Bisphosphonate Fractures as a Cause of Painful Total Hip Arthroplasty

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abstract

Osteoporotic fractures pose a significant health concern for postmenopausal women. Bisphosphonate therapy has been shown to decrease the risk of these fractures. The bisphosphonate alendronate was approved by the US Food and Drug Administration for use in the United States in 1995, but questions have recently arisen concerning low-energy subtrochanteric femur fractures sustained by chronic users. Although no definitive association or causality between bisphosphonates and these fractures has been established, numerous cautionary reports exist concerning the duration of use and safety of alendronate in osteoporotic patients.

This article reports 3 occurrences of bisphosphonate-associated atypical femur fractures as an etiology of periprosthetic hip pain in the total hip arthroplasty (THA) patient. These fractures are particularly concerning because these patients are often not advised to protect their weight bearing simply due to a painful THA and may sustain a catastrophic failure if not followed closely. Several theories have been suggested concerning the pathophysiology of atypical low-energy subtrochanteric fractures following bisphosphonate use. Each patient described in this article carried a diagnosis of rheumatoid arthritis and underwent chronic medical therapy; each patient experienced a delay in the diagnosis and onset of therapy due to low suspicion for bisphosphonate-associated fracture. This problem may become more common in the clinical setting; therefore, one must be vigilant and aware of this etiology of periprosthetic hip pain.
Osteoporotic fractures pose a significant health concern for postmenopausal women. Bisphosphonate therapy has been shown to decrease the risk of these fractures.1 The bisphosphonate alendronate was approved by the US Food and Drug Administration for use in the United States in 1995,2 but questions have recently arisen concerning low-energy subtrochanteric femur fractures sustained by chronic users. Although no definitive association or causality between bisphosphonates and these fractures has been established, numerous cautionary reports exist concerning the duration of use and safety of alendronate in osteoporotic patients.3-5

Many postmenopausal women who have undergone total hip arthroplasty (THA) take bisphosphonates to treat their osteoporosis. Unfortunately, on occasion these patients present with thigh or hip pain following THA. Multiple etiologies must be considered by the evaluating physician, including loosening, sepsis, synovitis, or referred radicular pain. To our knowledge, the percentage of patients concurrently prescribed bisphosphonates and undergoing THA has not been described; however, in our clinical experience, the percentage seems to be increasing as osteoporosis is being more aggressively treated both by primary care physicians and orthopedic surgeons.

This article describes another etiology of postoperative hip pain following THA: bisphosphonate-induced subtrochanteric stress fracture. The patients described here were informed that their case data would be submitted for publication, and they gave their consent. Institutional Review Board approval was obtained.

**CASE REPORTS**

**Patient 1**

A 52-year-old woman with rheumatoid arthritis underwent a proximal femoral osteotomy with lateral plate fixation for hip dysplasia in 1973. This was followed by a conversion THA and hardware removal without complications in 2007. The patient was asymptomatic until July 2010, when she presented to her primary care physician reporting back pain and radiating left leg pain. She was referred to a physiatrist, who obtained negative hip radiographs and spine radiographs depicting degenerative joint disease at L4-5. A left sacroiliac joint injection and a left L5 nerve root block was performed with some relief for her back and leg pain.

In October 2010, she presented to her THA surgeon reporting pain in her upper thigh that had intensified over the past 2 months and required 2 crutches for ambulation. She reported no rest pain or trauma at that time. She had used nonsteroidal anti-inflammatory drugs, analgesics, ice, heat, and a transcutaneous electrical nerve stimulation unit over the past 2 months unsuccessfully to control her symptoms. Radiographs at that time were interpreted as negative except for residual periostitis distal to the implant, felt to be related to the hardware removal (Figure 1A). Her pain was felt to be radicular in nature by the THA surgeon, who referred her back to the physiatrist for a L3 nerve root block, which was performed in October 2010 without relief. A bone scan was interpreted as positive for femoral loosening (Figure 1B).

At this time, she was referred to our hip and knee center for a second opinion. She was noted to have significant pain to forceful rotation of the hip, palpatory pain along the lateral aspect of her femur, and negative stretch signs for radiculopathy. Her gait was antalgic, even with the use of a single crutch. Medications at presentation included alendronate, diclofenac, prednisone, and azathioprine, all of which she had been taking for a minimum of 5 years. Radiographs taken to include the femur distal to the implant showed an anterolateral stress fracture below the prosthesis (Figure 1C).

![Figure 1: AP radiograph at presentation (A). Bone scan (B). Six-week follow-up radiograph (C).](image-url)
The patient was instructed to discontinue alendronate and begin calcium 500 mg 3 times/day and vitamin D 2000 IU/day and continue with limited weight bearing with 2 crutches. After 8 weeks of this treatment, her pain improved, and she was weaned from crutches to a cane. At 6-month follow-up, she was asymptomatic and weaning completely from her cane.

