Approach to the woman with long-term bisphosphonate therapy

Susan M. Ott
University of Washington
Seattle, WA 98195
September, 2009
Bisphosphonates, Osteoporosis, Bone turnover
This article has been funded, in part, by NIAMS #R01 AR051938-04.
The author has no conflicts of interest.

Abstract
Bisphosphonates are commonly used to treat osteoporosis because randomized clinical trials have shown reduction of fracture incidence. The data about long-term use after 5 years are sparse, but several extensions of clinical trials have suggested that these drugs have a satisfactory safety profile up to ten years. Patients who have taken alendronate for 5 years have similar clinical fracture rates for the next 5 years if they continue the drug or if they take placebo. Bone biopsies of patients taking bisphosphonates show bone formation rates that are decreased by 75 to 95%, and in one study one third of patients with long-term used had unmeasureable tetracycline double labels. Recent reports about atypical fractures associated with low bone formation rates are of concern but the risk of these types of fractures with long-term use is unknown. Because the available data suggests limited efficacy beyond 5 years, I am cautious about continuing bisphosphonates. If patients are doing well, I discontinue the bisphosphonates and monitor bone turnover, realizing that there is not much evidence for this strategy. For frail or severely osteoporotic patients I consider a change to another medication. If they are not doing well they require re-evaluation. If patients have fractures or fail to respond to bisphosphonates and they have suppressed bone turnover, I suggest anabolic therapy with teriparatide. Further research is needed to determine the best approach for these patients.

Illustrative case

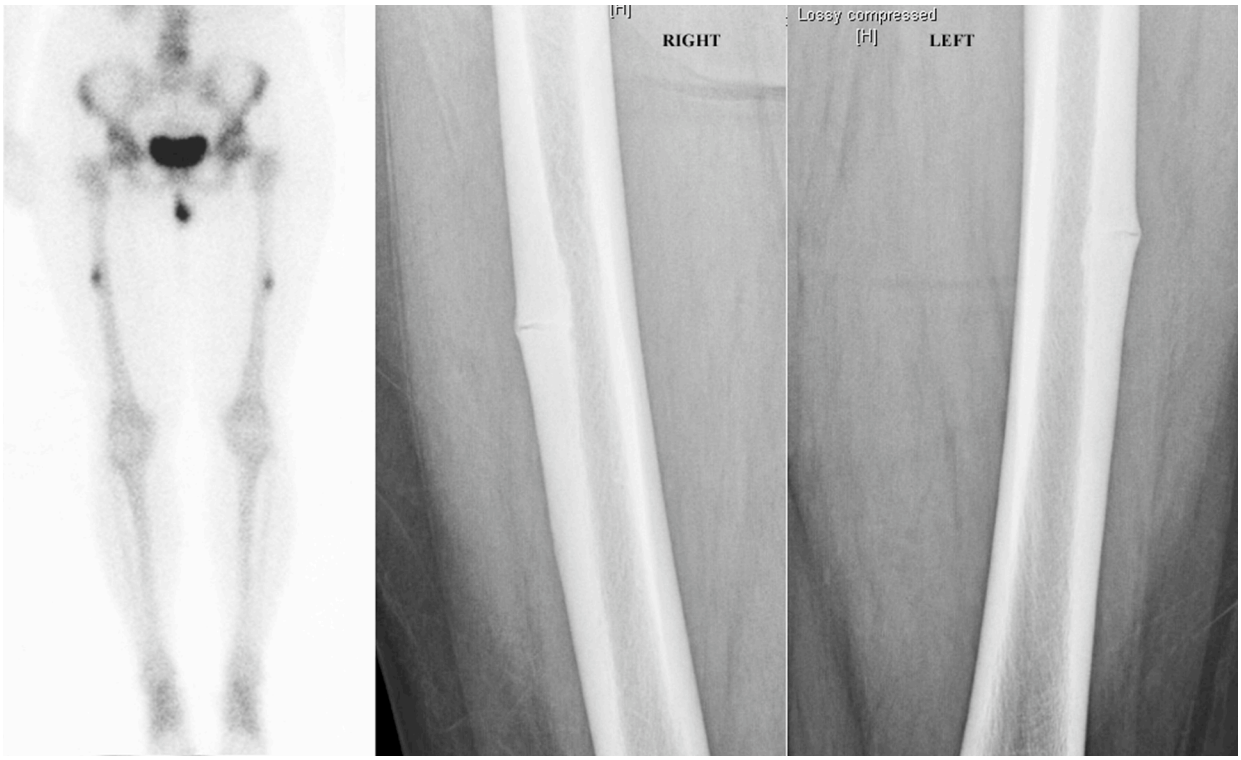
A 61 year old lawyer was referred for evaluation of bilateral midfemoral shaft stress fractures. She was health-conscious without serious medical problems, and underwent screening bone densitometry when she was 48 years old. The T-scores were -2.2 at the spine and -1.7 at the hip. She was prescribed alendronate to prevent osteoporosis, which she had continued for 13 years. She was not underweight, had no previous fractures, did not have rheumatoid arthritis, had not taken corticosteroids, did not smoke cigarettes or drink more than 2 alcoholic beverages daily, and neither parent had fractured a hip.

