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Original Article

Atypical femur fractures associated with bisphosphonates treatment: Retrospective single-center study

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Abstract

Aim: Osteoporosis is a very common condition caused by an imbalance between bone production and resorption. The first-line treatment of osteoporosis and the most commonly prescribed medication group is bisphosphonates. In recent years, several researches have reported that atypical femur fractures are seen following long term bisphosphonate usage. However, time of usage is not clearly defined yet. Our purpose of this study was to unveil the correlation between long term bisphosphonate usage and atypical femur fractures.

Material and Methods: Patients with a history of bisphosphonates treatment with atypical femur fracture were retrospectively analyzed. The collected data included patient demographics, the presence of trauma or history of the fracture, concomitant medical diagnoses, and history of bisphosphonates usage, type of bisphosphonates used, concomitant fractures, and other complications related to atypical femur fractures, mortalities.

Results: Twenty-two patients were included. All patients were female, and the mean age was 79.36±8.71 (mean ± SD) years. Sixteen patients were taking alendronate for an average of 6.81±2.74 (mean ± SD) years while six patients were taking ibandronate sustained atypical femur fractures in a shorter time average of 4.66±1.49 (mean ±SD) years. Atypical femur fractures are started to be diagnosed after 3 years of usage with having peak numbers in forth year.

Conclusion: Our study supports correlation between long term bisphosphonates usage and atypical femur fractures as reported in several studies. In the use of long-term bisphosphonates more than 3 years, care should be taken for atypical femur fractures, with investigating prodromal symptoms and performing radiological imaging.

Keywords: Bisphosphonates; atypical femoral fracture; osteoporosis treatment; fragility fractures

INTRODUCTION

Osteoporosis, estimated to affect millions of people worldwide, is a condition caused by an imbalance between bone production and bone resorption. It has been known that female gender, age, genetics, low body mass index, race, certain habits (e.g., smoking), and chronic exposure to certain medications (e.g., corticosteroids) are the risk factors for osteoporosis (1). Although the recommended first-line treatment of osteoporosis and the most commonly prescribed medication group is bisphosphonates (BPs), which can reduce the incidence of vertebral and non-vertebral fractures and suppress the loss of bone volume in patients with osteoporosis (2), it has been reported in recent literature that BPs absorbed by osteoclasts cause premature osteoclastic apoptosis and induce the reduction of the number of osteoclasts that uncouple bone formation and bone resorption. As a result, these processes disrupt the process of bone remodeling, increase bone fragility, and cause accumulation of microdamage (2). Currently, many reports demonstrate that BP therapy is associated with adverse effects because the absolute risk of an atypical femur fracture in patients taking BPs is approximately 3.2 to 50 cases per 100,000 people/year. The risk might be higher in patients with long-term bisphosphonate use, potentially up to 100 per 100,000 people/year. Consequently, long-term BP usage is shown to cause a seven-fold increase in micro damage and results in a 40% reduction in the energy required to cause a fracture (3). Schilcher et al. reported that the risk of atypical femur fractures increases steadily with longer time of usage and drops off by approximately 70% per

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year after last use (4). These fractures are usually femoral stress fractures localized at subtrochanteric and shaft regions of the femur that were defined as "atypical" femur fractures (AFFs). AFFs were first described by Odvina et al. in 2005, suggesting long-term bisphosphonate use may lead to over suppression of bone remodeling, resulting in an impaired ability to repair skeletal microfractures and increased skeletal fragility (5,6). In 2013, the "American Society for Bone and Mineral Research" (ASBMR) task force clarifies the features that distinguish AFFs from common osteoporotic femur fractures. In the second report of the task force, it revised the case definition as the fracture must be located from just distal to the lesser trochanter to just proximal from the supracondylar flare and at least 4 of 5 major features must be present and none of the minor features are required but have sometimes been associated with these fractures (7).

The purpose of this study is to show the correlation between long-term BP usage and atypical femur fractures, and, thus, to increase awareness of these fractures during osteoporosis treatment.

MATERIAL and METHODS

This study was approved by the Başkent University Institutional Review Board (Project No: KA19/147). The principles outlined in the Declaration of Helsinki were followed, and written informed consent from all participants was obtained.

