Published online 2021 December **Original Article**

Characteristic features and surgical outcome in bisphosphonate-associated atypical femoral fracture: A retrospective observational study

Karim Pisoudeh[1] , Kaveh Gharanizadeh[1] , Mohammad Reza Naderan[1*], Mohammadreza Sarshar[1], Masoud Mirkazemi[1] , Hamed Tayyebi[1]

[1] Bone and Joint Reconstruction Research Center, Shafa Orthopedic Hospital, Iran University of Medical Sciences, Tehran, Iran

*** *Corresponding author:*** Mohammad Reza Naderan, Shafa Orthopedic Hospital, Baharestan Square, Tehran, Iran. Tel: +98(21)33542000-8. Fax: +98(21)33542020. dr.naderan1967@gmail.com

Received 2021 March 16**; Accepted** 2021 August 28

Abstract

Background: Bisphosphonate-associated atypical femoral fracture (AFF) is a rare and serious condition with poorly understood characteristics and management.

Objectives: This study aimed to evaluate the characteristic features and outcomes of AFF in a two-center cohort study.

Methods: In this retrospective survey, the medical records of 22 AFF patients were reviewed, who have used alendronate for > 12 months. The demographic characteristics (e.g., age, gender, and body mass index), clinical features (e.g., symptoms and symptom duration), radiologic characteristics (e.g., fracture site, the severity of the fracture, and contralateral involvement), surgical characteristics (e.g., the type of surgery union period), and postoperative complications (e.g., fixation failure and union problems) were extracted from the patients' profiles.

Results: The study population included 4 males and 18 females with a mean age of 70.6±11.9 years. The mechanism of fracture was falling in 21 (95.5%) patients. The mean duration of bisphosphonate consumption was estimated at 3.8±2 years. Prodromal symptoms (pain and limping) were recorded in 12 (54.55%) patients. The fractures were in the femoral shaft and subtrochanteric in 15 (68.2%) and 7 (31.8%) patients, respectively. The fixation device was the intramedullary nail and plate in 18 (81.8%) and 4 (18.2%) patients, respectively. The mean union period was obtained at 8.3±2.8 months. Union complications (delayed or nonunion) occurred in 6 (27.3%) patients. It was reported that fixation failed in 5 (22.7%) patients, including 3 nails and 2 plate fixations.

Conclusions: Based on the results, AFF was associated with a prolonged union. The intramedullary nail provided a more secure fixation. Prodromal symptoms could be used for earlier detection of patients.

Keywords: Atypical femoral fracture, Bisphosphonate, Alendronate, Surgery, Outcome

Introduction

Bisphosphonates are a class of medications that are used in the treatment of osteoporosis. They inhibit bone resorption by impairing the osteoclast's activity (1). Alendronate is a widely administered bisphosphonate that considerably reduces the rate of vertebral and hip fractures in osteoporotic men and women (2). Despite their efficacy in the treatment of osteoporosis, bisphosphonates are also associated with some serious adverse effects (3-5).

Atypical femoral fracture (AFF), a serious bisphosphonate-associated side effect, is a low-energy fracture of the femoral shaft or subtrochanteric region that might occur bilaterally and can be complicated by delayed or nonunion in 26%–39% of patients (6). The incidence of AFF is about 1.8 per 1,000,000 people/year in patients who use bisphosphonates for less than 2 years, and 113 per 100,000 people/year for those with more than 8 years of consumption (7).

Atypical femoral fracture management includes discontinuation of antiresorptive agents, supplementation of calcium and vitamin D, and evaluation of the contralateral femur. In terms of operative treatment, the use of intramedullary nailing and the avoidance of locking plates have been recommended (8-11). However, these guidelines are based on experts' opinions and anecdotal case reports. Therefore, more complementary studies are required to be performed to further characterize the features of AFF patients and their management approach (12).

Objectives

This retrospective research aimed to evaluate the demographic, clinical, and radiologic characteristic features of 22 AFF patients, their management approach, and the outcome of treatment in a two-center cohort study.

