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ORIGINAL ARTICLE

Bisphosphonate therapy associated with bilateral atypical femoral fracture and delayed union

István Gárgyán[1], Dávid Dózsai[3], István Csonka[1], Ferenc Rárosi[2], Tamás Bodzay[3], Ákos Csonka[1]

[1]Department of Traumatology, University of Szeged, Szeged, Hungary
[2]Department of Medical Physics And Informatics, University of Szeged, Szeged, Hungary
[3]Department of Traumatology, National Institute of Traumatology, Budapest, Hungary

ABSTRACT

Objectives: The aim of this study was to identify the risk factors for developing atypical femoral fractures (AFF) and to examine the effect of bisphosphonate (BP) therapy on delayed bone union and bilateral fractures.

Patients and methods: Between January 1st, 2012 and December 31st, 2020, a total of 74 AFF patients (8 males, 66 females; mean age: 75.4±7.2 years; range, 51 to 94 years) were recorded in two centers and retrospectively analyzed. A control fragility fracture group (n=143) was compared to the AFF group according to fracture characteristics, surgical fixation methods, comorbidities, and medications. The AFF patients were selected and subdivided according to their BP therapy: Group 1 (without BP) and Group 2 (with BP). Group 2 was further classified into Group 2a (<5 years of BP) and Group 2b (>5 years of BP).

Results: The multivariate logistic regression model showed that, BP drug use was the most significant risk factor in development of AFF (p<0.001, odds ratio= 10.749, 95% confidence interval: 3.886-29.733). The patients on BP showed longer bone union (Group 2 - 8.3±3.5 *vs*. Group 1 - 6.4±3.1 months, p=0.02; Group 2b - 9±3.8 *vs*. Group 2a - 7.3 ±3.9 months, p=0.09). Of all 19 cases of bilateral fractures, 14 were in Group 2 with BP use (p=0.11). Of 74 cases, 26 (35%) contralateral femoral X-rays were taken on admission and 24 (92%) showed AFF minor criteria signs. Of these 24 patients, 10 (42%) developed contralateral AFF.

Conclusion: The most significant risk factor in development of AFF was BP drug use. Longer BP therapy (>5 years) showed longer delayed bone union, which was not significant. There was a relatively high risk of developing AFFs and bilateral fractures on BP therapy. In case of an AFF, a contralateral femoral X-ray must be always performed for signs of an impending fracture.

Keywords: Atypical femoral fractures, bilateral fracture, bisphosphonate therapy, delayed bone union, stress fracture.

The proportion of atypical femoral fractures (AFFs) is very low compared to normal osteoporotic lower extremity fractures, accounting for approximately 1 to 2% of all femoral fractures in the aging population, who mainly suffer from osteoporosis.[1,2] In the literature, bisphosphonates (BPs) have the ability to increase bone mineral density and decrease the risk of hip and vertebral fractures by as much as 40 to 70%.[3] Furthermore, the relationship between BP use and AFFs has become more compelling. Such fractures are more common in patients who have been exposed to long-term BPs, usually for more than three to five years.[4,5] In a study by Meier et al.,[6] they found that among 39 AFFs, longer BP exposure (5 to 9 years) was associated with a greater risk of AFFs than shorter exposure, although the risk was higher even with less than two years of use. Shane et al.[4] reported that relative risk on AFFs on BP was very high ranging from 2.1 to 128, and their absolute risk was extremely low ranging from 3.2 to 50 cases/100,000 person-years.

Delayed bone union is defined as a fractured bone that did not heal completely within six months of

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Correspondence: Ákos Csonka, MD. Department of Traumatology, University of Szeged, Szeged, Hungary.

