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Bilateral low-energy sequential femoral shaft fractures in patients on long-term bisphosphonate therapy

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Objective: The aim of this study was to evaluate the demographic characteristics of patients with bilateral bisphosphonate-related low-energy femoral shaft fractures.

Methods: The clinical registry was reviewed for patients with bisphosphonate-related low-energy fractures localized at femoral shaft between January 2008 and January 2012. Patients with a diagnosis of postmenopausal osteoporosis, bisphosphonate usage of at least 5 years and prodromal pain prior to fracture were included the study.

Results: Five women met the inclusion criteria. All patients had bilateral low-energy sequential femoral shaft fractures. Fracture patterns were similar and atypical (transverse-short oblique fractures with lateral cortical thickening). Mean period of bisphosphonate treatment was 8.6 years. Mean patient age was 76.2 years. Union time of three patients was between 20 and 28 weeks. The remaining two fractures were revised for delayed union or nonunion.

Conclusion: Long-term (over 5 years) use of bisphosphonates may cause insufficiency fractures due to increased fragility and brittleness which have a close relationship with depressed bone remodeling. While there is still no causal relationship between bisphosphonates and atypical, low-energy femoral shaft fractures, we have some concerns about the optimal usage time and long-term safety of bisphosphonate drugs.

Key words: Atypical femoral shaft fracture; bisphosphonate; subtrochanteric fracture.

Osteoporosis is a skeletal disease in which a low-density and micro-architectural defects in bone tissue increase susceptibility to fractures.[1] Currently it is estimated that more than 10 million patients have been diagnosed with osteoporosis in the US alone.[2] Considering a lifetime fracture risk of 40% for white females, these cases represent an approximately 9 million new osteoporotic fractures per annum.[3] Prevention of further bone resorption and fractures is the backbone of treatment. Following current evidence-based guidelines, bisphosphonates are often first considered for the treatment of osteoporosis.[4] This class of medication may account more than 80% of total prescriptions given for osteoporosis in some countries and their efficiency in treatment of postmenopausal osteoporosis was reported to reduce vertebral fractures by nearly 50% and hip fractures by 20 to 50%.[5] Bisphosphonates were shown to be well tolerated and safe in large-scale clinical trials.[6] Several rare and potentially serious adverse events have been reported to be associated with long-term bisphosphonate use from post-marketing reports and epidemio-

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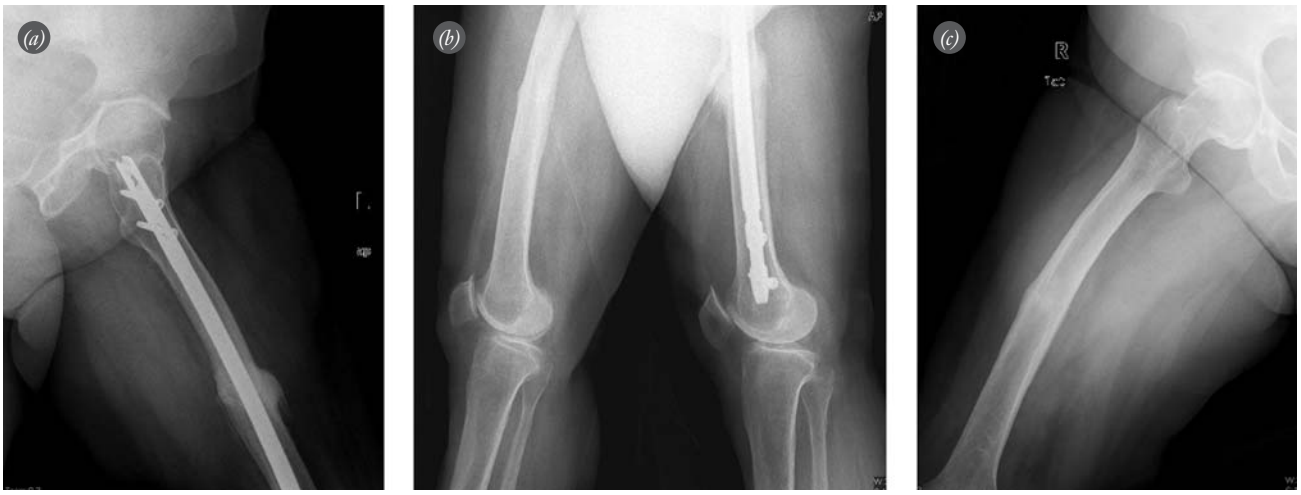