Methods

This retrospective study was approved by the review board of the Iran University of Medical

Sciences, Tehran, Iran, under the code of IR.IUMS.FMD.REC.1399.233. The medical records of patients with a femoral fracture who underwent surgical treatment at our referral orthopedic centers within 2014-2019 were reviewed, and patients with bisphosphonate-associated were identified. The radiographs of these patients were re-evaluated separately by two authors to find whether they met the criteria for AFF, including the site of fracture (from lesser trochanter to the flair of the femoral condyle), the origination of the fracture (at the lateral cortex), characteristics of the fracture (cortical beaking, periosteal thickening, and the horizontal orientation of fracture). Any disagreement between the two authors was resolved by a third author.

The identified cases of AFF were assessed for the eligibility criteria. The inclusion criteria were at least 12 months of bisphosphonate consumption and a complete or incomplete fracture of the femur. On the other hand, immature patients, patients with bone metabolic disorders (e.g., Paget's disease), disorders associated with vitamin D metabolism, history of long-term use of corticosteroids, history of kidney, thyroid, and parathyroid disorders, and fractures associated with high-energy trauma were excluded from the study. The remaining patients were included in the final study.

The demographic, clinical, radiologic, and surgical characteristics of the eligible patients were extracted from their medical records. The demographic characteristics included age, gender, body mass index (BMI), comorbid disorders, duration of bisphosphonate consumption, type of bisphosphonate, and mechanism of injury. The clinical features included symptoms, duration of symptoms, and symptoms in the contralateral limb. Radiologic characteristics were the location of the fracture, severity of fracture (i.e., complete or incomplete), and contralateral involvement. Surgical characteristics consisted of the type of surgery, number of implemented proximal and distal screws, fixation device, union period, and prophylactic surgery of the contralateral limb.

The first visit of the patients was 2 weeks after the surgery. The next follow-ups were 1, 1.5, and 3 months after the first visit and every 3 months afterward until observing radiologic union. Postoperative complications, such as fixation failure, revision surgery, nonunion, delayed union, fracture displacement, and infection were recorded in each visit. Nonunion and delayed union were defined as failure to observe callus formation in plain radiograph within 6 and 3 months after the surgery, respectively.

Results

In this study, among the total 22 AFF patients, 4 (18.2%) and 18 (81.8%) of cases were males and females, respectively, with the mean age of 70.6±11.9 years (range 41-89). The mean age scores of male and female patients were estimated at 76.7±9.5 and 69.2±12.1 years, respectively. The mean BMI of the patients was obtained at 24±4.3 kg/m2 (range 18.5-35.2). The mean follow-up of the patients was calculated at 4.2±2.3 years (range 20-78 months). It was revealed that 11 (50%) patients had hypertension and 112 (45.5) cases had other comorbid disorders, such as rheumatoid arthritis and diabetes. The mechanism of the fracture was falling down in 21 (95.5%) patients and lifting a heavy object was reported in 1 (4.5%) patient. It was also found that the type of bisphosphonate was alendronate in all patients, and the mean duration of drug consumption was 3.8 years (range 1-8).

According to the results, 2 patients had a history of AFF in the contralateral limb, and 12 (54.5%) patients were presented with prodromal symptoms, which included pain and limping in 10 and 2 patients, respectively. The other 10 (45.5%) patients had no clinical symptoms. The mean duration of prodromal pain was 13.6±11.1 months (range 1-36). One of the patients had a six-year history of pain in the contralateral limb, the radiographic evaluation of whom revealed bilateral AFF. It was reported that two other patients had AFF of the contralateral limb with no clinical symptom, and the AFF of both limbs was fixed simultaneously in these patients.

The fractures were in the femoral shaft and the subtrochanteric region in 15 (68.2%) and 7 (31.8%) patients, respectively. Moreover, the fracture was incomplete and complete respectively in 1 (4.5%) and 21 (95.5%) patients. The surgery was open in 10 (45.5%) patients and closed in the remaining cases. The fracture was fixed with a nail and a plate in 18 (81.8%) and 4 (18.2%) patients, respectively. The nail was conventional and proximal femoral nail (PFN) in 15 (83.3%) and 3 (16.7%) patients, respectively (Figure 1). In the majority of patients (n=16) 2 distal and 2 femoral screws were used to fix the nail in place. Characteristic features of patients are demonstrated in Table 1.