E-mail: csonka.akos81@gmail.com

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injury. For delayed and non-unions, the most important clinical criterion was the lack of weight bearing, followed by pain at the fracture site and weight bearing status; however, in the literature, there is a lack of a standardized clinical definition of union.[7] In case of AFFs, relatively longer (7 to 9 months) bone unions were recorded in several studies.[5,8] The AFFs are associated with a high prevalence rate of prodromal pain and contralateral impending fracture which needs a close follow-up and probable surgical fixation.[5]

Atypical fracture patterns have occurred in patients with no history of BP therapy; however, there may be other potential risk factors in bone turnover.[9,10] The pathomechanism of atypical fracture includes every risk factor that impairs bone turnover of previously developed microfractures (with a new bone matrix) by decreasing bone tissue remodeling.[11] Bone geometry, chronic disease (e.g., diabetes, hypothyroidism), genetic mutation or genetic alteration that decreases bone remodeling can be a potential risk factor of AFFs.[12-15]

In the present study, we hypothesized that the long-term (>5 years) use of BP increased the incidence of AFFs, duration of bone union, and the bilateral fracture occurrence. We, therefore, aimed to identify the risk factors for developing AFFs and to examine the effect of BP therapy on delayed bone union and bilateral fractures.

PATIENTS AND METHODS

This two-center, retrospective study was conducted at National Institute of Traumatogy, Budapest and Universtity Hospital Szeged, Department of Traumatology between January 1st, 2012 and December 31st, 2020. A total of 4,190 patients by the International Classification of Diseases-10 (ICD-10) coding who were diagnosed with subtrochanteric (AO-32A3.a) or diaphyseal (AO-32A3.b) femoral fracture were reviewed. Three orthopedic surgeons retrospectively and independently examined X-rays, according to the revised AFFs case definition criteria of the American Society for Bone and Mineral Research task group (ASBMR) (Table I)[4] and established a consensus that there were 74 (1.7%) AFFs. At least four out of five major features had to be present to confirm the diagnosis. No minor features are required, but are mainly associated with the fracture.[4]

Inclusion criteria were patients having sustained low-energy trauma. Exclusion criteria were polytrauma patients, patients younger than 50 years of age, and patients with incomplete medical records. These 74 patients (8 males, 66 females; mean age: 75.4±7.2 years; range, 51 to 94 years) were reviewed using the inclusion and exclusion criteria and all were found to be eligible. A control group of 143 patients were reviewed with the same inclusion and exclusion criteria mentioned above with a fracture type of AO 32A1.a - subtrochanteric-, 32A3.b - diaphyseal- and some 31A1 - pertrochanteric femoral fractures as fragility fractures. In the AFF group, the patients were also divided by their BP therapy history into two groups: those without BP therapy (Group 1) and with BP therapy (Group 2). Group 2 was further subdivided by the length of the BP therapy (Group 2a: <5 years of BP, Group 2b: >5 years of BP). The study flow chart is shown in Figure 1.

A written informed consent was obtained from each patient. The study protocol was approved by the Regional Institutional Ethics Committee, Budapest (date/no: 2021.10.01,18/2021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

TABLE I
ASBMR Task Force Revised Case Definition of AFFs

Major criteria	Minor criteria	Exclusion criteria
• Transverse or slightly oblique fracture line • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex • Minimal or no trauma • Non or minimally comminuted • Localized periosteal or endosteal thickening of the lateral cortex at the fracture site	• Increase in cortical thickness of the femoral diaphyses • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral incomplete or complete diaphysis fractures • Delayed healing	• Femoral neck fracture • Intertrochanteric fractures with spiral subtrochanteric extension • Periprosthetic fractures • Pathological fractures related to primary or metastatic bone tumors and miscellaneous bone diseases

ASBMR: American Society for Bone and Mineral Research task group; AFFs: Atypical femoral fractures.

Assessment

Data on potential risk factors were gathered from hospital electronic health records including age, sex, comorbidities such as hypertension and antihypertensive medication, diabetes, rheumatoid arthritis, thyroid disease, malignancy, neurological disease, as well as BP and glucocorticoid therapy history (all listed comorbidities are in association with AFFs according to the literature - and in the case of hypertension and its medication, there is no such study available - it was added only for the heterogeneity of data).[14,16-18] Fracture characteristics (delayed bone union cases and duration, contralateral X-ray case number, contralateral signs), surgical fixation methods and complications (bilateral fractures) were analyzed. Our criteria for bone union were as follows: complete cortical bridging (3 out of 4), and a fracture line either barely visible or undetectable. We did not calculate any bone union scores. Delayed bone union was noted, if it exceeded six months. Follow-up at Weeks 6, 12, 26, and 52 were recorded, and X-rays were retrospectively analyzed for bone union. In this study, all patients who were operated by cephalomedullary nails with a proximal- and middle- third fracture location were encouraged to attempt and achieve full-weight bearing as soon as possible postoperatively, according to the AO Surgery Reference guidelines. In cases where delayed union was recognized, more frequent X-rays (every two or

