The Outcome of Surgically Treated Femur Fractures Associated With Long-Term Bisphosphonate Use

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Introduction: Bisphosphonates (BPs) evolved as the mainstay for the treatment of osteoporosis, reducing the incidence of fractures. Recently several publications described the occurrence of low-energy subtrochanteric and femoral shaft fractures associated with long-term BP use. The aim of this study was to describe the outcome of surgically treated femur fractures associated with prolonged BP use.

Patients: Fifteen patients suffering from 17 atypical femoral fragility fractures associated with long-term (>3 years) BP use were located. Data included fracture type, time of BP use, last bone mineral density DEXA scores for the femoral neck and spine, type of surgery, and the need for revision.

Results: Fourteen female patients and one male patient were identified. The median age was 73 years (range, 51–80 years). The mean BP use was 7.8 years (range, 4–13 years). Fourteen patients had low-energy traumatic femoral shaft (proximal and distal) or low subtrochanteric fractures. The mean lumbar spine (for 13 patients) bone mineral density T-score was −3.0, whereas mean femoral neck T-score was −1.8 with only three patients in the osteoporotic range.

Fracture healing after the first procedure for patients treated with nails was 54%, with 46% of patients requiring revision surgery. These included nail dynamization, exchange nailing, and one revision to a blade plate. All of these eventually healed.

Conclusions: BP-related fractures are a recently described phenomenon. Despite initial osteoporosis, the DEXA scan may appear outside the osteoporotic range for the femoral neck in these patients. In addition, a much higher failure rate with intramedullary nailing requiring revision surgery may occur with these patients.

Key Words: Bisphosphonates, Femur Fractures, Osteoporosis, Fragility Fractures.

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During the last two decades, bisphosphonates (BPs) evolved as the mainstay therapy of osteoporosis. Their efficacy in reducing the incidence of fractures, including proximal femur fractures, in osteoporotic women has been demonstrated in several studies.[1,2] The efficacy and safety of even long-term (5–10 years) therapy has also been established.[3,4]

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Recently, several publications described subtrochanteric and low-energy femoral shaft fractures among patients associated with long-term BP use.[5–10] These fractures differ from the typical proximal femoral fracture associated with osteoporosis. They are caused by low-energy mechanisms, with typical radiographic features of thickened medial cortex and a beaking of the lateral cortex, appearing as insufficiency fractures.[8,11] Other typical described features include contralateral fractures in up to one half of the cases and localized thigh pain as a prodromal phase, which may precede the fracture by months.[8,11,12] Although these descriptions are becoming more frequent, the information regarding the treatment and outcome of these fractures still remains unknown. Our hypothesis was that the significantly altered bone metabolism caused by prolonged BP treatment would adversely affect bone healing.

Between the years 2005 and 2009, we have treated 17 femoral fractures in 15 consecutive osteoporotic patients previously treated with BPs. The aim of this study was to describe the outcome of surgically treated femur fractures associated in these patients and to add relevant clinical information about these uncommon fractures.

PATIENTS AND METHODS

Osteoporotic patients, previously treated with BPs, who sustained atypical fragility fractures of the femur, were retrospectively included. Patients with active malignancies involving bone were excluded. These fractures consisted of low-energy transverse subtrochanteric, femoral shaft, and distal femoral fractures, all featuring the same morphology and characteristics described for atypical femur fractures associated with BP use.[11,12] Fracture classification was made according to the Association of the Study of Internal Fixation and the Orthopaedic Trauma Association classification system.[13] All patients were operated in our institution.

Follow-up visits and radiographs were performed in our outpatient clinics at 6 weeks, 12 weeks, 6 months, and 1 year postoperatively. Fracture healing was assessed by an independent observer (G.R.). Radiographic healing was defined as callus bridging of three of four cortices on anteroposterior (AP) and lateral radiographs,[14] corresponding to RUST score of at least 8 to 9,[15] as well as painless weight bearing on the affected extremity. When available, we have reviewed, through the medical records, the results of the last bone mineral density (BMD) study at the anteroposterior (AP) lumbar spine and femoral neck region before the fracture. BMD was measured by dual-energy x-ray film absorptiom-