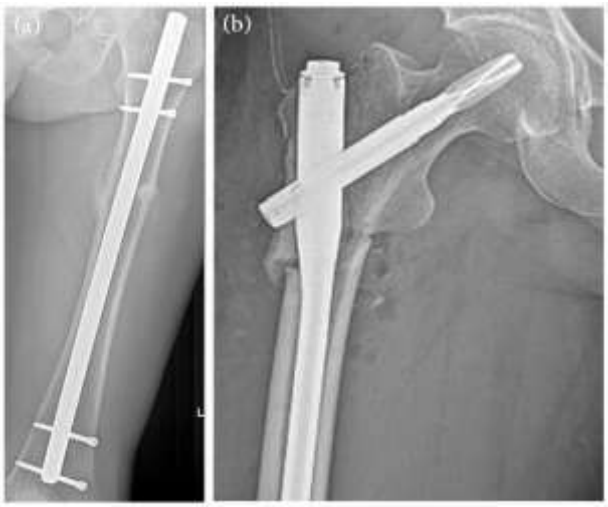

Figure 1: Implication of conventional (a) versus proximal femoral nail (b) for the fixation of atypical femoral f

Table 1: Demographic information of patients with bisphosphonate-associated atypical femoral fracture

Variable	AFF patients(n=22)
Age (year)	70.6±11.9
Gender • **Male** • **Female**	4 (18.2) 18 (81.8)
BMI (kg/m²)	24±4.3
Follow-up (year)	4.2±2.3
Mechanism of fracture • **Falling down** • **Lifting heavy object**	21 (95.5) 1 94.5)
Hypertensions	11 (50)
Other comorbidities	10 (45.5)
Duration of bisphosphonate use (year)	3.8±2
History of AFF	2 (9.1)
Prodromal pain	10 (45.5)
Pain duration	13.6±11.1
Contralateral involvement	3 (13.6)
Location of fracture • **Femoral shaft** • **Subtrochanteric region**	15 (68.2) 7(31.8)
Severity of fracture • **Complete** • **Incomplete**	21 (95.5) 1 (4.5)
Type of surgery • **Open** • **Close**	10 (45.5) 12 (54.5)
Fixation device • **Nail** • **Plate**	18 (81.8) 4(18.2)
Nail type • **Conventional** • **Proximal femoral nail**	15 (83.3) 3 (16.7)
Union period (month)	8.3±2.8
Union problem • **Delayed union** • **Non-union**	2 (9.1) 4 (18.2)
Fixation failure	5 (22.7)
Failed device • **Nail** • **Plate**	3.18 (16.7) 2.4 (50)

Data are shown as mean ± SD or number (%).
AFF: Atypical femoral fracture; BMI: Body mass index

Postoperative complications The non-complicated union of fracture occurred

in 16 cases during a mean period of 8.3±2.8 months (range 4-12). In 2 patients the union was delayed (18 and 24 months), while in the remaining 4 patients, the union was not observed until the last follow-up and failure occurred. Infection of the surgical site did not occur in any patient. Displacement of fracture occurred in one patient.

Failure of fixation occurred in 5 (22.7%) patients. In the first failure, the fracture was fixed with a plate and failed after 1 month. In the revision surgery, the fixation was performed with plate and nail, and the union of fracture was seen after 4 months. In the second failure, the fracture was first fixed with a conventional nail that was failed after 36 months. In the revision surgery, the fracture was fixed with a plate, which was failed after 7 months. In the third surgery, the fracture was fixed with a plate and autologous bone graft, in which union was observed after 12 months. In the third failure, primary fixation was accomplished with a plate that was failed after 3 months. In the revision surgery, fixation was performed with a longer plate and bone graft. The union was observed after 15 months. The fourth failure occurred in a bilateral AFF patient. The primary fixation was done with a conventional nail for both limbs and failed in the left side after 2 months. In the revision surgery, the fracture was fixed with PFN and united after 12 months. In the fifth failure, the primary fixation was performed with PFN and failed after 2.5 years. In the revision surgery, an angle blade plate was used for fixation and failed after 6 months. The patient passed away 1 month after the failure of revision surgery.