**Patient 2**

In May 2010, an 85-year-old woman who underwent THA in 1995 sustained a fall onto her left side, injuring her ribs. Three weeks after her fall, she presented to her primary care physician with new-onset right hip pain. Negative radiographs were taken, and a diagnosis of trochanteric bursitis was made. She was treated with physical therapy and ultrasound to the area.

In July 2010, she was referred to our hip and knee center reporting painful THA. Physical examination at that time included an antalgic gait, tenderness over the trochanter, and mild pain with rotation of the hip. Negative radiographs were taken (Figure 2A), and a presumptive diagnosis of an occult pelvic or trochanteric fracture was made. She was treated with physical therapy and ultrasound to the area.

At 6-month follow-up, the patient’s pain was minimal, and she had returned to her previous household ambulatory activity level with the use of a walker for stability.

**Patient 3**

A 79-year-old woman who underwent left THA in 1991 presented in November 2009 with new-onset left hip pain of approximately 1 month’s duration. Medical history was significant for rheumatoid arthritis and osteoporosis. Medications taken by the patient included prednisone, hydroxychloroquine, and alendronate, each for at least 9 years; however, the patient could not recollect the exact timing of medication initiation. The patient was placed on a walker with limited weight bearing and asked to return for follow-up radiographs in 3 weeks. She subsequently saw her rheumatologist, and a bone scan was positive for a diaphyseal stress fracture (Figure 2B).

She was then referred back to our center, where radiographs depicted a subtrochanteric stress fracture (Figure 2C). Her medications at this time included prednisone, risedronate, and methotrexate; they had been taken for many years, but the patient was unable to recollect the exact timing of medication initiation. The patient was instructed to discontinue risedronate and begin calcium, vitamin D, and protective weight bearing with a walker. She was also started on teriparatide by her rheumatologist.

After 3-month follow-up, the patient showed improvement and was given an additional month of teriparatide. At 6-month follow-up, she no longer required any assistive devices for ambulation and reported no pain in her left hip. Radiographs showed evidence of a healed fracture (Figure 3B). Eighteen months following diagnosis, the patient was pain free with no additional interventions required.

**DISCUSSION**

Painful THA can be a diagnostic dilemma in some patients. As described by Hanssen, it is crucial to first elucidate whether the pain is from an intrinsic (the hip itself) or extrinsic (referred) source. Extrinsic sources include spinal pathology, neurologic compression, vascular disease, tendonitis, or bursitis about the hip. Intrinsic sources include loosening or fracture of the prosthesis, hip instability, prosthesis impingement, modulus of elasticity mismatch, metal hypersensitivity, wear debris with associated synovitis, or infection. We add bisphosphonate-associated fracture to the list of etiologies to be considered in the workup of the painful THA.

![Figure 2: AP radiograph at presentation (A). Bone scan (B). Ten-week follow-up radiograph (C).](image-url)
It is important to note worsening symptoms in patients with painful THAs who also take bisphosphonates. This is particularly concerning because these patients are often not advised to protect their weight bearing simply due to a painful THA and may sustain a catastrophic failure if not followed closely.

A recent study by Capeci and Tejwani concerning alendronate-associated femur fractures suggested radiographs of the contralateral femur and consideration of discontinuing alendronate in consultation with an endocrinologist. In these cases, protected weight bearing and cessation of alendronate was sufficient to alleviate the symptoms and promote fracture healing.

More experience with this type of fracture is needed to determine whether this is adequate treatment or if prophylactic fixation should be recommended. However, in these cases, unlike the treatment of a virgin femur, spanning intramedullary prophylactic fixation is not an option, and treatment may require a much more invasive procedure such as plate fixation or stem revision. The key point in management of these patients is recognition before a catastrophic displaced fracture occurs.

Atypical subtrochanteric femur fractures in association with bisphosphonate use have been described in numerous case reports and case-control studies. A study by Neviaser et al in 2008 found the risk of having an atypical subtrochanteric fracture was significantly associated with alendronate use and concluded that there are unique features to bisphosphonate fractures. These features include a simple, transverse, or short oblique fracture pattern in areas of cortical hypertrophy with a cortical beak. These commonalities seen with atypical femur fractures were described further in a 2010 task force report of the American Society for Bone and Mineral Research to standardize these fractures for the purpose of reporting their incidence and future research. Another study by Nieves et al in 2010 found the rate of subtrochanteric and femoral shaft fractures to be higher than that of other fractures in women taking oral bisphosphonates. The Fracture Intervention Trial study reported by Black et al in 1996 reported no significant increase in the risk of subtrochanteric/diaphyseal fractures with alendronate use when compared with placebo; however, interpretation was difficult due to the paucity of fractures and large confidence intervals.

Several theories have been suggested concerning the pathophysiology of atypical low-energy subtrochanteric fractures following bisphosphonate use. Bisphosphonate treatment reduces bone turnover, with resultant increased overall mineralization leading to a homogenous bone structure. Homogenous bone has been shown to have greater risk of fracture compared with more heterogeneous bone. Reduced bone turnover also increases the accumulation of microdamage, which subsequently reduces bone toughness and increases susceptibility of new cracks. Odvina et al also reported markedly suppressed bone formation with reduced or absent osteoblastic surface in alendronate-treated patients presenting with spontaneous nonvertebral fractures.