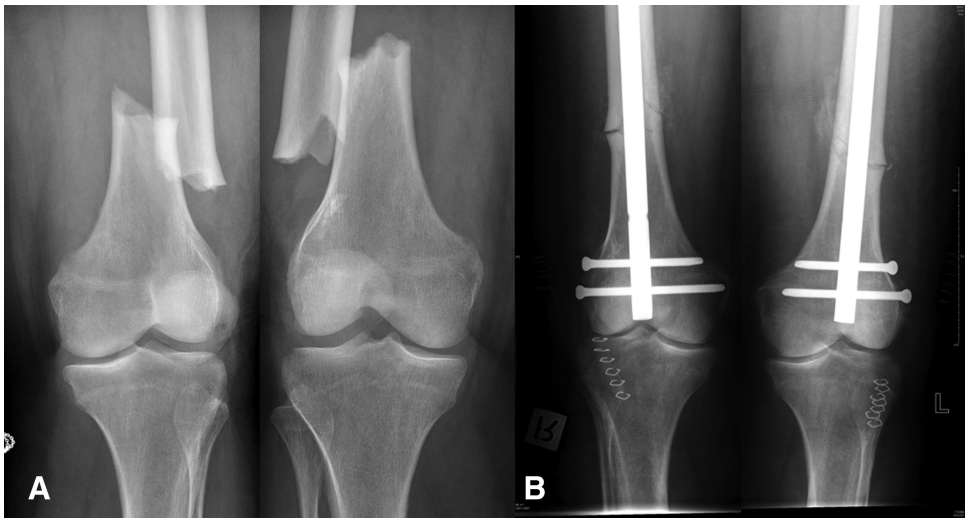

Figure 1. A 73-year-old female patient with a 7-year history of BP use. She sustained bilateral distal femoral shaft fracture after a simple fall on the sidewalk (*A, B*). After reduction and fixation with bilateral retrograde nails, the preexisting medial thickening and preinjury callus formation probably caused by a stress reaction are visible (*C*). The patient underwent uneventful healing at 3 months.

etry, using either a Hologic or a GE-Lunar machine. BMD T- and Z-scores, comparing the measured value to the peak bone mass and mean age-matched BMD, respectively, were derived using manufacturers' database for the spine and NHANES II data for the femoral neck.[16]

Nine femoral shaft fractures were treated with antegrade, locked, reamed intramedullary (IM) nails inserted through the piriformis fossa (AO universal IMN, Synthes, Battlach, Switzerland). These were performed by trauma surgeons, using a radiolucent table. Four subtrochateric fractures were treated with cephalomedullary nails (PFN, Synthes, Oberdorf, Switzerland) using a fracture table and a trochanteric entry point. Of the three distal-third femoral shaft fractures, one was treated with antegrade nail and one with retrograde femoral nails (bilateral case; Smith and Nephew, Memphis TN; Fig. 1). Another patient with a similar fracture was treated with a submuscular locked plate (LCP 4.5-mm titanium distal femoral locking plate; Synthes). As in the early years in treating these low-energy femur fractures, in several cases the fracture sites were opened for obtaining tissue for biopsy to rule out malignancy. Thus, seven cases of open nailing with biopsy were performed. It should be noted, however, that the incision and stripping at the fracture area were minimal and did not include excessive retraction and placement of bone clamps. In two additional cases, the fracture site was opened because of failed attempts for closed reduction. In six other cases, nailing was performed in a closed fashion. In one case, plating was performed through a minimally invasive submuscular approach. In most cases, early partial weight bearing using a walker was encouraged, with progression to full weight bearing in 6 weeks.

RESULTS

Seventeen fractures in 15 patients (14 females and 1 male patient) were identified. Three of the patients had bilateral fractures, two on the same instance (patients 9 and 10; Tables 1 and 2). The median age was 73 years (range, 51–85 years).

The mean BP use was 7.8 years (range, 4–13 years). The BP used varied and included etidronate, pamidronate, alendronate, risedronate, and zoledronate. However, alendronate was the most frequently prescribed BP.

BMD data were available in 14 patients (Table 1). The mean (±SD) lumbar spine T-score was -3.0 ± 1.0. In 71% of the patients, the T-score was ≤ -2.5, which defines osteoporosis according to the World Health Organization classification.[17] The mean femoral neck BMD T-score was -1.8 ± 1.0, only 20% had T-scores within the osteoporotic range.