She had been experiencing bilateral pain in the mid-femurs for about 4 years. Initially this was treated with exercises without resolution. Six months prior to her visit she had an F^{18} bone scan which demonstrated bilateral increased uptake in the mid-femur, lateral surface. An MRI of the hip was reported to be normal and not the etiology of her pain. The bone scan was repeated 5 months later and showed persistence of the uptake in the mid femur.

She had taken estrogen for 3 years after her menopause, and for the past 3 years was taking tamoxifen to prevent breast cancer. Her other medications were levothyroid .125 mg/day, simvastatin 20mg/day, vitamin D_2 50,000 units/week, aspirin 81mg/day, and calcium and vitamin supplements.

The physical examination was unremarkable except for bilateral mild tenderness over the anterior thighs. The laboratory chemistry panel

was normal, 25-OH-vitamin D was 127 nMol/L (normal 50-150), PTH was 34 pg/mL (normal 12 to 88), and urine N-telopeptide was 38 nM BCE/mM Cr (post-menopausal normal 26-124). Bone density showed T-scores of -2.5 at the spine and -1.6 at the hip. Her radiographs are shown in Figure 1.



Background

Alendronate, the first amino-bisphosphonate, became available in 1996. Large clinical trials of 3 to 5 years duration have provided consistent evidence that fracture incidence is reduced when patients with osteoporosis are treated with bisphosphonates. Beyond 5 years the data are relatively sparse. There may be some adverse effects from the bisphosphonates. Osteonecrosis of the jaw has received wide-spread publicity, but the risk in patients with osteoporosis is estimated to be less than 1/10,000 (1). Atrial fibrillation has been seen more often in alendronate groups than in placebo groups in two clinical trials (2, 3) and in one case-control study (4) but it has not been related to bisphosphonates in a large population-based case control study (5) or in an analysis by the U.S. Food and Drug Administration (FDA) (6). A letter from the FDA (FDA) stated that 23 cases of esophageal cancer had been reported in patients using oral bisphosphonates, and they suggested there could potentially be a relationship and called for further research (7). Nephrotic syndrome and bone pain could be related to these drugs but these cases are rare, particularly in doses used to treat osteoporosis. Recent reports of patients with unusual long-bone fractures have raised concern about possible adverse skeletal effects with prolonged use of the bisphosphonates. This side effect is very difficult to define because study designs must take into account confounding by indication.

Physiological mechanisms

The bisphosphonates are rapidly cleared from the circulation, but they bind to calcified tissues so strongly that they remain deposited in the skeleton longer than ten years. On a molecular level, they inhibit farnesyl pyrophosphate synthase, and the end result of this is inhibition of osteoclastic bone resorption

(8). A major cause of poor bone quality seen in patients with osteoporosis is the increased bone turnover caused by estrogen deficiency and other factors (9). This results in local areas of weakness and in perforation of trabecular plates. With bisphosphonates, the osteoclasts are less likely to cause this perforation. Patients taking bisphosphonates therefore have stable bone micro-architecture, whereas those taking placebo continue to lose bone structural elements (10).

When a patient initially takes a bisphosphonate, the osteoblasts in the recently resorped cavities continue to form new bone. On average, it takes about 3 months to fill in a resorption cavity (one formation period), so gradually all those cavities will be filled and the bone surfaces become quiescent. During this interval the overall bone volume can increase. New resorption cavities occur less frequently because the osteoclasts are inhibited. In normal remodeling bone, the bone formation follows bone resorption, so when bone resorption decreases, bone formation eventually decreases as well. The mineralizing surface, which is labelled with tetracycline, directly reflects the bone formation rate. Bone biopsies from patients treated with bisphosphonates longer than 5 years show mean mineralizing surfaces of 0.4% (11), 1.4% (2), and 3.6% (12). A study of 50 women treated with bisphosphonates for a mean of 6.5 yrs found that 33% had did not have sufficiently visible tetracycline labels to measure the bone formation rate (11). For comparison, the mean mineralizing surface in studies of untreated women with osteoporosis is 5.5 to 6.5% (12-14), and is about 7% in normal postmenopausal women (15, 16) and 6 to 8% with a standard deviation of 3% in normal premenopausal women (15, 17, 18).