Discussion

This study evaluated the characteristic features and outcome of AFF in a cohort of 22 patients. Based on our experience, AFF was associated with a prolonged union, compared to the typical femoral fracture group, as well as a higher rate of union complications (27.3%), such as delayed union or non-union. The frequency of fixation failure was obtained at 22.7%. The risk of failure was more when the plate was used for fixation purposes.

Shin et al. reported the union period in AFF in a series of 15 patients. In the mentioned study, 15 cases with typical femoral fractures were included as the control group. The mean age of the AFF patients was estimated at 77.9 years. Alendronate was the bisphosphonate of choice in the majority of patients. The mean duration of bisphosphonate consumption was 73 months. The fracture was in the subtrochanteric region and femoral shaft in 7 and 8 patients, respectively. Fixation was done with a nail and plate for 14 and 1 patients, respectively. Revision surgery was performed for only one patient that was due to nonunion. The mean duration of the union was 11.9 and 4.3 months in the AFF and control groups, respectively. The duration of bisphosphonate consumption was positively correlated with the union period (13). In the present study, the mean age of the patients was obtained at 70.6 years. The rate of revision surgery was greater (5 out of 22) that could be attributed to the greater number of plate fixation (4 out of 22). In line with the results of a study conducted by Shin et al., the union process was prolonged in our patients (average 8.3 months).

Based on the findings of earlier studies, younger age, obesity, and early menopausal age were observed among AFF female patients (14). In the current study, the majority of female patients had normal BMI. The age of patients was considerably lower in females than in males (69.2 vs. 76.7 years).

Rajput et al. reported the outcome of surgical fixation of 11 AFF in 10 bisphosphonate-treated patients. In the mentioned research, all patients were females with a mean age of 68.6 years, 9 fractures were located in the subtrochanteric region. The mean duration of bisphosphonate consumption was obtained at 58.3 months. All the fractures were fixed with the intramedullary device, and the union of fracture was observed in all patients at a mean duration of 9.9 months. Delayed union was reported in 5 patients; however, no surgical failure was recorded. They concluded that intramedullary nails could provide much more axial stability for the fixation of AFF (15). The mean duration scores of union and union complications in our patients were comparable to those in the study performed by Rajput et al. Similarly, intramedullary nail provided a better fixation in our patients and was associated with less failure than plate fixation (16.7% vs. 50%).

Sahemey et al. introduced a novel technique including over-reaming the intramedullary canal by 2.5 mm greater than the diameter of the implant and rigid fixation with cephalomedullary nailing in AFF patients. In the aforementioned research, 28 AFFs were cured with this approach. All patients achieved a union within a mean period of 6 months and no revision surgery was required. They concluded that their variations in surgical technique improved fracture union and reduced intraoperative complications (16). The mean union period was 8.3 months in the present study. In addition, 5 patients (22.7%) experienced a union problem. Therefore, the technique introduced by Sahemey et al. could be implemented in the future management of AFF to reduce the union period and complications.

Bhadada et al., in a case-series study of 8 patients, evaluated the predictors of AFF during long-term bisphosphonate therapy. Based on their results, a history of prodromal pain and thickened cortex with cortical beaking could be considered predicting clues for AFF. Consequently, patients with these risk factors should be closely monitored for early detection of AFF (17). In the present study, 10 (45.5%) patients had prodromal pain. The mean duration of prodromal pain was 13.6±11.1 months.

Earlier screening of these patients could have resulted in earlier detection and less complicated outcomes.