Patients who were admitted to our clinic with atypical femur fracture between 1 December 2011 and 1 December 2017 were retrospectively analyzed, and those who had a history of BP treatment obtained from the electronic medical records were included in this study. The ASBMR definition mentioned previously was used to identify AFFs (Table 1). The patient data consisted of demographic findings, presence of trauma, history of fracture, concomitant medical diagnoses, history of BP usage, type of BP, concomitant fractures, other complications related to AFF, morbidities, and mortality. Further data were obtained from the patients through telephone interview and outpatient appointment. High-energy injuries and visible pathological fractures were excluded.

Patients' clinical data and radiographs were reviewed. The radiographs were classified according to the AO/OTA fracture classification system described as follows:

- type A: simple transverse or short oblique;
- type B: comminution with a medial or lateral wedge;
- type C: severe comminution with segmental discontinuity.

RESULTS

The demographic data of the patients are shown in Table 2. This study consisted of twenty-two patients, all female, with mean age at 79.36±8.71 (mean ± SD) years. Ten patients had left atypical femur fractures, and six had right atypical femur fractures. Six of the patients had a bilateral complete or incomplete atypical femur fracture at the time of admission to the hospital. Sixteen patients were taking alendronate for an average of 6.81±2.74 (mean±SD) years, whereas six were taking ibandronate for an average of 4.66±1.49 (mean ± SD) years. Distribution of the fracture types according to AO/OTA fracture classification system and its association with bisphosphonate types was shown in Table 3. Most common fracture type was 32A3 (13/22).

Table 1. 2010 ASBMR Task Force Case Definition of AFFs

Major featuresa
Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
Associated with no trauma or minimal trauma, as in a fall from a standing height or less
Transverse or short oblique configuration
Noncomminuted
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
Minor features
Localized periosteal reaction of the lateral cortexb
Generalized increase in cortical thickness of the diaphysis
Prodromal symptoms such as dull or aching pain in the groin or thigh
Bilateral fractures and symptoms
Delayed healing
Comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia)
Use of pharmaceutical agents (eg, BPs, glucocorticoids, proton pump inhibitors)

Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.
AFF=atypical femur fracture; BP=bisphosphonate.
aAll major features are required to satisfy the case definition of AFF. None of the minor features are required but have been sometimes associated with these fractures.
bOften referred to in the literature as "beaking" or "flaring."

Nine patients had a history of previous bone fractures before admission to our hospital, and most common fractures were atypical femoral shaft fracture and lumbar vertebrae compression fracture. There was a wide range of comorbidity ranging from diabetes to breast cancer, and the most common comorbidity was hypertension. Eight patients had prodromal pain at the lateral aspect of the tight, and mean duration of the prodromal symptoms was 4.37 months (min: 2; max: 7). Two of 22 patients died in the follow-up period (Figures 1 and 2).

Table 2. Demographics

Patient	Age	Sex	SOF	Comorbidities	Previous Fractures	BP agent and DUT (Year)	DPS (months)
1	82	F	L	HT, CAD, HL	-	Alendronate, 5	No
2	83	F	L	HT, NL, Hypothyroidism	-	Alendronate, 4	No
3	71	F	R	HT	-	Alendronate, 8	No
4	97	F	L	HT	Pubic Fracture	Alendronate, 12	5 months
5	76	F	R	-	L3 Vertebrae Compression Fracture	Alendronate, 12	No
6	85	F	L	HF, HT	-	Ibandronate, 3	2 months
7	86	F	L	HT, PKD	-	Alendronate, 5	No
8	68	F	R	HT, Hypothyroidism	Left femoral shaft atypical fracture	Alendronate, 10	7 months
9	86	F	R	HT	Left femoral shaft atypical fracture	Alendronate, 7	6 months
10	85	F	R	HT, PTE, CVA	Left femoral shaft atypical fracture	Ibandronate, 4	4 months
11	90	F	B	Arrhythmia, CAD	L2 Vertebrae Compression Fracture	Alendronate, 10	No
12	74	F	B	HT, Vertigo	-	Alendronate, 3	No
13	83	F	L	Hypothyroidism	-	Ibandronate, 5	No
14	89	F	L	HT, HL	-	Alendronate, 7	5 months
15	77	F	L	HT	Ankle Fracture	Alendronate, 4	No
16	81	F	R	HT	-	Alendronate, 6	No
17	69	F	R	RA	-	Alendronate, 5	No
18	67	F	B	HL, Breast Cancer	-	Ibandronate, 7	No
19	80	F	L	-	L3 Vertebrae Compression Fracture	Ibandronate, 3	3 months
20	85	F	R	HT, DM	Right distal radius fracture	Alendronate, 6	No
21	72	F	L	DM	-	Alendronate, 5	No
22	60	F	B	HT, HL, Ataxia	-	Ibandronate, 6	3 months