When bone turnover decreases, bone density increases because more mineral is deposited into the existing bone and dense older bone is not replaced with new bone. It takes 2 to 3 years to fully mineralize a bone structural unit. Bone biopsies from patients taking alendronate show increased mineralization density (19). A study including 10 patients on risedronate found a significant increase in mineralization density but it was similar to the placebo values (20). Some increase in mineralization density probably improves bone strength, but too much could potentially make the bone more brittle.

Bone, like any other structural material, may become damaged when subjected to mechanical forces. Small micro-cracks develop with normal activities of living. Bone that is more porous is more liable to become damaged, and this may explain why people of African ancestry, who have higher bone mass, also have lower bone formation rates (15). The bone volume is not consistently increased in biopsy studies of bisphosphonates, but moderate increases are difficult to detect because of the variance in this measurement. In cases where the bone volume does increase there may be lower likelihood of micro-damage. Also, the bisphosphonate-treated bones are less likely to develop perforations which weaken the bone; this may also limit damage. Micro-cracks stimulate bone resorption, and the damaged bone is replaced with new bone (21). The decreased bone turnover seen with bisphosphonates may cause accumulation of micro-cracks. Animal studies show increased micro-cracks during the first year of bisphosphonates, but apparent stabilization after that (22). Because the development and repair of micro-cracks is complex, it is difficult to predict what will happen with long-term bisphosphonate use. Studies of biopsies from women taking long-term bisphosphonates are inconsistent: - one study did find accumulation of micro-cracks (12) but one did not (11).

In summary, bisphosphonates decrease bone resorption. This reduces fracture risk by stabilizing the bone architecture. Bone volume probably increases during the interval following initiation of a bisphosphonate. Thereafter, the bone formation rate decreases substantially, the mineralization density increases, and micro-cracks may accumulate. The net effect on bone strength is complex, and the optimal bone turnover rate remains undefined. Whether any of these effects will eventually contribute to fractures in patients is unknown and vigorously debated.

Studies of long-term use of bisphosphonates

For this discussion, I consider long-term bisphosphonate use to be greater than 5 years. This is about as long as the lifespan of an

average cancellous bone structural unit (23). It is also as long as clinical trials included untreated controls.

A 2-yr uncontrolled extension (24) followed a trial of risedronate which had blinded controls for 5 years (25). Initially 407 women were in the risedronate group; 115 completed 5 years, and 83 were enrolled in the extension. Vertebral fracture rates were 4.7%/yr during yrs 0-3 and 3.8%/yr during yrs 6-7, significantly lower than the rate in the placebo group of 7.6% during yrs 0-3. Non-vertebral fractures were seen in 10.9% of risedronate-treated patients during the first 3 yrs and in 6% during the 2 yr extension. Markers remained suppressed throughout the 7 yrs. BMD of spine and hip did not change from yrs 5 to 7.

A controlled trial of alendronate (26) lasted 3 yrs, and was extended without controls up to ten yrs (27). There were 398 patients randomly assigned to alendronate, and 164 remained in the study for yrs 8-10. During yrs 8-10 BMD of spine increased by about 2%; no change was seen at the hip or total body. Non-vertebral fracture rate was similar in yrs 0-3 and yrs 6-10. Vertebral fractures occurred in approximately 3% of women the first 3 years and 9% the last 5 years. No insufficiency fractures or non-union were reported.

In the FIT trial 3236 women were in the alendronate group (28). After a mean of 5 yrs on alendronate, 1099 of them were re-randomized into alendronate and placebo groups (29). During the next 5 yrs, the hip BMD in the placebo group decreased 3.4% and in the alendronate group it decreased by 1.0%. At the spine, the placebo group gained less than the alendronate group (1.5% vs. 5.3%). Markers were stable in those continuing alendronate, and gradually increased in those who discontinued, but they were still lower than the baseline (pre-alendronate) values. There were no significant differences between all clinical fractures, nonvertebral fractures or vertebral fractures as measured on radiographs. There was also no difference in the number of severe vertebral fractures (those with >2-grade change on the radiograph) (30). There were, however, fewer "clinical spine" fractures in the group continuing alendronate (2.4% vs 5.3% over 5 years). In those 39 women with a "clinical spine" fracture, mean height loss was 3.5cm in the alendronate group and 2.1cm in the placebo group. Subgroup analysis showed that there were no significant differences in fracture rates between placebo and alendronate groups in those with baseline BMD T scores less than -2.5 or greater than -2, or in those with or without baseline vertebral fractures. Overall the nonvertebral fracture rate was similar during the first 5 years as during the last 5 years when adjusted for age. This implies that alendronate had a lasting beneficial effect even after discontinuation (as opposed to an adverse effect on bone strength of long-term alendronate).