Fig. 1. Radiographies of patient no. 5. **(a)** The patient had left femur shaft fracture without any significant trauma and was treated with interlocked intramedullary nailing. **(b)** After 5 months, she had thigh pain at right leg and admitted to our clinic. **(c)** There was an impending fracture site at right femoral shaft showing unique pattern; transverse, unicortical and showing beaking and cortical thickening at anterolateral cortex.

logical studies. These adverse events include dyspepsia, nausea, muscular pain, osteonecrosis of the jaw (ONJ), and atrial fibrillation.[7] In recent years, however, there have been increasing numbers of cases or case series about atypical subtrochanteric/femoral shaft fractures related to bisphosphonate treatment.[8-19]

The aim of this study was to evaluate the demographic characteristics of patients with bilateral bisphosphonate-related low-energy femoral shaft fractures.

Patients and methods

In this retrospective observational study, the clinical registry of GATA Haydarpaşa Training Hospital (Istanbul, Turkey) was reviewed for patients with femoral fractures between January 2008 and January 2012. Patients with a diagnosis of low-energy fractures at the femoral shaft were sorted out and along with the radiological appearance of these fractures, patients' demographics were recorded. Fractures occurring from a fall from standing height without any significant trauma were assessed as 'low-energy fractures'. Patients with a diagnosis of osteoporosis using bisphosphonate drugs for a minimum of 5 years and who had prodromal pain prior to fracture were included in this study. Included patients' fractures were labeled 'bisphosphonate-related low-energy fracture'. Local ethical committee approval was obtained.

Results

Fifty-two patients had femoral shaft fractures. Patient histories were reviewed for low-energy fractures and

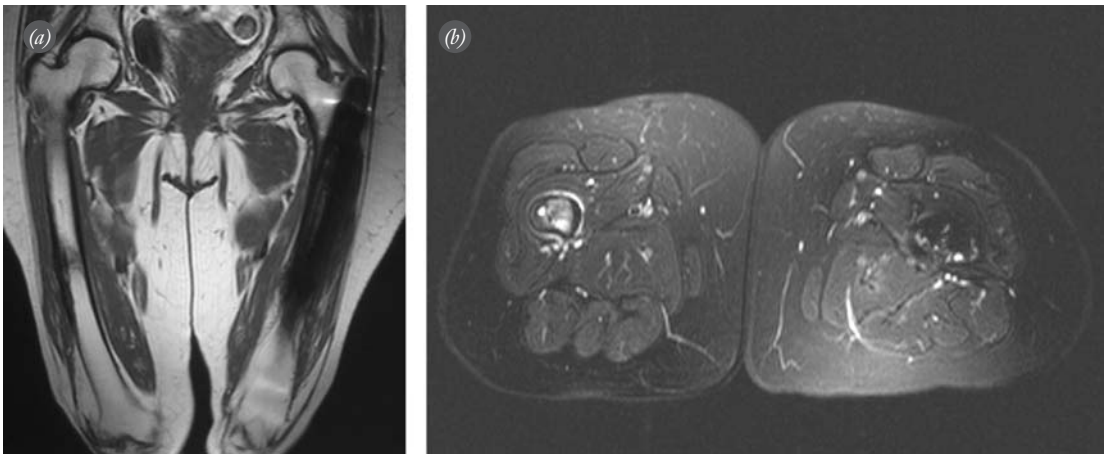

Fig. 2. MR images of patient no. 5. MRI sections of impending fracture localized at the right femoral shaft. **(a, b)** Unicortical fracture line localized at lateral cortex of femoral shaft, medullary and soft-tissue edema seen around fracture site and periosteal reaction with cortical thickening can be seen.