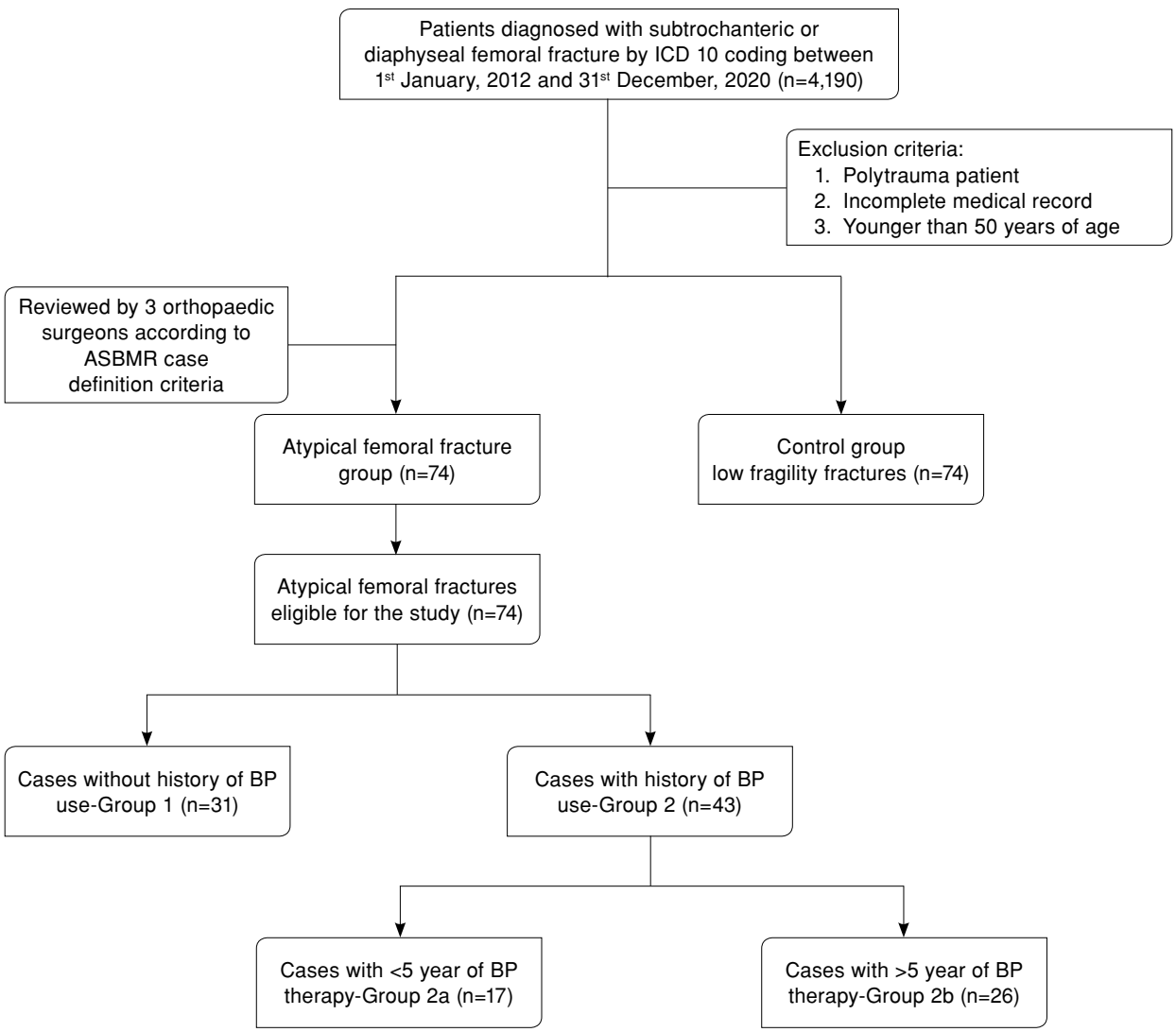

FIGURE 1. Study flow chart.
ICD: International Classification of Diseases; ASBMR: American Society for Bone and Mineral Research; BP: Bisphosphonate.