An analysis of an administrative database from a healthcare organization evaluated 9,063 women who were prescribed bisphosphonates. Those who discontinued or were non-compliant during the first 2 years had higher rates of hip fractures than compliant patients. After 3 years of use, those who discontinued the bisphosphonates had similar rates of hip fractures during the next year as those who continued taking the medication (31). The level of evidence from these observational studies is uncertain.

Atypical fractures

Recent reports have described unusal fractures in patients who have taken bisphosphonates (Table 1) (32-43). Many of the patients had been taking other medication that could supress bone remodeling (such as estrogen or prednisone). These fractures are often proceeded by leg pain, typically in the mid thigh. Radiographs and bone scans show stress fractures on the lateral side of the femur, which resemble Looser's zones. These radiographic features are not typical for osteoporosis, but are reminiscent of the stress fractures seen with hypophosphatasia, an inherited disease characterized by severely decreased bone formation (44). The cortical bone is thick and may show beaking. Fractures often occur prior to falling, after very minor mis-steps - such as tripping, stepping off an elevator, or being jolted by a subway stop. Bone biopsies, when performed, show very low bone formation rates. Pathologists from St. Louis reviewed all bone biopsies from patients who were seen between

2004 and 2007 who had an unusual cortical fracture while taking a bisphosphonate. A total absence of double tetracycline labels was seen in 11 of the 16 patients (45).

These case reports are all anecdotal, and do not allow calculation of the risk of fractures in patients taking bisphosphonates. Certainly subtrochanteric fractures occur in people who have never taken bisphosphonates and have high bone turnover. The bone biopsies do not necessarily show complete suppression of bone formation. Low turnover alone, however, does not explain the occurance of these fractures, because a large percentage of patients taking bisphosphonates have very low or absent bone formation, yet the vast majority of them have not experienced unusual fractures. Other factors as yet unknown may predispose some patients to develop these fractures.

Two groups have done systemic surveys of subtrochanteric fractures from their hospitals. Goh et al (33) identified 13 non-traumatic subtrochanteric fractures from a review of medical records over a 10 month period. Nine of the patients were taking bisphosphonates, and they were younger, had higher bone density, and thicker bone on the radiographs of the femur. During the next 10 months 8 more patients taking alendronate had non-traumatic subtrochanteric fractures (35). The second series included all low-energy subtrochanteric fractures seen over 5 years from a large New York hospital (37, 46, 47). There were 69 patients, and 36% of them had been taking alendronate with mean duration of 6.2yrs. Twenty patients had an unusual radiographic appearance of thick cortices and a unicortical beak; 19 of them were taking alendronate. These cases were then matched to patients with hip fractures who were the same age, race, and body mass index. A higher percentage of subtrochanteric fractures cases were associated with bisphosphonates. The unusual appearance of the radiographs is the main reason that physicians think bisphosphonates may play a role in the development of these fractures. These studies still do not allow an estimation of the incidence rate among patients who are taking these drugs.

Investigators from Denmark took advantage of the computerized databases of hospital discharge codes and of medication usage. There were 160,565 persons whose first fracture was between 1997 and 2005. The rate of alendronate use in those with subtrochanteric and diaphyseal femur fractures was similar to those with hip fractures (6.7%). A cohort of fracture cases (excluding hip fractures) older than 51 who started taking a bisphosphonate after the index and continued for at least 6 months (N=5,187) were matched to two controls with the same age, gender and fracture site, and the subsequent hip or subtrochanteric fracture rates were recorded. The rate per year of subtochanteric or diaphyseal femur fractures was 0.28% in alendronate group and 0.17% in control; the rate of hip fractures was 1.82% in alendronate group and 1.18% in controls. They concluded that the subtrochanteric fractures were like typical osteoporotic fractures because the adjusted hazard ratio for an atypical fracture (1.46) was similar to that for a hip fracture (1.45). Unlike findings in randomized clinical trials, there were more fractures in those taking alendronate, even though they were matched by age, gender, and location of the first fracture. Perhaps this was because physicians had prescribed alendronate to patients who were at a higher risk. In this registry-based study, details about the fracture or the degree of trauma could not be analyzed, and distal femur fractures were included with subtrochanteric ones. Only 178 patients had been taking the bisphosphonates longer than 6 years and 1.1% of them had a subtrochanteric fracture, while 0.8% of their controls also had a subtrochanteric fracture (48).