osteoporosis diagnosis. All patients used alendronate. Five patients with bilateral atypical femoral shaft fractures treated surgically were included in our study. Radiographic findings for atypical femoral shaft fractures were short-oblique-transverse fracture, transverse fracture with medial spike, cortical thickening or hypertrophy at the lateral cortex, and stress fracture line. Patients' mean age was 76.2 (range: 70 to 87) and mean period of bisphosphonate treatment was 8.6 (range: 5 to 14) years. All five patients were female. All patients complained of prodromal pain and general discomfort in the affected thigh days to weeks before the impending fracture. Union time of three patients was between 20 and 28 weeks. Patient number 2 had delayed union at 5 months after initial surgery and the fracture revised using an exchange nail with interlocked intramedullary nail. Patient number 4 had no union at 8 months after intramedullary nailing and the fracture was revised using open reduction, plate fixation and bone autografting. Union time was 26 weeks for both patients. Radiographs and MRI appearance of impending fracture of Patient number 5 are shown in Figures 1-3. Demographic data is given in Table 1.

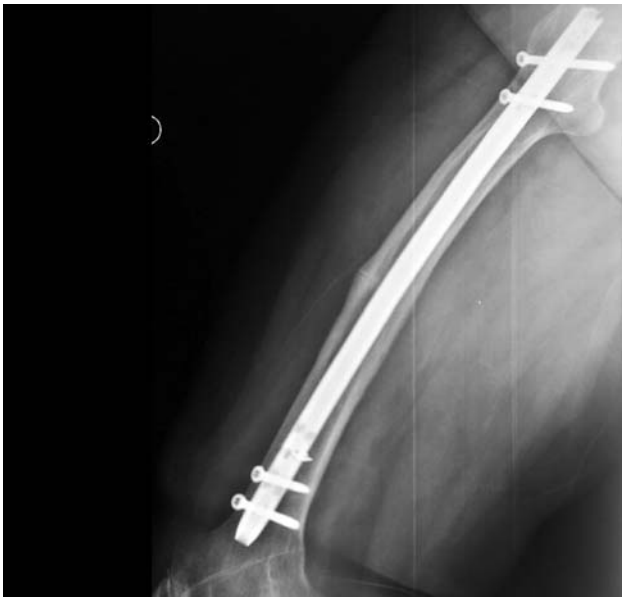

Fig. 3. This impending fracture localized at the right femur diaphysis was also treated with interlocked intramedullary nailing.

Discussion

Osteoporosis is a common health problem in the elderly population. Increased risk of fracture can result in disability, morbidity, decreased life quality, higher costs, and mortality. In postmenopausal osteoporotic patients, bisphosphonates have been shown to decrease the risk of vertebral and femoral neck fractures.[20-23] Bisphosphonates are potent inhibitors of bone resorp-

Table 1. Demographic data of the patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	74	72	70	78	87
Sex	Female	Female	Female	Female	Female
Localization	Femoral shaft (Bilateral)	Femoral distal shaft (Left) Femoral shaft (Right)	Femoral shaft (Bilateral)	Femoral proximal shaft (Left) Femoral shaft (Right)	Femoral shaft (Bilateral)
Alendronate therapy duration (year)	7 years	10 years	14 years	5 years	7 years
Alendronate dosage	10 mg/day	10 mg/day	10 mg/day for 8 years; 70 mg/week for 6 years	10 mg/day	10 mg/day
Fracture pattern	Short oblique-transverse fracture (Both sides)	Transverse fracture with medial spike, lateral cortical thickening (Left)	Transverse short oblique fracture with thickening at the lateral cortex (Right) and short oblique fracture with medial spike (Left)	Transverse fracture with medial spike (Both sides)	Transverse stress fracture line at the lateral cortex and mild cortical hypertrophy (Right) and transverse fracture (Left)
Prodromal pain	+	+	+	+	+
Treatment	Interlocked intramedullary nailing (Both sides)	Interlocked intramedullary nailing (Right) and Expandable intramedullary nailing (revised with interlocked intramedullary nailing) (Left)	Expandable intramedullary nailing (Both sides)	Expandable intramedullary nailing (revised with plate fixation and autografting) (Right) and plate fixation (Left)	Interlocked intramedullary nailing (Both sides)
Time to union (week)	Right (24) Left (22)	Right (24) Left (26) (after revision surgery)	Right (28) Left (26)	Right (26) (after revision surgery) Left (27)	Right (20) (impending fracture) Left (26)