Lumbar spine *z*-score of ≤ -2.0, which defines significantly reduced BMD compared with age-matched controls, was observed in 46% of the patients. None of the study patients had a femoral neck *z*-score ≤ -2.0.

None of the patients were smokers. BP therapy was discontinued immediately after the fracture in seven patients diagnosed in recent years. In six patients from the early study period, BP therapy was discontinued a couple of years later, along with the emerging awareness to the possibility of the association of this treatment with atypical subtrochanteric fractures (data were not available for the remaining two patients). In three patients, treatment with teriparatide, a parathyroid hormone analog with anabolic effect on bone, was initiated after the fracture. Nonsteroidal anti-inflammatory agents were withheld in all patients after immediate postoperative period (first 6–12 weeks).

Although the patients were referred to the metabolic bone clinic of the senior author, a complete work-up was available only for the minority of patients who complied with the follow-up. Calcium, phosphate, and creatinine levels were normal for all examined patients. Parathyroid hormone levels were slightly increased in two patients and within normal limits in another six. Vitamin D levels were insufficient (<30

TABLE 1. Patient Demographics, Mechanism of Injury, and BMD Data

					DEXA Score			
					Spine		Femoral Neck	
Patients SN	Age (Yr)	Gender	Fracture Mechanism	Duration of BP Treatment (yr)	T-Score	Z-Score	T-Score	Z-Score
1	80	Female	Fall	5	−2.7	0.0	−2.2	>0
2	73	Female	Fall	4	−3.5	−1.2	−2.8	−0.9
3	62	Female	Fall	8	−4.5	−2.9	−2.7	−1.3
4	72	Female	Fall	4	−4.4	−2.1	−2.6	−0.7
5	73	Female	Fall	12	−2.3	−0.3	−1.9	−0.1
6	85	Female	Fall	7	N/A	N/A	−1.4	1.1
7	62	Female	Fall	8	−1.3	−0.1	−0.2	1.0
8	72	Female	Fall	12	N/A	N/A	N/A	N/A
9	75	Female	Fall	7	N/A	N/A	N/A	N/A
9	75	Female	Fall	7	N/A	N/A	N/A	N/A
10	51	Female	Fall	5	N/A	N/A	−1.8	−1.1
10	51	Female	Fall	5	N/A	N/A	N/A	N/A
11	73	Female	Fall	11	−4.4	−2.0	N/A	N/A
12	52	Male	Fall	13	−2.5	−2.1	−2.3	−1.5
13	63	Female	Fall	5	−1.9	−0.6	0.5	1.7
14	73	Female	Atraumatic	12	−3.0	−0.7	−2.4	−0.4
15	76	Female	Fall	9	−2.9	−0.5	−1.4	0.7

TABLE 2. Orthopedic Data Regarding Fracture Type, Index, and Revision Surgery

Patient SN	Fracture (AO/OTA)	Index Surgery	Open/Closed Reduction	First Revision	Second Revision
1	Shaft 32A3	IMN	Open + Bx	Dynamization	Exchange nail
2	Subtrochanteric 32A3.1	CMN	Open + Bx	Exchange nail	
3	Shaft 32A3	IMN	Open + Bx		
4	Shaft 32A3	IMN	Open + Bx		
5	Distal shaft 32A2	IMN	Closed		
6	Subtrochanteric 32A3.1	CMN	Closed	Blade plate	
7	Subtrochanteric 32A3.1	CMN	Open nailing	Dynamization	
8	Shaft 32A3	IMN	Open + Bx	Dynamization	
9	Distal shaft 32A2	IMN	Closed		
9	Distal shaft 32A2	IMN	Closed		
10	Shaft 32A3	IMN	Closed		
10	Shaft 32A3	IMN	Closed	Exchange nail	
11	Shaft 32A3	IMN	Open + Bx		
12	Shaft 32B1	IMN	Closed	Dynamization	
13	Distal shaft 32A3	IMN	Open nailing		
14	Distal shaft 32A3	LCP	Closed		
15	Subtrochanteric 32B1.1	CMN	Open + Bx		

IMN, intramedullary nail; CMN, cephalomedullary nail; LCP, locked compression plate; BX, biopsy.

ng/mL) in four patients and normal in two. Bone resorption markers (carboxy-terminal collagen crosslink or deoxypyridinoline) were in the low normal range in all five patients in whom they were measured. In one patient, osteocalcin, a bone formation marker, was measured and found to be extremely low.