Diagnostic and therapeutic strategies

To assess skeletal status, the most common diagnostic measurements are bone density using dual xray absorptiometry (DXA) and the biochemical markers of bone turnover: Bone alkaline phosphatase (BAP), procollagen type I N-terminal propeptide (P1NP) reflect formation and the collagen cross-linking molecules, N-telopeptide (NTX) and C-telopeptide (CTX) are correlated with resorption. The gold standard way to measure

bone formation is an iliac crest bone biopsy with tetracycline labelling.

Controversies that exist

First, it is important to state that there is consensus about treating patients with a high risk of fracture, especially elderly patients with a vertebral compression fracture or other low-trauma osteoporotic fracture, or hip BMD T-score lower than -2.5. Too often these men and women are ignored, and osteoporosis is considered just an ordinary part of getting older. When these patients are given bisphosphonates, the benefit from preventing another fracture definitely outweighs the risks of side effects. No drug is 100% perfect and I have heard of too many patients who are afraid to take bisphosphonates because of over-exaggerated adverse events.

Whether to use DXA measurements or biochemical markers to follow patients receiving bisphosphonates is currently controversial, and the topic of this review is as controversial as possible. The major question is whether to stop bisphosphonates after 5 years, or whether they should be continued indefinitely. There has been an unfortunate scare about osteonecrosis of the jaw, which is a problem in some patients with cancer who have received long-term high doses, but this is very rare in patients who are treated for osteoporosis (lower that 1 in 10,000 patients/year)(1). The rate of atypical fractures in those on bisphosphonates is less than 2 in 1,000, and there are only a few dozen cases in the literature. The risk of these fractures with use beyond a decade, however, is unknown because too few patients have been taking these drugs that long. There are theoretical concerns about long-term over-suppression of bone formation resulting in micro-damage accumulation or increased brittleness of the bone. On the other hand, there are theoretical concerns about stopping the drugs, because the bone resorption could resume before bone formation does, which would result in an interval of rapid bone loss and potential destruction of micro-architecture.

Appropriate approach to management

After a patient with osteoporosis has been taking a bisphosphonate for 5 years, there are three choices: continue the bisphosphonate, change to another kind of medicine, or discontinue the bisphosphonate. The only randomized clinical trial of continued bisphosphonates after 5 years of use does not provide compelling evidence of efficacy. During the last 5 years the medication did not improve the incidence of all clinical fractures, non-vertebral fractures and morphometric vertebral fractures. Therefore, in patients who have been doing well, who have shown some improvement in bone density during their 5 years of treatment and have not had any fractures, I usually measure a urine NTX, which is typically lower than 30 nM BCE/mM Cr. These markers have a diurnal rhythm and daily variation, but despite their errors they do help identify suppressed bone resorption. If this is as expected, I suggest a drug holiday, and discontinue the bisphosphonate. The patient remains on calcium and vitamin D supplementation, and is encouraged to get exercise. I am particularly likely to use this approach in those patients who did not have a high fracture risk when their physicians started alendronate. The bone density tends to be stable for one or two years after discontinuation, and the biochemical markers of bone resorption remain suppressed for several years. Although the evidence for this approach is poor, I follow the urine NTX annually, and restart an anti-resorptive medication when the value increases to about 40 nM BCE/mM Cr. Other physicians would continue the bisphosphonates because they are concerned about the rate of clinical vertebral fractures, which are better in patients who remain on the drugs. Also, the single trial of only 1099 subjects did not have adequate power to give a definite answer about long-term fracture rates, whereas several large trials clearly show fracture reduction during the first 3 to 5 years of bisphosphonate use.

If a patient has been prescribed a bisphosphonate for 5 years but the NTX is not suppressed I re-evaluate the patient. Some are not taking the medication, or are not taking it

properly. Some may have another disease, such as hyperparathryoidism, malignancy, hyperthyroidism, malabsorption, or vitamin D deficiency. If repeated biochemical tests show high bone resorption, and if the bone density response is suboptimal, and no other cause is found, I often switch to an intravenous form of bisphosphonate because some patients do not seem to absorb the oral doses.

If a patient is not doing well and has had a fracture despite several years of bisphosphonate therapy, I first check for any other medical problems. The bone markers are, unfortunately, not very helpful because they increase after a fracture and stay elevated for at least 4 months (49). If there are no contraindications, treatment with teriparatide is a reasonable choice. There is evidence from human biopsies that teriparatide can reduce the number of micro-cracks that were related to bisphosphonate treatment (50), and can increase the bone formation rate even when there has been prior bisphosphonate treatment (51) (52, 53) (although the anabolic effect is blunted, it is still there (54)).

