

Caveats of bisphosphonate abuse

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ABSTRACT

Background: Bisphosphonates (BPs) are the common drugs used for the treatment of postmenopausal osteoporosis. Short term benefits of the BPs are well known. However, there are concerns regarding their long term use. The aim of the study was to analyze the association between atypical femoral fractures and BP misuse/abuse as well as study the outcome of management of these fractures.

Materials and Methods: A retrospective study of a prospectively studied patients who presented with atypical femoral fractures between January 2010 and August 2012 and were followed up upto June 2014. The cohort consisted of nine female patients (12 fractures) with an average age of 71 years (range 58-85 years). Analysis was done for the indications, duration of BP use, configuration of associated fractures and method of treatment.

Results: The mean duration of BP use was 6.6 years (range 4-10 years). BP treatment was initiated without sufficient indication and continued without proper review and followup in most cases. Most patients did not followup and continued to consume BPs without any review by the doctors. All patients had prodromal thigh pain of various duration, which was inadequately investigated and managed before the presentation. Two cases with an incomplete fracture and no thigh pain were managed successfully with conservative treatment. The rest were treated by surgery with intramedullary nailing. The average union time was longer and two fractures went into nonunion which required further surgical intervention.

Conclusion: Atypical femoral fractures appear to be strongly related to abuse of BPs. Great care is to be exercised at initiation as well as the continuation of BP therapy, and regular review is required. There is a need for improved awareness among physicians about the possibility of such fractures, and interpretation of thigh pain and radiological findings, especially if the patient has been on BPs therapy. Internal fixation for complete fractures and for incomplete fractures with thigh pain is needed. Delayed union is common.

Key words: Abuse, bisphosphonates, fractures, antiresorptive agents, femur

MeSH terms: Abuse reporting, femoral fracture, osteoporosis, postmenopausal

INTRODUCTION

Antiresorptive agents are widely used for the treatment of postmenopausal osteoporosis. These drugs are shown to improve bone mineral density, prevent bone loss, and reduce the risk of spinal and nonspinal fractures.¹⁻³ Bisphosphonates (BPs) inhibit osteoclastic activity and therefore bone turnover. The short term efficacy of these agents is well known; however, there are

concerns regarding their long term use. With the long term use of these drugs, there is a potential risk of impairment of some of the biomechanical properties of the bone.⁴ They inhibit normal repair of microdamage which may lead to reduction in bone toughness.⁵⁻⁷ Due to reduced bone turnover, secondary mineralization continues which leads to the formation of hypermineralized bone⁸ with abnormal mechanical properties such as reduced stiffness, strength, and higher brittleness. This may ultimately lead to an increased risk of fracture.^{9,10}

The last two decades have witnessed better research and understanding in the field of osteoporosis. In the developing world, increased awareness, investigation facilities, and

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easy availability of antiosteoporotic drugs like BPs have helped many patients to avoid fragility fractures and lead a better quality of life. Initially, it appeared that BPs could be continued for many years without any untoward effects. However, side effects of BPs were observed in the last few years and reports of atypical femoral fractures secondary to BPs use have been published in last few years¹¹⁻¹⁴ after prolonged therapy.

There is insufficient data regarding atypical fractures and their correlation to BPs use in Indian population. The objective of this study was to review the cases of atypical femoral fracture associated with BP use and study their indications, duration of BP therapy, association with atypical femoral fractures, treatment of fractures, and clinical outcome.

MATERIALS AND METHODS

Nine patients with atypical femoral fractures between January 2010 and August 2012 were identified and included for analysis. All the patients presented with fractures and were on BP therapy initiated and continued elsewhere. The mean age was 70 years (range 58–85 years) and all were females. None of the patients gave a history of smoking, alcohol, or corticosteroid use.