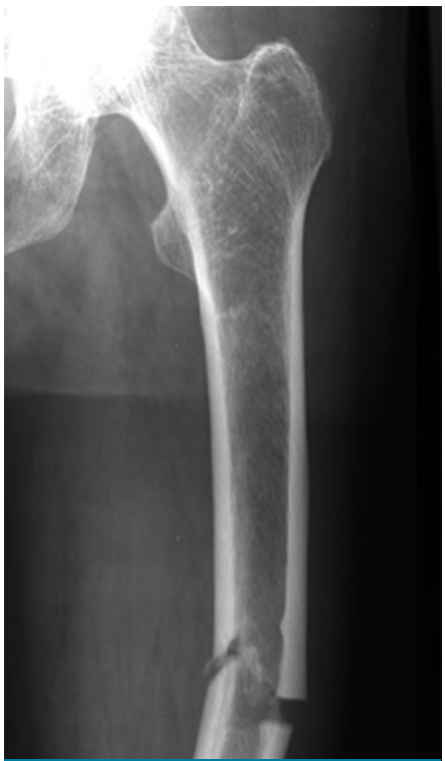

FIGURE 2. A case of a 79-year-old man who suffered from an atypical femoral fracture and received oral bisphosphonate therapy for eight years.

three weeks) were performed, until bone union was noted. The patients with contralateral minor signs were followed conservatively. Those who were on BP therapy and sustained an AFF had their BP therapy discontinued for at least one year.

Group 1 and 2, and Group 2a and 2b were compared by the duration of union, delayed bone union cases, and bilateral fracture occurrence.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Means of continuous variables in the formed groups were compared with the Welch's independent samples t-test. The relationship between categorical variables was tested using the chi-square test for independence and Fisher exact test. Further analysis was carried out with multivariate logistic regression model. Forward likelihood ratio model selection method was used. Possible risk factors were sex, diabetes, rheumatoid arthritis, thyroid disease, malignancy, neurological disease, hypertension, osteoporosis, and BP and corticoid use. Odds ratios (ORs) and 95% confidence intervals (Cis) were calculated. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 74 patients (19 bilateral, all together 93 AFFs), were diagnosed as with AFF, which was 1.7% of all femoral fractures (Figure 2). Demographic data, records of chronic diseases, and medications of patients are shown in Table II. Different types of statistical methods were performed on risk factors of AFFs (Table II).

In the AFF group, 43 patients received BP therapy, compared to only eight patients in the control group (p<0.001). The mean duration of drug use in the AFF group -7±3.5 years *vs.* the control group -2.9±0.8 years (p<0.001). In the AFF group, 26 patients received BP for longer than five years. In Group 2a, the mean time of the BP therapy was 4.3±0.9 (range, 3 to 5) years and, in Group 2b, it was 8.7±3.6 (range, 6 to 20) years. In the control group, there was no BP use longer than four years. In the study group, the most commonly used BPs were alendronic and ibandronic acids. In the control group, six patients were on alendronic and two patients on ibandronic acids. Discontinuing BP therapy for at least one year was the postoperative osteoporosis medical treatment protocol followed.

Among 93 AFFs, there were delayed bone unions in 65 fractures (70%). The mean duration of union in all AFF cases (7.5±3.5 months) was significantly higher compared to the control group (4.5±2.2 months, p<0.001). Also, delayed union time was significantly higher in BP user patients in the AFF group (Group 2, -8.3±3.5 months, p=0.003). The most common AFF fracture location was the shaft region (Table III). Data regarding contralateral X-rays and signs are shown in Table III. Contralateral radiographs were not applied in all AFF patients due to the fracture itself being rare; and, on primary admission, not being recognized in 65% of the cases by surgeons. The patients who were on BP therapy and had suffered from an AFF had a contralateral femoral X-ray, and along with noticing minor signs, their BP therapy was discontinued for at least one year, with a conservative follow-up. The application of a prophylactic surgical treatment was done only once, due to the patient suffering from severe pain on the contralateral femur, with an impending fracture later located.

Surgical fixation methods can be seen in Table III. The most common AFF fixation was Sanatmetal® Fi-nail (43%).