A frail patient with a very high risk of fracture, especially one who needs treatment with glucocorticoids or who had a hip T-score below -3, presents a challenge. Many physicians are uneasy about discontinuing all osteoporosis-specific medications, even after 5 years of successful bisphosphonates. I am cautious about further biphosphonates because these patients might have a greater chance of developing micro-damage or even subtrochanteric fractures. I will usually stop the bisphosphonate and change to another medication, such as a SERM (selective estrogen receptor modulator) or teriparatide. Until we have better long-term clinical evidence, there will be various different approaches to these patients and I can not be sure of the best one. Further research is greatly needed, because these drugs are now used very widely.

The case I chose to present is admittedly not a common one, but we have seen six similar cases recently and in two patients the femurs fractured while the stress fractures were being evaluated (see figure 2). There is no data at all about how many long-term bisphosphoante users may have these stress fractures and then heal them, or about whether treatment with teriparatide alone can cure the stress fractures. We had to make a decision without sufficient evidence. I consulted our skeletal radiologists and some of my colleagues, then had a long discussion with the patient and orthopaedic surgeon and decided to discontinue the alendronate, place intramedullary rods in both femurs, and begin a course of teriparatide.

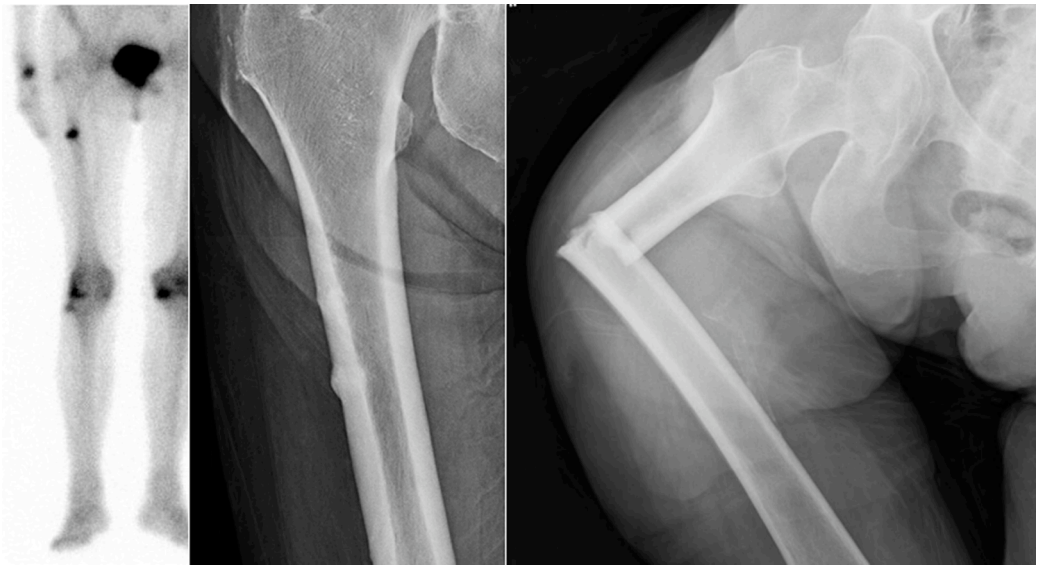


Figure 2. Left panel: Bone scan of another patient who presented with several months of thigh pain. She had been taking alendronate for ten years. Middle panel: Radiograph of a stress fracture corresponding to the area of increased uptake on the femur. Right panel: The patient had a minor fall and fractured her femur through the area of the stress fracture. A bone biopsy after a single tetracyline label showed no tetracycline uptake in the cancellous bone.