Patients diagnosed with either complete or incomplete atypical femoral fractures were included in this study. Only those patients with fractures following trivial trauma were included. Those with active malignancy, bone metastasis, or renal impairment were excluded from the study. Radiographs of the patients were independently studied by three senior orthopedic surgeons to confirm atypical fracture characterized by the presence of cortical stress reaction, dreaded black line on the lateral cortex of femur, and thickening and flaring of lateral cortex¹⁵ [Figure 1].



Figure 1: X-ray of (R) thigh with hip joint showing all the features of atypical fracture

The duration of BP therapy, *T*-score in DEXA scan at the initiation of treatment and followup scans, timing of the insufficiency fracture, treatment given, and involvement of contralateral hip/femur were studied with the help of magnetic resonance imaging (MRI) scans. Delay in treatment after recognition of stress fracture as well as any delay in surgery after displaced fractures was noted.

Operative records of the cases subjected to surgery were screened for the mode of reduction, implant used, bone graft, and any intraoperative complications. They were followed up on a regular basis till fracture union. This study was approved by the Institutional Review Board of the hospital.

RESULTS

The mean duration of oral BP therapy was 6.6 years (range: 4–10 years). Initially, all patients were on alendronate out of which two were switched to ibandronate [Table 1]. Only one patient had a drug holiday of 6 months. The minimum followup was for 9 months and maximum for 28 months.

Dual-energy X-ray absorptiometry scans

Dual-energy X-ray absorptiometry (DEXA) scan was done before starting BP in eight patients while in one patient it was never done with a mean *T*-score of -1.02 . The results showed osteopenia (worse *T*-score -1.6) in six patients. Two patients had osteoporosis before starting the treatment. Repeat DEXA scans were available for all the nine patients at their last followup visit which showed osteopenia with a mean *T*-score of -1.4 .

Fractures associated with bisphosphonate use

A total of 12 fractures in nine patients were available for the analysis. Four of the fractures were on the left, two on the right side, while remaining three had bilateral involvement. Of the three patients with bilateral fractures, one patient was treated with an intramedullary (IM) nail for low-energy trauma fracture of shaft of femur elsewhere. The contralateral side was neither radiographed nor was BPs stopped at that institute suggesting the surgeon had not realized the significance of the fracture. All the patients had sustained the fracture while walking without any history of a fall or significant trauma. Six patients (66%) felt a give way sensation in the thigh while walking just before the fracture. Eight patients had prodromal symptoms of thigh pain with a mean duration of 4.8 months (range 8 days to 1 year). There were seven complete fractures and five incomplete fractures. None of the patients had significant risk factors before initiation of BP treatment. There was no evidence of fragility fractures anywhere else in any of the study patients. Configurations of fractures are shown in Table 1.

All except one patient presented immediately after a displaced fracture. One patient presented 24 months after a displaced fracture. She had consulted at least three surgeons who had suggested surgery which she had refused.

Surgery was performed on the seven displaced fractures. One patient was already treated for a displaced fracture at another institute as mentioned earlier. Prophylactic fixation was performed in the form of IM nailing in one patient because of significant thigh pain. Surgery was suggested but refused by one patient and was lost for followup. Two patients with an incomplete fracture but no thigh pain were conserved and had been asymptomatic till the last followup.

The mean time of union was 7.3 months (range 6–11 months). All the patients treated by us were kept nonweight bearing with crutches till some evidence of callus formation on radiographs. They were then allowed partial weight bearing till union was achieved on radiographs. Of the operated patients, revision surgery was required in two patients who were treated with IM

nailing. One developed implant failure in spite of showing promising callus initially and had to be treated with removal of implant, condylar blade plate, and allograft at 6 months [Figure 2]. In the other patient, exchange nailing was done from a short proximal femoral nail to long proximal femoral nail antirotation nail with iliac crest bone graft. Healing occurred 7 months after the revision surgery. Two patients showed delayed healing with the union at 9 months. Patients with delayed healing and nonunion were also treated with teriparatide (recombinant human parathyroid hormone).

