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Atypical Fractures as a Potential Complication of Long-term Bisphosphonate Therapy

Deborah E. Sellmeyer, MD

CASE PRESENTATION

A 58-year-old white woman taking bisphosphonates presented for evaluation of a nonhealing subtrochanteric left hip fracture. Ten years prior, she experienced a right foot stress fracture and underwent bone mineral density testing. She was subsequently told that her bone density was in the osteopenia category and she started bisphosphonate therapy. After 10 years of bisphosphonate treatment, she developed left thigh pain. Initial imaging did not show any abnormalities and she was treated conservatively. One month after developing thigh pain, the patient stepped down a stair and felt a "crack" in her left thigh followed by inability to bear weight on her left leg, resulting in a fall. Imaging showed a subtrochanteric left femur fracture that was treated with intramedullary rod placement.

Two months after surgical repair, bisphosphonate therapy was stopped and treatment with teriparatide therapy was initiated. Six months after surgery, imaging showed persistence of her fracture with very little callus formation. Evaluation for secondary causes of skeletal fragility was undertaken; measurements included a metabolic panel, phosphorus, complete blood cell count, 25-hydroxyvitamin

The development of bisphosphonate therapy represented an important advance in the treatment of low bone mass and osteoporosis, conditions that affect more than half of individuals older than 50 years. Currently available bisphosphonates have been shown to reduce spine, nonspine, and hip fractures in individuals at increased risk of fracture. Case reports and limited clinical series over the past 5 years have raised concern that prolonged bisphosphonate therapy may suppress bone remodeling to the extent that normal bone repair is impaired, resulting in increased fracture risk. Fractures potentially resulting from suppressed bone turnover have been described as "atypical," affecting sites such as the subtrochanteric femur that are infrequently affected by osteoporotic fractures. A prodrome of thigh pain, lack of trauma prior to the fracture, and specific radiological characteristics have also been reported. Data are limited on the prevalence of, risk factors for, and treatment of this potential problem. Current strategies include fracture risk assessment, targeting bisphosphonate therapy appropriately to individuals at increased risk of fracture, considering a 12-month interruption in therapy after 5 years in patients who are clinically stable, and considering teriparatide treatment in individuals who experience an atypical fracture while receiving bisphosphonate therapy.

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D, celiac antibodies, serum and urine protein electrophoresis, thyroid function, and 24-hour urine calcium. No abnormalities were found. After 3 months of teriparatide treatment, serum osteocalcin, a marker of bone formation, was 34.8 ng/mL (premenopausal normal range, 8.2-35.4 ng/mL) and serum C-telopeptide, a marker of bone resorption, was 373 pg/mL (premenopausal normal range, 78-573 pg/mL). Serial radiographs since her fracture showed some suggestion of callus formation, but the fracture line remained 1 year later (FIGURE).

Case reports of atypical fractures such as the subtrochanteric hip frac-

ture described above, occurring in patients receiving long-term bisphosphonate therapy, have raised the question of whether prolonged treatment with bisphosphonates can suppress bone remodeling to the degree that the skeleton has insufficient bone turnover to maintain skeletal strength.

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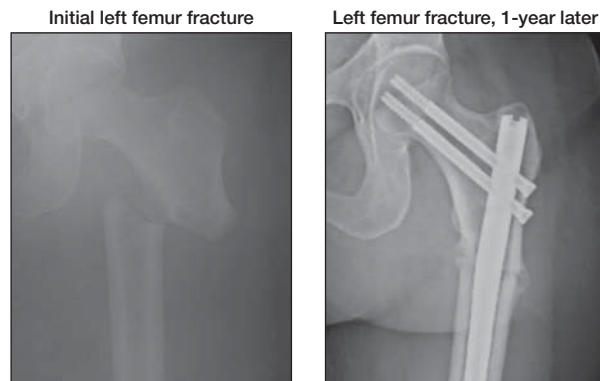
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Bisphosphonate Treatment and Bone Remodeling

Bisphosphonates have been shown to reduce bone turnover, increase bone density, and reduce fracture risk in multiple randomized clinical trials.¹⁻⁶ These agents were used by 4.7 million US individuals in 2005.⁷ Although their mechanism of action targets the osteoclast and thus bone resorption, treatment with bisphosphonates decreases both bone resorption and bone formation, as these 2 skeletal processes are closely linked. Bone resorption decreases initially, followed within weeks to months by decreased bone formation.