tion that inhibit osteoclast function and induce osteoclast apoptosis.[13,24] Alendronate was approved by the FDA in 1995 for the treatment of osteoporosis. The pathophysiology of bisphosphonate associated fractures is thought to be associated with the inhibition of bone turnover and repair of microscopic trauma. In recent decades, human biopsy and experimental animal studies have reported suppressed bone turnover with bisphosphonate use.[17,25-28] As a result, a cycle of defective repair and continual micro-trauma compounded over time gradually weakens and creates more mineralized and brittle bones, an architectural conduit for transverse or insufficiency fractures.[13,29-31] It has been advocated that some osteoclastic activity is necessary to repair microdamage and continuity of remodelization.[17,32] In a recent study, Bala et al. reported that long-term (6 to 10 years) alendronate use compromises the micromechanical properties of bone and problems were related with lower crystallinity, associated with elastic modulus and contact hardness.[33] Our cases also had a minimum of 5 years of alendronate usage (range: 5 to 14 years). Extended alendronate use may diminish mechanical properties of bone and may result in more brittle bone which in turn can result in insufficiency fractures. In a detailed review, Ott[34] demonstrated the mechanism of action of bisphosphonates. First, the author emphasized the common misunderstanding that 'bisphosphonates build bone'. Second, she cited an article on fluoride treatment for osteoporosis treatment and underlined that despite increased bone density, the bone becomes more fragile. This can be example for this clinical picture of what bisphosphonate drugs do. It was also reported that overall fracture risk is similar in patients with more than 5 years of bisphosphonate use and individuals who stopped therapy.

Recently, atraumatic, low-energy or insufficiency femoral shaft/subtrochanteric site fractures have been reported in patients on prolonged bisphosphonate therapy.[8-19] These studies are evaluated in detail in Table 2. Similar to our cases, some reports were of bilateral sequential femoral shaft fractures.[10,11] Most of the alendronate-related fractures in literature reported differences from usual osteoporotic fractures, high-energy fractures and periprosthetic fractures, including:

1. Minor or no trauma
2. Alendronate use history for postmenopausal period
3. Prodromal (thigh) pain prior to fracture
4. Different localization from those commonly seen in osteoporotic fractures (spine, hip, wrist…etc.)
5. Bilaterality (sequential or simultaneous or impending)
6. Cortical hypertrophy or thickening at fracture site on radiographs
7. Unusual fracture pattern (transverse or short oblique; medial spike/beak)
8. Delayed fracture union time

All 5 of our cases showed all the features mentioned above. These characteristics may be useful in the diagnosis of 'alendronate-related low-energy fractures'.

The subtrochanteric site of the femur is subjected to maximal bending forces and is known as its strongest region.[13,18,35] Low-energy stress fractures usually occur in athletes or military recruits.[36] Bilateral femoral fractures are also usually seen as pathological fractures or following high-energy trauma such as motor-vehicle accidents. Subtrochanteric fractures (especially bilateral) occurring after low-energy events are rare and are resultant of an underlying cause that weakens the bone. With inhibition of osteoclasts and impairment of the remodelization cycle, microarchitectural damage at the site of highest stress may occur. Gaeta et al. analyzed the CT scans of tibial stress fractures and found some resorption areas inside the typical cortical thickness site.[37] Our radiological findings on the contralateral impending fracture can be postulated to result from chronic suppression of bone remodeling by long-term bisphosphonate treatment with accumulation of old, highly-mineralized osteons and increased brittleness of bone (especially caused by increased Young's modulus).[38,39]