DISCUSSION

BPs were initiated without appropriate indications in most of the cases in our study [indication for BP use is given in Table 2]. In our study, all patients had prolonged use of BPs. In most cases, BPs were initiated to “play safe.” Though BMD was done in eight out of nine cases, it did not show osteoporosis requiring BP treatment in seven patients.

Table 1: Duration of bisphosphonate use and configuration of fractures

Age	Bisphosphonate	Duration of therapy (years)	Affected side	Contralateral side	Treatment	Outcome
85	Alendronate (6 years) Ibandronate (4 years)	10	Left-ST fracture - displaced	-	Open reduction	Healed
67	Alendronate	10	Midshaft fracture femur right - displaced	Left cortical stress reaction - ST	Conservative Closed procedure: Right side	6 months symptoms relieved
58	Alendronate	4	Cortical stress reaction - ST	Cortical stress reaction - ST	Conservative: Left side Open reduction: Right side	Healed
72	Alendronate	4	Left-ST - displaced	-	Open reduction	Healed
77	Alendronate	6	Left side - dreaded black line - Undisplaced - ST	Cortical stress reaction - ST	Closed procedure	Healed
61	Alendronate	10	Right-ST -displaced	-	Closed procedure	Healed
80	Alendronate (4 years) Ibandronate (3 years)	7	Left-ST - displaced	-	Open reduction	Nonunion
60	Alendronate	5	Right-ST -displaced	-	Open reduction	Nonunion
70	Alendronate	4	Left-ST - displaced	-	Open reduction	Delayed union

ST=Subtrochanteric



Figure 2: X-ray of thigh with hip joint anteroposterior view showing (a) subtrochanteric atypical fracture. (b) Intramedullary nail (c) Failure of the intramedullary nail (d) Revised nail with a condylar blade plate

To facilitate future case reporting and research, the European Medicines Agency’s Committee for Medicinal Products for Human Use has adopted a definition of atypical femoral fracture based on the American Society for Bone and Mineral Research provisional case definition of atypical femoral fracture – major and minor features [Table 3].¹⁶ All of the major features should be present to designate a fracture as atypical and distinguish it from more common osteoporotic hip fractures. The minor features have also been described in association with atypical femoral fractures, but they are not required for diagnosis. All our patients fulfilled the criteria for being atypical fractures.

BPs are commonly used as a treatment for osteoporotic patients because of its effectiveness in reducing the risk of fractures.^{2,17-19} They are one of the approved agents for the treatment of osteoporosis. According to the National Osteoporosis Foundation,²⁰ treatment for osteoporosis should be started for patients with hip or vertebral fractures, those with *T*-scores < -2.5 at the femoral neck, total hip, or lumbar spine by DEXA, after appropriate evaluation, and for postmenopausal women and men >50 years with low bone mass at the femoral neck, total hip, or lumbar spine by DEXA. FRAX tool is now used in several parts of the world to assess the probability of fracture based on clinical parameters (early menopause, history of fragility fractures, use of steroid therapy, malignancy, or long term chemotherapy treatment) and DEXA and a 10-year hip fracture probability >3% or a 10-year major osteoporosis-related fracture probability >20% is considered an indication for starting antiosteoporosis treatment. In our study group, only two patients had *T*-score of < -2.5 and started on BP therapy. Seven other patients did not have any associated risk factors such as early menopause, history of fragility fractures, and use of

steroid therapy, malignancy or long term chemotherapy treatment before starting on BP therapy.

We observed “abuse” of BPs as per the WHO (1969) definition persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice,²¹ especially in patients where use was not indicated initially. According to NOF²⁰ and NICE²² guidelines, seven out of nine patients (78%) from our study did not require BP therapy. It is reasonable to stop the use of BPs after the patients have improved and not in osteoporosis range. Even for those patients who have not improved, it is now advisable to discontinue BP after 3 years of use because of the scanty evidence for use after 5 years.²³ Many papers have been published demonstrating the occurrence of atypical femoral fractures in patients on long term BP therapy.^{14,24-27} Patients in our study received BPs for a mean duration of 6.6 years which shows the inappropriate use of these agents by many orthopedic surgeons and rheumatologists or the patients without consulting doctors for many years. Increased awareness about the right indications and criteria for the use of BPs in the management of osteoporosis is necessary.