TABLE II
Demographic and chronic diseases data on AFF and control group patients

	AFF group (n=74)			Control group (n=143)			
Demographic data of patients	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			75.4±7.2			74.3±11.8	0.403*
Sex							0.017†
Male	8			35			
Female	66			108			
Diabetes	9	12		33	23		0.054†
Rheumatoid arthritis	4	5		2	1		0.184‡
Thyroid disease	11	15		10	7		0.063†
Malignancy	5	6		5	3		0.315‡
Neurologic disease	7	9		9	6		0.398†
Hypertension	49	66		115	80		0.021†
Osteoporosis	50	67		25	17		<0.0001†
Bisphosphonate use	43	58		8	6		<0.0001†
Corticosteroid use	5	6		4	3		0.279‡

AFF: Atypical femoral fractures; SD: Standard deviation; * Welch two sample t-test; † Chi-squared test; ‡ Fisher exact test.

TABLE III
Fracture type and characteristics with surgical fixations

	AFF group (n=74)			Control group (n=143)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Fracture type and characteristics							
Total number of femoral fractures	93			143			-
Femoral shaft	71			34			-
Subtrochanter	22			85			-
Pertrochanter	-			24			-
Delayed union	65			26			-
Duration of union all patients			7.5±3.5			4.5±2.2	<0.001*
Duration of union on BP			8.3±3.5			4.4±2.9	=0.003†
Duration of union on steroid			7.3±3.6			4.1±1.9	-
Bilateral fracture	19			-			-
Interval between primary and contralateral fracture occurrence in bilateral form			27.7±7.3	-			-
Contralateral X-ray	26			-			-
Contralateral signs (minor criteria)	24	92.3		-			-
Contralateral signs and bilateral fracture incidence	10	41.6		-			-
Surgical fixation type							
Stryker®-gamma 3 system	28	30		4	4.1		-
Sanatmetal®-fi-nail	40	43.1		119	83		-
Synthes®-lateral femoral nail	4	4.3		1	0.7		-
Küntscher nail	17	18.3		13	9.1		-

SD: Standard deviation; BP: Bisphosphonate; * Welch two sample t-test; † Independent sample t-test.

TABLE IV
Characteristics in different groups by duration of union, delayed union and bilateral fracture cases

	Group 1 (without BP therapy, n=31)		Group 2 (with BP therapy, n=43)		
	n	Mean±SD	n	Mean±SD	*p*
Duration of union		6.4±3.1		8.3±3.5	0.02*
Delayed union	16		34		0.01†
Bilateral fracture	5		14		0.11†
	Group 2a (<5 years of BP, n=17)		Group 2b (>5 years of BP, n=26)		
	n	Mean±SD	n	Mean±SD	*p*
Duration of union		7.3±2.9		9±3.8	0.099*
Delayed union	12		22		0.445‡
Bilateral fracture	4		10		0.307†

BP: Bisphosphonate; SD: Standard deviation; * Welch two sample t-test; † Chi-squared test; ‡ Fisher exact test.

Patients in Group 2 (on BP therapy) showed a significantly longer bone union (8.3±3.5 months) compared to Group 1 (without BP) (6.4±3.1 months, p=0.02) (Table IV) The number of cases with delayed bone union was also significantly higher in Group 2 (n=34) *vs.* Group 1 (n=16) (p=0.01) (Table IV).

Group 2b showed a longer union time (9±3.8 months) compared to Group 2a (7.3±2.9 months, p=0.1). Group 2b, compared to Group 1, had a strong, statistically significant difference by union time (p=0.001).

Fourteen of the total 19 bilateral fractures were in Group 2, with a history of BP use (p=0.11). There was no significant difference between Group 2a and 2b regarding the bilateral occurrence (p=0.307) (Table IV).

Multivariate analysis revealed that the most important risk factors for development of AFFs were hypertension (p=0.019, OR=0.387, 95% CI: 0.175-0.858), osteoporosis (p=0.008, OR=3.258, 95% CI: 1.367-7.767), and BP use (p<0.001, OR= 10.749, 95% CI: 3.886-29.733).