Bisphosphonates bind the bone tightly and the skeletal half-life of alendronate has been estimated at over 5 or 10 years.[4,20,24,40-43] Therefore, nonunion rates for such insufficiency fractures may be higher and union may be slower or incomplete even following the discontinuation of bisphosphonates. Weil et al. studied the surgical outcomes of bisphosphonate-related fractures and reported a much higher failure rate with intramedullary nailing which requires revision procedures.[44] In our cases, we also detected longer union time after surgical treatment and one patient required revision due to nonunion after 8 months (with additional autografting). We now believe that these bisphosphonate-related fractures must be thoroughly evaluated and treated using different and augmented approaches, such as autografting or recombinant bone morphogenetic proteins. Treatment modality should be chosen individually.

Questions and concerns for the long-term safety of bisphosphonates have arisen from reports of atypical femoral fractures, with studies reporting both increased or no increased risk available in the literature.[15,45-52] A meta-analysis based on database of three large randomized studies found that the occurrence of subtrochanteric or diaphyseal femur fracture (i.e. insufficiency fracture of the femur) was very rare, although there were insufficient numbers of events to reach defin-

Table 2. Studies reported atypical fractures related with bisphosphonate therapy.

No	Study, year, journal	Patients no.	Age	Sex	Duration of drug use (years)	Used drug	Additional drugs	Prodromal pain	Fracture site	Bilateral	Fracture pattern on X-ray	Biochemical marker	Bone biopsy	BMD -2.5	Time to union (months)
1	Odvina CV, 2005, J Clin Endocrinol Metab	9	60	F	3-8	Alendronate	Estrogen (3), prednisone (2)	NM	ST (4), sacrum, rib, ischium, pubic rami, lumbar spine	2/9	NM	N-terminal telopeptide was low (7/9)	+	NM	Delayed (6)
2	Schneider JP, 2006, Geriatrics	1	59	F	7	Alendronate	Estrogen	+	ST	-	Cortical thickness, transverse with spike	NM	NM	NM	-
3	Cheung RK, 2007, Hong Kong Med J	1	82	F	10	NM	NM	NM	FS	+	NM	High OH-proline	+	NM	NM
4	Demiralp B, 2007, Arch Orthop Trauma Surg	1	65	F	7	Alendronate	Steroid, thyroxine	+	FS	+	Fracture line, cortical thickening, bowing deformity	NM	NM	NM	NM
5	Goh SK, 2007, JBJS-Br	9	66.9	F	4.2 (2.5-5)	Alendronate	NM	+ 5/9	ST	-	Simple, transverse, short oblique; cortical thickening on the lateral	NM	NM	+ (normal)	Delayed
6	Lee P, 2007, J Endocrinol Invest	1	73	F	1,5	Alendronate	NM	+	FS	+	NM	NM	NM	+ (-2.8)	NM
7	Kwek EB, 2008, Injury	17 (9*)	66	F	4.4 (2-8)	Alendronate	Calcium	+ 13/17	ST; FS	+ (10/17)	Cortical thickening; transverse or short oblique; medial cortical spike	NM	NM	10/17	NM
8	Lenart BA, 2008, NEJM	15	NM	NM	5,4	Alendronate	NM	NM	ST/FS	NM	Simple transverse or oblique fracture with beaking of the cortex and diffuse cortical thickening	NM	NM	NM	NM
9	Neviaser AS, 2008, JOT	19	69.4	F	6.9 (min 4)	Alendronate	None	NM	ST; FS	NM	Simple transverse fracture, unicortical beak in area of cortical hypertrophy	NM	NM	NM	NM
10	Sayed-Noor AS, 2008, Acta Orthop	1	72	F	7	Alendronate	Calcium	+	ST	+	Transverse, thickening of the lateral femoral cortex and medial spiking at the fracture site	NM	NM	NM	6

DS: distal shaft, FS: femoral shaft, ST: subtrochanteric; NM: not mentioned. *Nine of these patients are also mentioned in the fifth study by Goh et al.

Table 2. *[Contunued]* Studies reported atypical fractures related with bisphosphonate therapy.