Altogether, AFF is poorly pathologically understood and future large-scale standard studies are required to shed more light on the different aspects of this disorder, including its risk factors and management. According to the current state of evidence, AFF is associated with a prolonged period of union, and intramedullary nail provides a more secure fixation in these fractures. The main limitation of this study was related to its retrospective design that did not allow evaluation of several potential factors involved in the pathogenesis of AFF, such as the BMI, serum vitamin D, and serum calcium level. The other limitation was regarded to the small sample size, which was not large enough for statistical analysis of the data.

Conclusions

Based on the results of the study, AFF was associated with a prolonged union period and considerable union complications, including delayed union and nonunion. It was revealed that fixation failure was a frequent observation among AFF patients. Moreover, the intramedullary nail provided a better fixation and was associated with a smaller rate of fixation failure than plate fixation. Prodromal pain was observed in a considerable number of patients and could be used for earlier detection of fracture.

References

1. Fleisch H, Reszka A, Rodan G, Rogers M. Bisphosphonates: mechanisms of action. Principles of bone biology. 2002:1361-XLIII.
2. Favus MJ. Bisphosphonates for osteoporosis. New England Journal of Medicine. 2010;363(21):2027-35.
3. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. Mayo Clin Proc. 2009;84(7):632-8. PubMed PMID: 19567717. eng.
4. Abrahamsen B. Bisphosphonate adverse effects, lessons from large databases. Current opinion in rheumatology. 2010;22(4):404-9.
5. Papapetrou PD. Bisphosphonate-associated adverse events. Hormones. 2009;8(2):96-110.
6. Giusti A, Hamdy NA, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. Bone. 2010;47(2):169-80.
7. Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. Journal of Bone and Mineral Research. 2012;27(12):2544-50.
8. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. Journal of Bone and Mineral Research. 2010;25(11):2267-94.
9. Saita Y, Ishijima M, Kaneko K. Atypical femoral fractures and bisphosphonate use: current evidence and clinical implications. Therapeutic advances in chronic disease. 2015;6(4):185-93.
10. Giaconi JC, Watterson CT. Bisphosphonate-Related Atypical Femur Fractures and Their Radiographic Features. The Duration and Safety of Osteoporosis Treatment: Springer; 2016. p. 107-24.
11. Pisoude K, Elahifar O, Sohrabi MB, Khajemozafari J. Comparison of proximal femur locking compression plate and intramedullary nailing in the treatment of sub-trochanteric fractures. Journal of Research in Orthopedic Science. 2019;6(2):0-.
12. Eisenstein N, Kasavkar G, Bhavsar D, Khan FS, Paskins Z. Incidence and medical management of bisphosphonate-associated atypical femoral fractures in a major trauma centre: a retrospective observational study. BMC musculoskeletal disorders. 2017;18(1):1-6.
13. Shin JS, Kim NC, Moon KH. Clinical features of atypical femur fracture. Osteoporosis and sarcopenia. 2016;2(4):244-9.
14. Franceschetti P, Bondanelli M, Caruso G, Ambrosio MR, Lorusso V, Zatelli MC, et al. Risk factors for development of atypical femoral fractures in patients on long-term oral bisphosphonate therapy. Bone. 2013 Oct;56(2):426-31. PubMed PMID: 23871850. Epub 2013/07/23. eng.
15. Rajput IM, Kumar J, Siddiqui AA, Jamil M, Soughat M, Ahmed MW. Surgical Fixation of Atypical Femur Fractures in Bisphosphonate-treated Patients. Cureus. 2019;11(5).
16. Sahemey R, Nikolaides A, Bhattacharya S, Simons A, Makrides P. Bisphosphonate-related atypical femoral fractures: A novel strategy to improve patient outcomes. Journal of Orthopaedics, Trauma and Rehabilitation. 2020;27(2):192-7.
17. Bhadada SK, Sridhar S, Muthukrishnan J, Mithal A, Sharma DC, Bhansali A, et al. Predictors of atypical femoral fractures during long term bisphosphonate therapy: A case series & review of literature. The Indian journal of medical research. 2014;140(1):46.