mechanical intervention. *J Bone Min Res,* 2002;17:349-357.

15. Kemmler W, et al. Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women: results of the Erlangen Fitness Osteoporosis Prevention Study (EFOPS). *Arch Intern Med*, 2004;164:1084-1091.

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