Reoperations occurred in seven patients (46%; Table 2). Out of the femoral shaft and subtrochanteric fractures treated with nails (16 fractures), seven (53%) underwent secondary procedures that composed of nail dynamization (three fractures), exchange nailing to a larger diameter nail (three fractures), and revision to a blade plate (one fracture). The overall surgical treatment and fracture types are depicted in Table 2. Two illustrative cases are presented in Figures 1 and 2.

In one patient, we retrospectively reviewed a contralateral fracture fixed a few years earlier that was morphologically suspicious of atypical subtrochanteric fracture. Because surgery was performed elsewhere before the study period, it was not included. In another patient, a radiographic stress reaction caused by contralateral thigh pain was observed and prophylactic intramedullary nailing was performed.

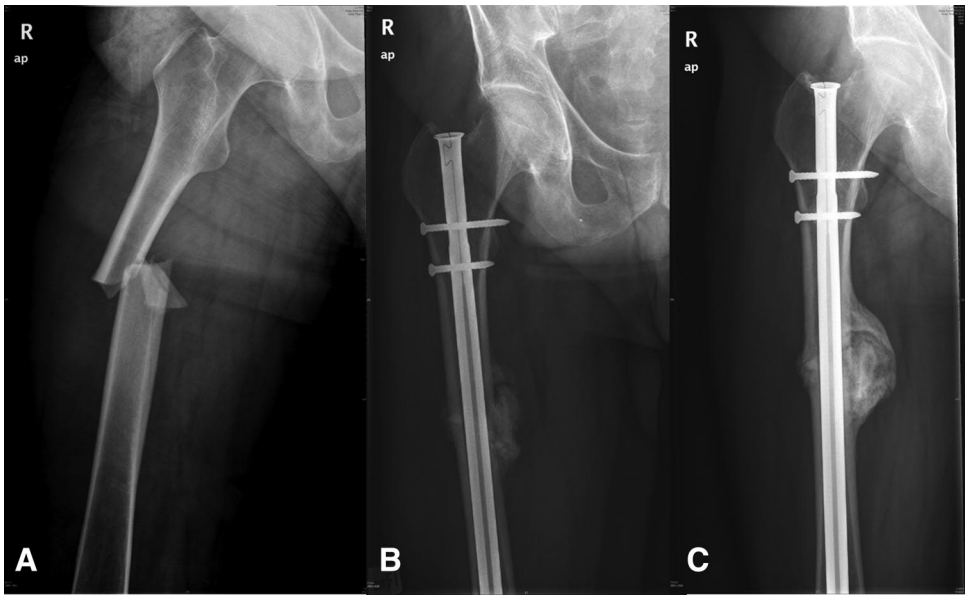

Figure 2. A 51-year-old liver transplant patient who was treated with alendronatefor the past 13 years because of osteoporosis. (*A*) AP radiograph of the broken femur after a domestic fall demonstrates typical thickened cortex and lateral beaking. (*B*) At 6 months after operation patient complains of pain during weight bearing—radiographs demonstrate scant woven bone-like callus formation. Patient was given systemic PTH analog injections, and the distal locking screws were removed, 18 months after index surgery, a solid union appeared and the patient is asymptomatic (*C*).

DISCUSSION

In this study, we report our experience with fractures as well as their problematic outcome, BP-associated atypical femoral.

Traditionally, IM nailing of femoral shaft fractures is reported as a very successful surgical procedure, with 98% to 99% healing rate.[18,19] However, in our study, we observed healing of these fractures after IM nailing in only 54%, with 46% of patients requiring additional procedures. Surgical revision ranged from minor revision surgery such as nail dynamization to more extensive procedures consisting of exchange nailing and plating. Because our results with IM nailing of femoral fractures in more than 1,500 unselected patients are consistent with the acceptable nonunion rates of less than 2%,[20] the higher failure rate obtained with BP-related fractures might reflect an impaired bone healing process rather than differences in surgical technique.