REFERENCES

1. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E 2007 Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 22:1479-91
2. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR 2007 Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 356:1809-22
3. Cummings SR, Schwartz AV, Black DM 2007 Alendronate and atrial fibrillation. N Engl J Med 356:1895-6
4. Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM 2008 Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med 168:826-31
5. Sorensen HT, Christensen S, Mehnert F, Pedersen L, Chapurlat RD, Cummings SR, Baron JA 2008 Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. Bmj 336:813-6
6. Food and Drug Administration 2008 Update of Safety Review Follow-up to the October 1, 2007 Early Communication about the Ongoing Safety Review of Bisphosphonates. Online at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm, posted 11/12/08.
7. Wysowski DK 2009 Reports of esophageal cancer with oral bisphosphonate use. N Engl J Med 360:89-90
8. Russell RG, Xia Z, Dunford JE, Oppermann U, Kwaasi A, Hulley PA, Kavanagh KL, Triffitt JT, Lundy MW, Phipps RJ, Barnett BL, Coxon FP, Rogers MJ, Watts NB, Ebetino FH 2007 Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. Ann N Y Acad Sci 1117:209-57
9. Heaney RP 2003 Is the paradigm shifting? Bone 33:457-65
10. Borah B, Dufresne TE, Ritman EL, Jorgensen SM, Liu S, Chmielewski PA, Phipps RJ, Zhou X, Sibonga JD, Turner RT 2006 Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: sequential triple biopsy studies with micro-computed tomography. Bone 39:345-52
11. Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux JP, Portero-Muzy N, Delmas PD 2007 Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: a bone biopsy study. J Bone Miner Res 22:1502-9
12. Stepan JJ, Burr DB, Pavo I, Sipos A, Michalska D, Li J, Fahrleitner-Pammer A, Petto H, Westmore M, Michalsky D, Sato M, Dobnig H 2007 Low bone mineral density is associated with bone microdamage accumulation in postmenopausal women with osteoporosis. Bone 41:378-85
13. Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ 1997 Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest 100:1475-80
14. Eriksen EF, Melsen F, Sod E, Barton I, Chines A 2002 Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. Bone 31:620-5.
15. Han ZH, Palnitkar S, Rao DS, Nelson D, Parfitt AM 1997 Effects of ethnicity and age or menopause on the remodeling and turnover of iliac bone: implications for mechanisms of bone loss. J Bone Miner Res 12:498-508
16. Recker RR, Kimmel DB, Parfitt AM, Davies KM, Keshawarz N, Hinders S 1988 Static and tetracycline-based bone histomorphometric data from 34 normal postmenopausal females. J Bone Miner Res 3:133-44

17. Parisien M, Cosman F, Morgan D, Schnitzer M, Liang X, Nieves J, Forese L, Luckey M, Meier D, Shen V, Lindsay R, Dempster DW 1997 Histomorphometric assessment of bone mass, structure, and remodeling: a comparison between healthy black and white premenopausal women. J Bone Miner Res 12:948-57
18. Vedi S, Compston JE, Webb A, Tighe JR 1983 Histomorphometric analysis of dynamic parameters of trabecular bone formation in the iliac crest of normal British subjects. Metab Bone Dis Relat Res 5:69-74
19. Boivin G, Meunier PJ 2002 Effects of bisphosphonates on matrix mineralization. J Musculoskelet Neuronal Interact 2:538-43
20. Zoehrer R, Roschger P, Paschalis EP, Hofstaetter JG, Durchschlag E, Fratzl P, Phipps R, Klaushofer K 2006 Effects of 3- and 5-year treatment with risedronate on bone mineralization density distribution in triple biopsies of the iliac crest in postmenopausal women. J Bone Miner Res 21:1106-12
21. Mori S, Burr DB 1993 Increased intracortical remodeling following fatigue damage. Bone 14:103-9
22. Allen MR, Burr DB 2007 Three years of alendronate treatment results in similar levels of vertebral microdamage as after one year of treatment. J Bone Miner Res 22:1759-65
23. Parfitt AM 2002 Misconceptions (2): turnover is always higher in cancellous than in cortical bone. Bone 30:807-9
24. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA 2004 Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 75:462-8
25. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R 2000 Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 11:83-91
26. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW, Jr., Dequeker J, Favus M 1995 Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 333:1437-43
27. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA 2004 Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189-99.
28. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 348:1535-41
29. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR 2006 Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. Jama 296:2927-38
30. Ott SM 2007 Use of alendronate after 5 years of treatment. Jama 297:1979; author reply 1980-1
31. Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG 2008 Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. Osteoporos Int
32. Cheung RK, Leung KK, Lee KC, Chow TC 2007 Sequential non-traumatic femoral shaft fractures in a patient on long-term alendronate. Hong Kong Med J 13:485-9
33. Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT, Howe TS 2007 Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br 89:349-53
34. Imai K, Yamamoto S, Anamizu Y, Horiuchi T 2007 Pelvic insufficiency fracture associated with severe suppression of bone turnover by alendronate therapy. J Bone Miner Metab 25:333-6
35. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS 2008 An emerging pattern of subtrochanteric stress fractures: a long-term