SOF= Side of the Fracture, BP= Bisphosphonate, DUT= Duration Of Treatment, DPS= Duration of Prodromal Symptoms, F=Female, L=Left, R= Right, B=Bilateral, HT=Hypertension, CAD= Coronary Artery Disease, HL=Hyperlipidemia, NL= Nephrolithiasis, HF=Heart Failure, PKD: Polycystic Kidney Disease, PTE= Pulmonary Thromboembolism, CVA=Cerebrovascular Accident, RA= Rheumatoid Arthritis, DM= Diabetes Mellitus,

Table 3. Classification of the fractures and its association with BP agents

AO/OTA Classification	BP Agent		Total (n)
	Alendronate (n)	Ibandronate (n)	
32A1	1	1	2
32A2	3	1	4
32A2.1	1	1	2
32A3	11	2	13
32A3.1	-	1	1
Total (n)	16	6	22

BP=Bisphosponate, AO/OTA=arbeitsgemeinschaft für osteosynthesefragen / Orthopaedic trauma association

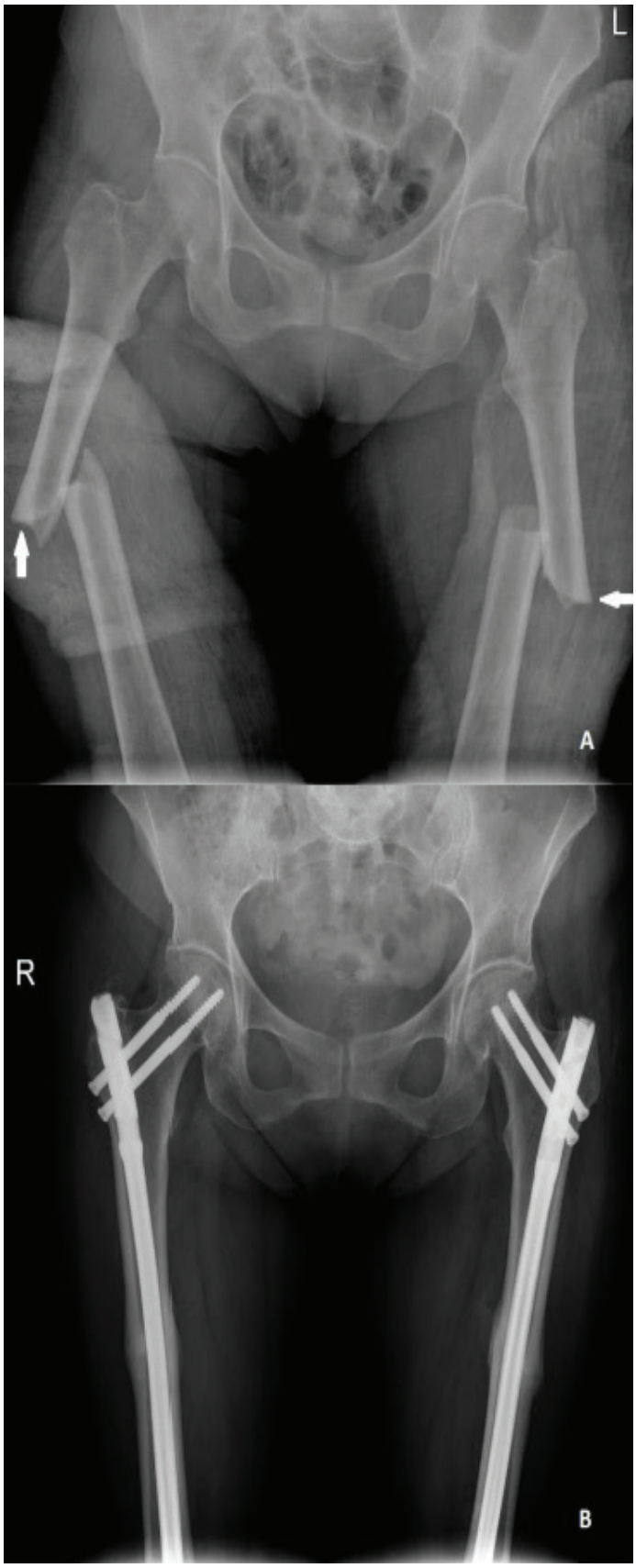

Figure 1. Bilateral atypical femur fracture (AO/OTA 32A3) A. Pre-operative anterior–posterior (AP) plain radiograph of the patient. White arrows show cortical thickening at the femoral shaft. B. AP plain radiograph of the patient at 6-month postoperatively which show fracture healing

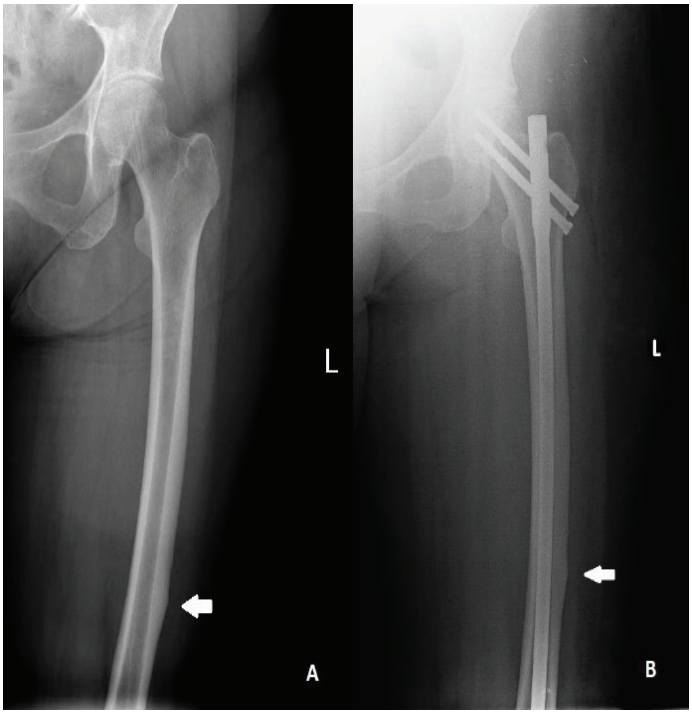

Figure 2. Atypical femur fracture A. Pre-operative AP plain radiograph of the patient. White arrow shows cortical thickening and cortical fissure. B. Post-operative AP plain radiograph shows prophylactic intramedullary nailing; white arrow shows persistent thickening.

DISCUSSION

Atypical femur fractures are rare, and the incidence is increased in patients using bisphosphonates. Considering that the world population is getting older and becoming more osteoporotic, it can be predicted that more atypical femur fractures will be encountered in the future. Therefore, it is aimed to plan osteoporosis treatment with less risk by increasing interest and studies on atypical femur fractures associated with bisphosphonate usage.

In the literature, compatible with our data, AFFs associated with bisphosphonate use are more common in female patients, with average age that ranges between 60 and 80 years (8-10). The most common concomitant diseases in these patients are collagen diseases, chronic pulmonary diseases (CPD), asthma, rheumatoid arthritis (RA), diabetes, thyroid diseases, and renal diseases (8,11). Although diseases like CPD, asthma, and RA may be associated with chronic use of systemic steroids, some studies have shown that AFFs are associated with systemic steroid use (12), whereas others have not (4). In our study, comorbid diseases were found to be compatible with those in the literature, but hypertension is the most common conversely. In this group of patients, a history of previous fragility fractures is common, like distal radius or vertebral fractures (8). In our study, the most common non-femoral fracture is vertebral compression. Prodromal thigh or groin pain is a common symptom in clinical presentation, and it may be present for weeks to years (11).