Assessing an individual's level of bone remodeling is challenging. An estimation of bone turnover can be made by measuring bone turnover markers. In the case patient, serum C-telopeptide, a collagen cross-link protein released when bone is resorbed, and osteocalcin, a protein product of osteoblasts that reflects bone turnover including bone formation, were measured. However, direct measurement of bone formation requires a tetracycline double-labeled bone biopsy. Tetracycline labeling has been used to examine bone remodeling in patients thought to have atypical fractures. Tetracycline binds to newly forming bone and fluoresces in histologic samples. Patients are given 2 short courses of tetracycline separated by a 10-day period, followed by transiliac crest bone biopsy. Biopsy allows examination of the bone architecture and direct assessment of bone formation, as represented by the extent of tetracycline labeling. In normal bone, 2 linear lines of tetracycline can be seen, separated by the amount of new bone that was formed between the 2 courses of tetracycline. From the tetracycline labels, a number of variables reflecting bone formation and bone turnover are derived, including the bone formation rate (determined by how much tetracycline has been incorporated and how far apart the lines of tetracycline labels are) and the activation frequency (which reflects how often in a year a single site on the bone will enter the bone formation period).

Figure. Subtrochanteric Hip Fracture in Patient Described in Case Presentation



Reports of Skeletal Fragility in Patients Receiving Bisphosphonate Therapy

In 2005, a case series of patients receiving bisphosphonate therapy who had experienced “atypical” fractures was published.⁸ This series of 9 patients treated with bisphosphonates included femoral shaft fractures in half of the patients as well as 6 who were perceived to have delayed fracture healing. The patients had been receiving bisphosphonate treatment for 3 to 8 years. When tetracycline double-labeled bone biopsies were obtained, none of the biopsies showed both lines of tetracycline labels and only 5 had evidence of a single label, suggesting a very low rate of new bone formation. This case series raised concerns about oversuppression of bone turnover with bisphosphonate therapy. There were several mitigating factors that make interpretation of this small case series challenging. First, 3 of the women in this case series were also taking estrogen (known to decrease bone turnover) and 2 were taking glucocorticoids (which also suppress bone formation). Second, markers of bone turnover were not uniformly suppressed in these patients. Osteocalcin values were on the low end of the normal range in 5 patients and below the lower limit of normal in 4 patients. However, values for bone-specific alkaline phosphatase, a marker of bone formation, and N-telopeptide, a marker of bone resorption, were in the middle of the normal range in most

patients. Four patients had bone-specific alkaline phosphatase values above the upper limit of normal. Finally, lack of tetracycline labeling can occur in up to 30% of postmenopausal women with osteoporosis who are not receiving treatment.⁹ Thus, while raising a potential concern, the implications of this case series are difficult to assess.

Bone Biopsy and Bone Turnover Marker Data From Bisphosphonate Randomized Trials

Data from randomized trials of bisphosphonate-treated patients have not shown evidence of oversuppression of bone turnover, but these trials have been relatively short in duration and a limited number of biopsies were performed, typically 30 to 80 in each study. Tetracycline-labeled bone biopsy data are available after 3 years of treatment for the bisphosphonates currently used for osteoporosis treatment. Bone formation rates and activation frequencies were significantly decreased in those receiving bisphosphonate treatment, but only 1 or 0 patients from each study showed lack of tetracycline in biopsy specimens.¹⁰⁻¹² Additionally, no qualitative defects in skeletal histology were seen.

Longer-term data are much more limited. Bone biopsy data are available from 1 study after 10 years of treatment with alendronate. After an initial 5 years of alendronate treatment, participants were randomized to receive another 5 years of alendronate or

5 years of placebo. After a total of 10 years of alendronate, 15 participants underwent tetracycline-labeled bone biopsies.¹³ All of the biopsies showed double labeling, indicating new bone formation after 10 years of alendronate treatment. Additionally, there were no qualitative defects in skeletal histology. These data are somewhat limited in that there was no control population; all participants had at least 5 years of alendronate treatment and half had 10 years of treatment.

Another study gathered bone biopsy data after 5 years of treatment with risedronate or placebo among 74 participants in an extension arm of a randomized controlled fracture trial. Similar to alendronate, all biopsies showed the presence of double labeling and similar decreases in bone-forming measures.¹¹ No biopsy showed any qualitative defects. In contrast with the alendronate study, in which all biopsies were obtained at the end of the study, in the risedronate study baseline biopsies were obtained prior to treatment as well as second biopsies after 5 years of treatment. While still higher than the values measured in bisphosphonate-treated participants, the bone formation rates and activation frequencies decreased significantly with 5 years of placebo, showing the importance of having adequate control samples when evaluating these histomorphometry data because the bone-forming measures in participants receiving placebo decreased by about 50%, presumably due, at least in part, to the calcium and vitamin D supplementation provided to the placebo group.