No	Study, year, journal	Patients no.	Age	Sex	Duration of drug use (years)	Used drug	Additional drugs	Prodromal pain	Fracture site	Bilateral	Fracture pattern on X-ray	Biochemical marker	Bone biopsy	BMD -2.5	Time to union (months)
11	Visekruna M, 2008, J Clin Endocrin Metab	3	51-75	NM	5-10	NM	Estrogen (2), prednisone (3)	NM	NM	2/3	NM	NM	+ 2/3	+ (normal)	22
12	Ali T, 2009, Age Aging	1	82	NM	8	NM	NM	-	FS	-	Transverse with marked cortical thickening	C-terminal telopeptide crosslinks were slightly elevated	-	+ (normal)	3
13	Armamento-Villareal R, 2009, Calsif Tissue Int	15	43-75	F (12) M (3)	4-10	Alendronate	NM	NM	FS (7)	2/15	NM	NM	NM	NM	NM
14	Bush LA, 2009, Radiol Case Rep	1	85	F	6	Risedronate	Steroid	+	ST	-	Mild, diffuse cortical thickening and a focal, domed, conical, projection along the lateral cortex	NM	NM	NM	NM
15	Capeci CM, 2009, JBJS Am	7	61	F	8.6 (5-13)	Alendronate	None	+ 4/7	ST (6); FS (1)	+	Cortical thickening, transverse, cortical spiking or beaking	NM	NM	NM	NM
16	Glennon DA, 2009, Bone	6	60-87	F	1.5-16	Alendronate (5), risedronate (1)	NM	NM	ST	+(1)	Transverse, unicortical beaking, cortical thickening	NM	NM	NM	NM
17	Sayed-Noor AS, 2009, CORR	2	78; 55	F	9; 8	Alendronate	Vit D	+	ST (Periprosthetic)	1/2	Lateral cortical reaction, transvers fracture	NM	NM	NM	5; 9
18	Goddard MS, 2009, Orthopedics	1	67	F	16	Alendronate	NM	NM	FS	+	Cortical thickening, unicortical beaking, transverse	NM	NM	NM	NM
19	Grasko JM, 2009, J Oral Maxillofac Surg	1	NM	NM	NM	NM	Steroid	NM	ST	NM	NM	NM	NM	NM	NM
20	Ing-Lorenzini K, 2009, Drug Safety	8	67	F	16 months - 8 years	Alendronate	Proton pump inhibitor (7), prednisone (4)	+(2)	ST	4/8	Cortical thickening at lateral cortex with a horizontal fracture line	NM	NM	NM	Delayed (2/8)
21	Lee JK, 2009, Int J Rheum Dis	1	82	F	8	Alendronate	NM	NM	NM	+	Horizontal fracture line involving the thick lateral cortex with short oblique fracture pattern	NM	NM	NM	NM
22	Leung F, 2009, BMJ Case Rep	10	55-92	F	0.5-10	Alendronate	NM	NM	ST, FS	NM	Femoral diaphyseal cortical thickening and lateral cortex beaking	NM	NM	NM	NM
23	Schilcher J, 2009, Acta Orthop	5	>75	F	5.8	NM	NM	NM	FS	1/5	NM	NM	NM	NM	NM

DS: distal shaft, FS: femoral shaft, ST: subtrochanteric; NM: not mentioned. *Nine of these patients are also mentioned in the fifth study by Goh et al.

Table 2. *[Contunued]* Studies reported atypical fractures related with bisphosphonate therapy.