Various studies have shown bilateral involvement in 28–44% of patients, which may be asymptomatic in the early stage.²⁸ Wang *et al.*²⁶ reported eight cases of atypical femoral fractures with cortical stress reaction on the contralateral femurs of three patients. Egol *et al.* reported outcomes of patients with incomplete BP-related femoral fractures. They studied 31 patients with 43 fractures of which 13 patients had bilateral femur fractures. In our study, three patients (33%) had bilateral involvement of femur, and none of this was picked up by the initial treating surgeon. We therefore recommend a careful surveillance of patients presenting with atypical femoral fractures. MRI or a technetium bone scan may be necessary to confirm the diagnosis of stress reaction and treated accordingly.

In a study of nonoperative versus prophylactic, treatment of BP-associated femoral stress fractures, Banffy *et al.*²⁹ emphasized the importance of orthopedic surgeons

Table 2: Bisphosphonate indication for initiation

Postmenopausal osteoporosis if proved by DEXA
If DEXA is not done: Low trauma fracture of spine, wrist, or hip
Osteopenia on DEXA with risk factors such as patient on steroids or antimalignancy drugs

DEXA=Dual-energy X-ray absorptiometry

Table 3: Definition of atypical femoral fracture based on the American Society for Bone and Mineral Research

Major features	Minor features
The fracture is associated with minimal or no trauma, as in a fall from a standing height or less	Generalized increase in cortical thickness of the femoral diaphysis
The fracture line originates from the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur	Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex	Bilateral incomplete or complete femoral diaphysis fractures
The fracture is noncomminuted or minimally comminuted	Delayed fracture healing
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”)	

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five major features must be present. None of the minor features is required but have sometimes been associated with these fractures. AFF=Atypical femur fractures

recognizing incomplete BP-related femur fractures. Incomplete fractures often resemble stress or insufficiency fractures and may be missed clinically and radiographically. Radiographs of patients treated with BPs for 5 years or longer and have sustained low-energy subtrochanteric, and diaphyseal femoral fractures show characteristic imaging features such as focal lateral cortical thickening or transverse orientation of the proximal femoral fracture line which was noticed in all the study patients. If displaced, a medial cortical spike or beak, superior displacement of the distal fragment and varus angulation at the fracture site are seen.³⁰

All our study patients with a cortical stress reaction and no thigh pain healed with conservative management by 6 months. Patients with displaced fractures or undisplaced with the dreaded black line with thigh pain underwent surgical intervention. Most of the fractures (6/8) were treated with open reduction, freshening of the fracture edges, and IM nailing. Six out of eight fractures healed at a mean duration of 7 months. Two fractures were treated with closed reduction and IM nailing. Two of eight fractures had nonunion which required further surgery and autologous bone graft. Our findings suggest that surgical treatment, in these cases with IM nailing for the most part, improves clinical and functional outcomes for patients who have sustained BP-related femur fractures. Our results corroborate those of Banffy *et al.*²⁹ who suggested that nonoperative management of BP-associated stress fractures has a high likelihood of failure with the majority of fractures progressing to fracture completion. Egol *et al.*³¹ have also shown that the average time of union is higher in these types of fractures.

The study has some limitations including retrospective study design and small sample size with relatively less number of fractures. However, such type of fractures is relatively less common and hence we believe it is worth reporting. The statistical comparison between different groups was not possible due to small sample size.

CONCLUSION

We observed “abuse” of BPs in most of our patients with atypical fractures. None of the patients had any risk factors and most were in osteopenic range. Delay in diagnosis was also noted in some patients. We suggest careful observation, prompt diagnosis, and early surgical treatment for patients with these fractures.

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Conflicts of interest

There are no conflicts of interest.

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