Bone turnover markers in bisphosphonate randomized trials have shown sustained decreases of 30% to 50% in markers of bone turnover. No progressive decreases in these measures have been seen, even with up to 10 years of treatment.^{3,6,14}

Microdamage in Bone Biopsy Data From Clinical Patient Series

Microscopic cracking occurs in bone as a result of daily weight-bearing activity. Under normal conditions, these microcracks are repaired by ongoing bone re-

modeling. Accumulation of unrepaired skeletal microdamage as a result of reduced bone remodeling is among the potential mechanisms by which oversuppression of bone turnover might lead to increased skeletal fragility. One case series reported bone biopsy data from 50 outpatient postmenopausal women treated with bisphosphonates for at least 3 years.¹⁵ Controls consisted of histological samples from 12 recently deceased cadavers that had not been tetracycline labeled. Among the 50 patients receiving bisphosphonates, one-third had no double label, a distinct contrast with the randomized control trial data. In those who had labeling, the bone formation rate and activation frequencies were very similar to those seen in the randomized trial data. Microcracks were seen in less than half of both the cadaver samples and the samples from bisphosphonate-treated patients, and there was no difference between cadavers and bisphosphonate-treated patients in how much microdamage was evident.

Atypical Fractures

The case presented above has many of the clinical features described in patients receiving long-term bisphosphonate therapy who develop atypical subtrochanteric hip fractures. Unlike the more common hip fracture scenario involving fracture of the femoral neck or intertrochanteric region, where typically there is no prodrome, bisphosphonate-treated patients with subtrochanteric fractures are described as having weeks or months of discomfort at the site before the fracture occurs. Patients may report that the pain sensation originates deep within the thigh and often note that discomfort is worsened by weight bearing. Patients also describe hearing and feeling fractures occur during nontraumatic activities of daily living such as stepping down a stair, walking, or turning. Radiological features at the fracture site include thickening of the femoral cortex, presence of a transverse fracture, and a cortical beak. Presence of a stress reaction or visible fracture line on the contralateral femur is additionally reported in many cases. This radio-

graph finding also has been described in patients who have never been treated with bisphosphonates.^{16,17} However, in a retrospective chart review of 70 low-energy hip fracture patients admitted to a single hospital, this radiograph pattern was evident in 19 of 25 patients taking alendronate and in only 1 of 45 who had not been treated with bisphosphonates.¹⁸ Other case series have also reported a higher rate of bisphosphonate use among patients with atypical fractures.¹⁹⁻²⁴ Assessment of atypical hip fractures vs typical hip fractures in a registry study among 11 994 patients from Denmark showed no difference in cumulative incidence of atypical and typical hip fractures by bisphosphonate use.²⁵ In that cohort, there were only 178 individuals who had more than 6 years of bisphosphonate exposure. However, among those individuals, there was no increased risk of atypical femur fractures compared with controls.

Risk of subtrochanteric and diaphyseal femur fractures was examined among 14 195 women who participated in 3 randomized trials of alendronate and zoledronic acid.²⁶ There was no significant increase in risk of atypical femur fractures with bisphosphonate use; however, among 284 hip fractures observed, only 12 subtrochanteric or diaphyseal fractures occurred in 10 study participants, limiting statistical power. Nonetheless, this study emphasizes the low prevalence of subtrochanteric femur fractures, even among women taking bisphosphonates for as long as 10 years. However, the relatively small number of women with prolonged bisphosphonate use and the few subtrochanteric fractures limit the conclusions that can be drawn from these data.

Examination of discharge and medical claims data from 1996 to 2006 showed that the annual incidence of subtrochanteric and femoral shaft fractures appears stable at fewer than 20 fractures per 100 000 person-years. The overall incidence of hip fractures declined from 598 per 100 000 person-years in 1996 to 428 per 100 000 person-years in 2006.²⁷

The utility of bone turnover markers in the setting of a possible atypical fracture is not clear. Neither markers of bone formation nor markers of bone resorption have been shown to be consistently suppressed in patients with atypical fractures. A recent systematic review found normal or elevated bone turnover markers in more than 85% of patients thought to have atypical fractures.²⁸ Interpretation of these results is complicated by variability in the amount of time between the fracture and obtaining the marker measurement and whether the patients were still taking bisphosphonates or other agents that could affect bone remodeling. Whether levels of bone turnover markers or magnitude of change in bone turnover markers during treatment can help identify individuals at risk of an atypical fracture remains to be seen.

Approaches to Preventing and Treating Potential Oversuppression

Perhaps the most important step to maximizing the risk-benefit ratio related to bisphosphonate therapy is to optimize selection of patients for bisphosphonate treatment. Ideally, patients at increased risk of fracture should be identified accurately to target treatment appropriately, and treatment should be avoided in low-risk patients. The World Health Organization devised a multivariate model that uses bone density and risk factors for fracture to calculate a 10-year probability of any major osteoporotic fracture and, specifically, of hip fracture (available at <http://www.sheffield.ac.uk/FRAX/>). Based on cost-effectiveness analyses in the United States, general guidelines include treating any patient who has a 10-year major osteoporotic risk of more than 20% or hip fracture risk of more than 3%.²⁹ Guidelines using this fracture risk model have been published.^{30,31}