No	Study, year, journal	Patients no.	Age	Sex	Duration of drug use (years)	Used drug	Additional drugs	Prodromal pain	Fracture site	Bilateral	Fracture pattern on X-ray	Biochemical marker	Bone biopsy	BMD -2.5	Time to union (months)
24	Schneider JP, 2009, Geriatrics	3	59-66	F	5-9	NM	NM	1/3	NM	2/3	NM	NM	NM	NM	NM
25	Somford MP, 2009, J Bone Miner Res	1	76	F	8	Alendronate	Prednisone	+	ST/FS	-	NM	+	+	+	NM
26	Atik S, 2010, Eklem Hastalik Cerrahisi	1	76	F	10	NM	NM	NM	FS	NM	Transverse; medial spike at cortical thickness site	NM	NM	+ (T score 3.55 at hip)	NM
27	Black DM, 2010, NEJM	7	69-83	NM	>2	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
28	Bunning RD, 2010, PM&R	4	49-59	F (3), M (1)	4.5-6	Alendronate (2), pamidronate (1)	NM	+	ST/FS	1/4	Medial cortical thickening	NM	NM	NM	NM
29	Cermak K, 2010, CORR	4	59-77	F	>5	Alendronate	NM	-	ST	1/4	Transverse fracture with external cortical bone reaction and medial cortical spike	NM	NM	NM	NM
30	Chan SS, 2010, Am J Roentgenol	15	50-81	F	4-14	Alendronate	NM	NM	ST	NM	Medial beak	NM	NM	NM	NM
31	Das De S, 2010, JBJS Br	12	51-75	F	4.6	Alendronate	NM	NM	ST	6/12	Thickening of lateral femoral cortex, transverse or slightly oblique fracture	NM	NM	NM	Nonunion 3/12
32	Edwards MH, 2010, Osteoporos Int	1	60	F	8	Alendronate	Prednisone	+	FS	+	Minor cortical thickening	NM	NM	NM	NM
33	Girgis CM, 2010, Med J Aus	17			5	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
34	Giusti A, 2010, Bone	8	67.8	F	3-192 months	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
35	Ha YC, 2010, CORR	11		F	4.5 (3-10)	NM	NM	NM	NM	NM	NM	NM	NM	NM	5
36	Isaacs JD, 2010, CORR	41	73.7	F	7.1	Alendronate (40) risedronate (1)	NM	29/41	ST/MS	18/41	Transverse fracture line and lateral cortical thickening adjacent to the fracture	NM	NM	NM	NM
37	Koh JSB, 2010, JOT	16	68	F	4.5	NM	NM	7/16	ST/MS	NM	"dreaded black line" within the cortical stress reaction on both anteroposterior and lateral views	NM	NM	NM	NM
38	Napoli N, 2010, Osteoporos Int	1	56	F	6	NM	Prednisone	-	FS	-	NM	NM	NM	NM	NM

DS: distal shaft, FS: femoral shaft, ST: subtrochanteric; NM: not mentioned. *Nine of these patients are also mentioned in the fifth study by Goh et al.

Table 2. *[Contunued]* Studies reported atypical fractures related with bisphosphonate therapy.

No	Study, year, journal	Patients no.	Age	Sex	Duration of drug use (years)	Used drug	Additional drugs	Prodromal pain	Fracture site	Bilateral	Fracture pattern on X-ray	Biochemical marker	Bone biopsy	BMD -2.5	Time to union (months)
39	Osugi K, 2010, Acta Orthop	3	74	F	NM	Alendronate(2) risedronate (1)	NM	NM	FS	2/3	Spike-shaped cortical thickening laterally	NM	NM	NM	NM
40	Patel VC, 2010, Orthopedics	1	65	F	2	Ibandronate	NM	+	FS	+	NM	NM	NM	NM	NM
41	Porrino JA, 2010, Am J Roentgenol	4	66.5	F	>3	Alendronate	NM	3/+	ST/FS	2/4	Localized lateral cortical thickening, and the appearance of the fracture lucency	NM	NM	NM	NM
42	Venkatanarasimha N, 2010	2	69.5	F	7.4	Alendronate	Prednisolone	+	ST/FS	1/2	Beaking of cortex lateral femur and marked cortical hypertrophy	NM	NM	NM	NM
43	Banffy MB, 2011, CORR	34	68.5		6	NM	NM	NM	ST	6/34	NM	NM	NM	NM	NM
44	Gomberg SJ, 2011, J Clin Endocrin Metab	1	63		13	Alendronate	NM	+	ST	+	NM	NM	NM	NM	NM
45	Gudena R, 2011, J Osteop	1	74	F	10	Alendronate	None	+	FS	+	Lateral cortical cortical thickening of mid-diaphysis	NM	NM	NM	4
46	Gunawardena I, 2011, Am J Geriat Pharma	1	67	F	2	Alendronate	Glucocorticoids	+	ST	+	Transverse fracture pattern on the lateral half of the femoral cortex	NM	NM	T score was -2 at hip	NM
47	Weil YA, 2011, JOT	15	73	F	7.8 (4-13)	Alendronate	NM	NM	FS (9), ST(4), DS(4)	2/15	NM	+ (5) low normal range (carboxy-terminal collagen crosslink) (1) osteocalcin was low	NM	+ (T score was -3 at lumbar spine)	NM