complication of alendronate therapy? Injury 39:224-31
36. Kwek EB, Koh JS, Howe TS 2008 More on atypical fractures of the femoral diaphysis. N Engl J Med 359:316-7; author reply 317-8
37. Lenart BA, Lorich DG, Lane JM 2008 Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med 358:1304-6
38. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY 2005 Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 90:1294-301
39. Sayed-Noor AS, Sjoden GO 2008 Subtrochanteric displaced insufficiency fracture after long-term alendronate therapy--a case report. Acta Orthop 79:565-7
40. Sayed-Noor AS, Sjoden GO 2009 Case Reports: Two Femoral Insufficiency Fractures after Long-term Alendronate Therapy. Clin Orthop Relat Res
41. Schneider JP 2006 Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics 61:31-3
42. Schneider JP 2009 Bisphosphonates and low-impact femoral fractures: Current evidence on alendronate-fracture risk. Geriatrics 64:18-23
43. Odvina CV, Levy S, Rao S, Zerwekh JE, Sudhaker Rao D 2009 Unusual mid-shaft fractures during long term bisphosphonate therapy. Clin Endocrinol (Oxf)
44. Whyte MP 2008 Atypical Femoral Fractures, Bisphosphonates, and Adult Hypophosphatasia. J Bone Miner Res
45. Armamento-Villareal R, Napoli N, Panwar V, Novack D 2006 Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. N Engl J Med 355:2048-50
46. Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, van der Meulen MC, Lorich DG, Lane JM 2008 Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int
47. Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG 2008 Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma 22:346-50
48. Abrahamsen B, Eiken P, Eastell R 2008 Subtrochanteric And Diaphyseal Femur Fractures in Patients Treated with Alendronate: A Register-Based National Cohort Study. J Bone Miner Res
49. Ivaska KK, Gerdhem P, Akesson K, Garnero P, Obrant KJ 2007 Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. J Bone Miner Res 22:1155-64
50. Stepan JJ, Dobnig H, Burr DB, Li J, Ma YL, Sipos A, Petto H, Pavo I 2008 Histomorphometric Changes by Teriparatide in Alendronate Pre-treated Women with Osteoporosis. Presented at Annual meeting of American Society of Bone and Mineral Research, Montreal:#1019
51. Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R 2008 Retreatment with Teriparatide One Year After the First Teriparatide Course in Patients on Continued Long-Term Alendronate. J Bone Miner Res
52. Jobke B, Pfeifer M, Minne HW 2009 Teriparatide following bisphosphonates: initial and long-term effects on microarchitecture and bone remodeling at the human iliac crest. Connect Tissue Res 50:46-54
53. Miller PD, Delmas PD, Lindsay R, Watts NB, Luckey M, Adachi J, Saag K, Greenspan SL, Seeman E, Boonen S, Meeves S, Lang TF, Bilezikian JP 2008 Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. J Clin Endocrinol Metab 93:3785-93
54. Ettinger B, San Martin J, Crans G, Pavo I 2004 Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res 19:745-51

Table 1. Review of reported cases of atypical fractures in patients receiving treatment with bisphosphonates

Author	Year	Location	Source	N	Age	Years Therapy	Prodrome	Bilateral	Xrays	Other drugs	Marker	Bone biopsy	Comments
Odvina	2005	Detroit and Dallas	referral cases	9		3 to 8; mean 5.4				estrogen 3, prednisone 2	BAP variable, NTX low in 7/9	no db lb in all 9	some had delayed healing
Schneider	2006	Arizona	case report	1	59	7	3 mo		Ct. thick, transverse with spike	estrogen			fx preceded fall; delayed healing
Cheung	2007	HongKong	case report	1	82	10		yes			high OH-proline	no db lb	sudden thigh pain while walking caused fall
Imai	2007	Tokyo	case report	1	78	3				no	NTX 123	no db lb	pelvic fx no trauma
Kwek, Goh	2008	Singapore	all cases for 20 mo in one hospital	17	53-82; mean 66	2-10 ; mean 4.4	yes in 13/17	yes in 10/17	lateral Ct. thickening, transverse fx, medial Ct. spike	1 on steroids			7/17 had acute pain prior to fall
Neviaser, Lenert	2008	NY	all cases for 5 yrs in one hospital	25	69.4	6.2			unicortical beak				alen users younger
Sayed-Noor	2008	Sweden	case report	1	72	7	18 mo	yes	Ct. thick, transverse				no trauma; delayed healing
Sayed-Noor	2008	Sweden	case reports	2	55,78	9	3mo, 10 mo	yes in 1	Ct. lateral reaction, later transverse fx	ETOH			periprosthetic, no healing for 10 months then fx
Visekruna	2008	Wisconsin	case reports	3	51 - 75	5 to 10, mean 8.3		2 of 3	one non-displaced; others chalk-stick	estrogen 2 prednisone 3	in one, NTX 12 with stress fx	done in 2, both severe low tcn label	delayed healing; one given iPTH and healed
Schneider	2009	Arizona	referral cases	3	59 to 66	5 to 9	yes in 1 for 12 mo	in 2/3					fx before fall; two had prophylactic rodding
Odvina	2009	Dallas and Detroit	referral cases	13	38-72	7.3 ± 3		in 2/13	Ct. thick	estrogen 3 tamoxifen 2	within normal range	done in 6, low db lb	minimal trauma; many delayed healing

Ct: cortical; db lb: double label; fx: fracture; BAP: bone alkaline phosphatase; NTX: N-telopeptide