The mechanism of action associated with the bisphosphonates alendronate and resorionate, as well as osteopromotors such as teriparatide, deserves mention. Bisphosphonates show preferential localization to sites of bone resorption, specifically inhibiting the ruffled border active in resorption of bone by osteoclasts. In contrast, teriparatide is a recombinant human parathyroid hormone that directly stimulates osteoblastogenesis and inhibits osteoclast apoptosis. Additional physiologic actions include promoting renal tubular reabsorption of calcium and phosphate and intestinal calcium absorption.

The number of atypical subtrochanteric fractures in association with bisphosphonates has been estimated to be as high as 1 per 1000 per year, which provides a favorable risk–benefit ratio for the use of bisphosphonates in the treatment and prevention of osteoporosis. Bisphosphonates should not be discontinued for patients at risk of osteoporotic fragility fractures; however, prescribers should be aware of the possible associations linked to their use.

We recommend that our patients suspend all bisphosphonate use to allow the fracture to heal and hopefully prevent a contralateral fracture. Current endocrinology literature suggests that patients at mild fracture risk might stop bisphosphonate treatment after 5 years and remain off as long as bone mineral density is stable. Higher risk patients treated for 10 years may undergo a holiday of no more than 1 or 2 years with continued nonbisphospho-
nate therapy during that time. The patients described herein would most likely fall into the high-risk category, making their long duration of bisphosphonate therapy appropriate; however, restarting their therapy in the future will be an issue of timing and concerns for using the same agent. Changing to an osteopromoting drug such as teriparatide may be an option in these high-risk patients.

In a recent report, the median bisphosphonate treatment duration in patients with atypical subtrochanteric and femoral shaft fractures was 7 years. Recommendations were made for patients sustaining a recent fracture and with femoral neck T-scores $<-2.5$ in consideration of a drug holiday from the bisphosphonate. The benefit of discontinuation after 4 to 5 years in the low-risk patient is still unknown. No data exist to guide when therapy should be reinstated; however, the study recommended following patients with clinical assessment, bone turnover markers, and bone mineral density determination following resolution of the fracture.

Compliance with bisphosphonate therapy by the patients in our series was high. Each patient required relatively strict adherence to her medication protocols due to other medical comorbidities, resulting in regimented medication schedules. This is in stark contrast to a study by Siris et al23 that showed 43% refill compliance in patients taking bisphosphonates and only 20% of patients receiving continuous, gap-free coverage for a 2-year period. However, those patients with strict adherence to bisphosphonate therapy were shown to have relative risk reductions of 20% to 45% for osteoporotic fractures.

Interestingly, each of our patients carried a diagnosis of rheumatoid arthritis and underwent chronic medical therapy that included prednisone in addition to methotrexate, azathioptine, or hydroxychloroquine. It is well known that osteoporosis may occur with chronic inflammatory diseases, and risk is further increased with exposure to glucocorticoids. A study by Girgis et al22 showed an increased risk (odds ratio, 5.2) of subtrochanteric fracture in patients on both a bisphosphonate and glucocorticoids. Patients using glucocorticoids have fractures at higher bone density than those not using glucocorticoids. In a study by Saag et al,24 bone density increased in patients receiving either alendronate or teriparatide, despite continued treatment with glucocorticoids. In steroid users, the bone density with teriparatide was significantly better than alendronate. Teriparatide was therefore recommended in patients at high risk for fracture who required sustained use of glucocorticoids and who had either osteoporosis or low bone mass with a prevalent fracture. Any of the patients presented herein would most likely qualify as high risk and may have experienced greater benefit from teriparatide than alendronate therapy.

Unfortunately, our patients experienced a delay in the diagnosis and onset of therapy due to low suspicion. Fortunately, each was diagnosed prior to catastrophic fracture around the implant, which would have necessitated a more invasive surgical intervention. Regarding physical examination, each patient had specific pain in the proximal lateral thigh with initially negative radiographs. Two of the patients also underwent 3-phase technetium bone scans that clearly defined the site of fracture within the femur and confirmation of radiographic findings at the diagnostic follow-up visit. Earlier investigation with a bone scan may have provided a diagnosis sooner; however, this depends on clinical insight and availability.

While early detection may be difficult, high suspicion and awareness of this entity in patients taking bisphosphonates may aid in the diagnosis and treatment of this problem. This is further stressed in the 2010 recommendations that education of physicians and patients concerning the prodromal symptoms of thigh or groin pain may catch these impending fractures prior to catastrophic failure. Physicians should also ask patients on bisphosphonates and other potent antiresorptive agents such as glucocorticoids about thigh or groin pain. Plain radiographs should be used for initial assessment; however, if equivocal, more specific testing such as magnetic resonance imaging or bone scan should be considered if index of suspicion remains high.

**References**


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Case Report