DS: distal shaft, FS: femoral shaft, ST: subtrochanteric; NM: not mentioned. *Nine of these patients are also mentioned in the fifth study by Goh et al.

itive conclusions.[46] Several controlled epidemiological studies examining the association between bisphosphonate use and insufficiency fractures have also been published. Using a cohort created out of the Danish Hospital Discharge Registry and Prescription Database, Abrahamsen et al. found that high adherence to treatment was associated with a reduced insufficiency fracture risk, further suggesting that insufficiency fractures were caused by the extensive underlying osteoporosis instead of alendronate therapy.[45] Other studies have shown that atypical fractures have not increased.[47,49] In contrast, a notable interconnection between long-term bisphosphonate use and insufficiency fractures has been reported by controlled observational studies. A Canadian report suggests that the long-term use (≥5 years) was associated with increased risk of insufficiency fracture of the femur (adjusted Odds ratio 2.74; 95% CI, 1.25-6.02).[50] This association was not present in short-term users. Lenart et al. also reported significantly greater proportion of subtrochanteric or femoral shaft fractures in comparison to intertrochanteric or femoral neck fractures in patients who received long-term bisphosphonate therapy.[16] Another case-control study suggested that prolonged use of alendronate may cause suppression of bone remodeling and may be associated with insufficiency fractures of the femur.[13] We also believe that the long-term use (>5 years) of alendronate may be associated with its related fractures.

At the beginning of 2010, the FDA announced a report regarding bisphosphonate-related atypical fractures and reported no clear connection. However, the FDA also advised physicians to prescribe bisphosphonates according to guidelines and follow patients closely.[53] On the other hand, the Medicines and Healthcare products Regulatory Agency (MHRA), the drug regulatory agency in the UK, recommended the cessation of alendronate therapy in patients with atypical bisphosphonate-related fractures and the assessment of the benefits of alendronate treatment.[54] We believe that patients with atypical, bisphosphonate-related fractures should be individually reevaluated for risk factors with bone densitometry and biochemical bone turnover markers before making a decision on whether a drug holiday is necessary. The length of the drug holiday should be determined by close observation, bone mineral densitometry and biochemical bone turnover markers (urine cross-linked N-telopeptides of Type 1 collagen, cross-linked C-telopeptides of Type 1 collagen; bone-specific alkaline phosphatase, osteocalcin, pro-peptide of Type 1 collagen).[34,55] Consultation with an endocrinologist may be helpful in the evaluation process and fracture risk assessment may be completed using the FRAX®, WHO Fracture Risk Assessment Tool.[56] Teriparatide may be kept in mind for treatment continuation.[19]

We did not perform any animal study or histomorphological assessment for patients. There was also no detection of biochemical bone turnover markers. These features were the limitations of our study. Continuous assessment of bone turnover markers and their relationship with bone mineral densitometry measures may be helpful to determine the actual status of bone metabolism occurring inside the body which in turn may assist in the decision to continue bisphosphonate use.

In conclusion, long-term (over 5 years) use of bisphosphonates may cause insufficiency fractures due to increased fragility and brittleness which have a close relationship with depressed bone remodeling. Although there is still no causal relationship between bisphosphonates and atypical, low-energy femoral shaft fractures, we have some concerns about the optimal usage time and long-term safety of bisphosphonate drugs.

Conflicts of Interest: No conflicts declared.

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