Among patients for whom bisphosphonate therapy is appropriate, approaches such as treating for 5 years and then providing a "drug holiday" for 12 months or more have been suggested, with the length of the drug holiday determined by estimated level of current

fracture risk. While there are no data on whether intermittent gaps in therapy help prevent possible oversuppression, data from the Fracture Intervention Trial Long-term Extension (FLEX) trial suggest that discontinuation of alendronate therapy after 5 years of treatment results in fracture rates over the next 5 years that are similar to continued treatment with the exception of clinical vertebral fractures.¹⁴ Further analysis of these data showed that among women without vertebral fractures who had a femoral neck T score of -2.5 or less after the initial 5 years of alendronate therapy, continued alendronate therapy was associated with a reduced risk of nonvertebral fractures compared with 5 years of alendronate followed by 5 years of placebo.³² Of note, these analyses were post hoc subgroup analyses and the number of fractures in the subgroups was limited. Vertebral fracture risk remained reduced 1 year after medication discontinuation in participants previously treated with risedronate for 3 years compared with those who had received placebo for 4 years.³³ Although these data do support the concept of at least some degree of persistent fracture reduction after cessation of bisphosphonate therapy, there are no data on whether strategies such as drug holidays reduce the risk of atypical fractures, an already infrequent potential complication. Thus, the risks and benefits of stopping bisphosphonate therapy must be individualized, with consideration given to the patient's estimated fracture risk, bone density values, duration of previous treatment, and other risk factors for fracture. Several recent reviews are available that more fully discuss the controversies regarding bisphosphonate drug holidays.^{34,35}

Treatment of Patients With Possible Oversuppression

There are few data available to guide treatment decisions for patients believed to have atypical fractures or possible oversuppression of bone turnover. Teriparatide (recombinant parathyroid hormone) increases bone turnover in both treatment-naïve and

bisphosphonate-treated patients. Thus, there is a physiologic rationale to consider prescribing this agent in cases of possible oversuppression of bone turnover. However, there are no outcome data available regarding the use of teriparatide in patients with atypical fractures. Bone density increases when patients who have been taking a bisphosphonate switch to teriparatide. Some data suggest that there may be a delay of approximately 6 months before the bone density begins increasing in response to teriparatide, compared with the prompt increase that was demonstrated in patients that were switched from raloxifene to teriparatide.³⁶ There are no fracture data available among patients treated sequentially with a bisphosphonate and teriparatide or in patients with atypical fractures.

Teriparatide is self-administered as a daily subcutaneous injection. It is approved by the US Food and Drug Administration for 2 years of use in a patient's lifetime. Because of animal studies associating long-term exposure with osteosarcoma, teriparatide is contraindicated in patients with an increased risk of skeletal malignancies, including those with open epiphyses, a history of skeletal radiation, Paget disease of bone, or an unexplained high alkaline phosphatase level. Postmarketing data suggest that osteosarcoma risk does not appear to be increased in humans during treatment with teriparatide.³⁷ Of note, when treating patients with possible oversuppression of bone turnover, after using teriparatide for 2 years, it must be followed with antiresorptive therapy or the increases in bone density will be lost over the ensuing months.³⁸ This presents a challenge when dealing with patients who may have a complication of long-term bisphosphonate therapy, as returning to bisphosphonate or another antiresorptive medication may be necessary to maintain teriparatide-related gains. This issue has not been examined in patients with atypical fractures. Additionally, the length of antiresorptive treatment needed to maintain gains in bone

density accrued during teriparatide treatment is not known.

CONCLUSION

Osteoporosis diagnosis and treatment rates among individuals who have experienced a fracture are remarkably low.³⁹ Evidence to date suggests that atypical fractures in bisphosphonate users are infrequent, and this potential problem should not preclude initiation of therapy in patients at risk of skeletal events. Continued focus on identifying higher-risk patients and being judicious with initiation and continuation of therapy is appropriate. Medication holidays can be considered for patients receiving bisphosphonate therapy who have been treated for 5 years and who have stable bone density and no fractures, although data are lacking on the effects of such approaches. Post hoc analyses from clinical trials using alendronate suggest that individuals at higher risk of vertebral fractures and those whose bone density remains low after 5 years of treatment may benefit from continued therapy.

Clinicians should be alert to symptoms of deep thigh pain that worsens with weight bearing as a presenting symptom of a subtrochanteric hip fracture as well as to the frequent bilateral nature of this disorder. Teriparatide may be a therapeutic option for patients who experience an atypical fracture while receiving bisphosphonate therapy, particularly in the setting of low bone turnover. More research on the prevalence of atypical fractures, their association with bisphosphonate use and low bone turnover, and the effects of strategies such as drug holidays and teriparatide treatment is needed.

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