Odvina et al. examined the non-traumatic fractures of 9 patients who had been treated with alendronate for more than three years and pointed out the relationship of these fractures with bisphosphonates for the first time in the literature (6). Later, studies on the effects of long-term use of bisphosphonates, which are considered to be safe and tolerable in short-term use, have been increasing day by day (3). In addition, studies on bisphosphonates have shown no negative effect on fracture healing (13). When these studies are evaluated, it is seen that the majority of patients with AFFs after long-term use of bisphosphonates use alendronate (3,14-16). In our study, 6 of 22 patients who were evaluated had a history of ibandronate use. This may be because alendronate is the most widely used bisphosphonate that has been introduced. Also, the half-life of alendronate is long, and its effects may continue for five years after discontinuation of the drug (14). This may be the cause of the occurrence of AFFs even if the drug is discontinued. In a study by Favinger et al., 85.7% of patients with atypical femur fractures were using bisphosphonates for five years or longer; in that of Bannfy et al., it was 84%; in this study, it was 72.7% (14,15).

AP and lateral plain radiographs are usually sufficient to diagnose atypical femur fractures. Evaluation is made according to ASBMR criteria (7). Thickening of the lateral cortex is typical for atypical femur fractures, and, when these are classified radiologically, AO type A fractures are frequently seen. The results of our study are consistent with those in the literature (16,17). Computed tomography can be used as an additional radiological examination method. MRI is the most sensitive and specific imaging method. We also suggest dual-energy X-ray absorptiometry (DXA) screening for early diagnosis of atypical femur fractures (11). However, we do not use DXA screening for early diagnosis of AFFs in our clinic. Shane et al. reported that AFF affects the contralateral femur in 28% of cases (7). Therefore, the contralateral femur should be included in the radiographic screening.

Toro et al. investigated the relationship between the use of bisphosphonates and atypical femur fractures in their study, and they evaluated 132 studies in PubMed database (11). Their study showed that conservative treatment of the atypical femoral fractures had poor outcomes which eventually required surgery. However, Miyakoshi et al. suggest that the addition of teriparatide to the treatment may be beneficial for patients who cannot be operated for any reason (18). Because of the poor results of conservative treatment in the literature and cost of teriparatide treatment, we prefer surgery in our clinic.

In the surgical treatment of complete and incomplete atypical femur fractures, intramedullary nail application and plate–screw fixation are recommended. The plate–screw fixation is technically challenging and has high complication rates. Therefore, intramedullary nail surgery became a standard treatment method in the literature (11). As stated in our study; we applied long intramedullary nail to all patients because of its biomechanical properties. Particular attention should be paid to the bowing of the femur, the diameter of the medullary canal, and nail entry point during this surgical procedure. In our clinical practice, in the presence of increased anterior bowing of the femur, we prefer to apply the nail after contouring it with a bender. We did not have any problems with the mechanical properties of the nail during the follow-up of these patients. In patients with narrow femoral canals, the reaming process helps in the application of the nail, but care should be taken because of the complications. In the presence of simultaneous complete or incomplete AFF at the contralateral femur, we perform prophylactic nailing to ensure early mobilization, shortened hospital stay, and prevention of possible complications, as suggested in the literature (11,14).

Our study has some limitations. First, the inclusion of patients with atypical femur fractures who did not use bisphosphonates in our study would be better able to demonstrate the association of bisphosphonates with atypical femur fractures. Second, because most of the patients had the diagnosis and treatment of osteoporosis in different hospitals, bone mineral densitometry data could not be obtained.

CONCLUSION

TIn conclusion, although bisphosphonates are safe and effective first-line drugs in the treatment of osteoporosis, their long-term effects are not fully known. In long-term use of bisphosphonates, care should be observed for atypical femur fractures, presence of prodromal symptoms should be questioned regularly, and the necessary radiological imaging studies should be performed. Clinical recognition and prevention of non-displaced atypical femur fractures are essential for reducing the mortality and morbidity of patients.

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