As pointed out with respect to the high failure rate of the surgical procedures in these patients, qualitative bone defect caused by prolonged BP therapy could also be a causative mechanism of these atypical fragility fractures at the proximal and distal femur.

Cortical thickening appears to be one of the hallmarks of BP-associated femoral shaft fractures. This was quantified by Lenart et al.[11] who found a significantly higher cortical thickness and bone diameter ratio in the femur of BP-treated patients with femoral shaft fractures, compared with cases with femoral shaft fractures not exposed to BPs, as well as in control women who sustained intertrochanteric or femoral neck fractures (0.30 vs. 019). Our BMD data support this finding and manifest discordance between the severely reduced BMD at the spine compared with the relatively maintained values at the femoral neck. Thus, in this study, using the accepted definition of osteoporosis,[2] femoral neck BMD was within the osteoporotic range in only 20% of the study patients, compared with an osteoporotic BMD at the spine that was observed in 70% in the same patients.

A recent experiment in alendronate-treated animals with normal bone density, the actual mechanical strength adjusted for bone density was significantly reduced.[21] In another canine study, alendronate-treated animals were found to have hypermineralization and accumulation of microfractures resulting in decreased bone quality and increased brittleness albeit normal appearing mineral density.[22] In a human bone biopsy study on long-term BP-treated patients presenting with cortical fractures, suppressed bone turnover was found in vast majority (15 of 21) of them.[23] This is consistent with the findings of low levels of bone turnover markers in the subset of our patients in whom these markers were measured.

This apparently impaired bone metabolism associated with BP therapy may indicate a need for more aggressive medical and intraoperative biologic augmentation, such as primary bone grafting, the use of human recombinant bone morphogenic protein, or treatment with systemic parathyroid hormone analogs.[24–26] The latter drug had shown some initial promising clinical effects with osteoporotic fracture healing.[27]

Another finding, not mentioned in previous studies, is the occurrence of distal femoral shaft fractures. The distal femoral shaft fractures are similar in both mechanism and radiographic morphology to the more proximal femur shaft fractures (i.e., cortical thickening and lateral beaking).

Historically, BPs have been proven to be effective in the treatment of osteoporosis and the prevention of osteoporotic related hip, vertebral, and wrist fractures.[1,3] Current

knowledge suggests that the risk of a BP-related stress and atypical fracture is relatively small, compared with their benefit in reducing osteoporotic fractures. Thus, a recent study estimated the risk of a femoral stress fracture after long-term BP use to be about 1:1,000 patients, 46-fold higher than previously untreated patients.[12] In their study, the authors quoted this figure as an acceptable risk, because the BP therapy reduces the risk of fractures by a ratio of 15:1,000. Furthermore, several recent reports cast a shadow about the association of atypical femoral shaft fractures and BP use. An observational register-based study failed to find an association between BP use and atypical femur shaft fractures.[28] Post hoc analysis of three major phase 3 studies of BPs for postmenopausal osteoporosis found no difference in the incidence of femoral shaft fracture between the treatment and placebo groups.[29] An Food and Drug Administration Drug Safety Communication concluded that currently a clear connection between BP use and a risk of atypical subtrochanteric femur fractures has not been shown.[30] Obviously, further research on a larger number of cases is required to accurately answer this intriguing question.

The limitations of this study are common to all other published case series regarding BP-related fractures, consisting of a retrospectively collected small number of patients. Although definite conclusion cannot be made as to the recommended treatment period, the possible adverse effects of long-term BP treatment, namely the risk of fracture and possible complications after surgical treatment of these fractures, should be considered. In addition, not all patients were thoroughly evaluated for bone metabolic turnover as well for bone pathology. Further investigation is needed for establishing therapeutic guidelines based on patient-specific metabolic work-up.

In conclusion, we think that the approach to BP-related femoral fractures requires a different medical and surgical care strategy used for "conventional" subtrochanteric and femoral shaft fractures. These strategies are yet to be analyzed through a multidisciplinary approach. Further investigations and prospective studies are necessary to guide the clinician in regard to optimal approach of BP administration in osteoporotic patients to minimize these rare, but serious complications.

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