DISCUSSION

Regarding patient characteristics, the incidence of AFFs was 1.7% of all femoral fractures, which is consistent with reported AFF percentage in the literature.[1]

The published ASBMR report states that BP therapy is a relative (but not an absolute) risk factor to the occurrence of AFFs.[4] The absolute risk factor of AFFs by BP use is considered low, only as there are 3.2 to 50 cases/100,000 patients/year.[6] It is known in the literature that there is a strong correlation between BP use and AFFs.[4,6,19,20] In this study, similar results were shown, in that BP therapy was the most significant risk factor for the development of AFF compared to the control group (p<0.001, OR=10.749, 95% CI: 3.886-29.733). More interestingly, according to the patient data, in patients with hypertension and using hypertension medication, the risk of AFF development reduced. After searching the literature for an explanation, no publication or cause was found for this mechanism. Therefore, the correlation between hypertension and AFF incidence requires further investigation.

In our study, among 74 AFF cases, there were seven patients in whom there was no chronic disease, drug use or predisposing risk factor. In this group, the mean time of fracture healing was 4.9±2.3 months. This may be due to genetic mutation, individual predisposition, bone metabolic errors or bone geometric changes, which is reported in the literature.[10,12,21,22] Studies have shown that patients diagnosed with diabetes mellitus have a suppressed bone turnover, which is thought to be caused by osteocyte dysfunction and higher level of sclerostin, that forms microfractures in the bone.[14] Atypical fractures are associated with many medical conditions such as osteopetrosis, hypophosphatasia, vitamin D deficiency, pycnodysostosis, rheumatoid arthritis, and certain types of non-Hodgkin lymphomas, as these diseases inhibit bone metabolism as a mechanism of action.[23-25]

Several studies have reported that, in atypical fractures, delayed bone union and bilateral fractures can occur during BP therapy.[17,26-28] In the present study, we also examined in what proportion BP therapy increased duration of bone union and the incidence of bilateral fractures.

Both mechanical and histological factors are known to possibly have an effect on the pathophysiology of delayed unions.[28-30] In a study of 109 atypical fractures, one of the associated risk factors was long-term BP use in delayed unions.[28] Prasarn et al.[31] reported that long-term BP therapy was associated with longer bone union (6.5 *vs.* 4.8 months), compared to non-BP users. In a recent meta-analysis, the mean time of union in patients on BP was about 8.5 months, and a third of all BP-related fractures resulted in delayed or non-union.[32] In this study, of 74 patients (93 fractures), the mean time of union was 7.5±3.5 months and delayed bone union was recorded in a total of 65 fractures (70%). Among them, BP use was noted in 43 individuals (58%), indicating the suppression of bone remodeling that caused delayed bone union. Patients in Group 2 (on BP therapy) showed a significantly longer bone union, compared to Group 1 (without BP) (p=0.02). Delayed bone union case numbers were also significantly higher in Group 2 than Group 1. Group 2b showed longer union time compared to Group 2a, but was not statistically significant. Group 2b, compared to Group 1, had a strong, statistically significant difference by union time (p=0.001). As a result, longer BP therapy (>5 years) causes longer delayed bone union, although not statistically significant. It is known that AFF treatment can be challenging, but even in the most unfavorable of scenarios, the risk/benefit ratio is highly positive for BP use, particularly during three to five years of use.[33] The postoperative treatment protocol undertaken was a discontinuation of BP therapy for at least one year (a so-called drug holiday), which is recommended by the literature after an AFF.[34] A comparison of different groups based on the duration of drug holidays and the continuation of drug use later was not performed.

Probyn et al.[35] evaluated 124 patients who suffered from AFFs on BP therapy with 78 cases of bilateral fracture occurrence. They concluded that the likelihood to be diagnosed with a contralateral AFF was high within the first year of presentation. In this study, in 19 cases of bilateral fractures, the contralateral fracture occurred for one year period. In this study, bilateral fractures occurred mostly in BP users (Group 2), although there were no statistically significant differences. Longer BP therapy also showed no statistically significant difference in the occurrence of bilateral fracture. In all 26 cases where contralateral X rays were taken on primary admission, signs of localized periosteal or endosteal thickening were found in 92.3% of the cases. Of 24 cases, 10 cases confirmed a bilateral fracture afterwards.

Clinical studies have reported that prophylactic intramedullary (IM) nailing can be beneficial for patients who have a risk of secondary stress fracture displacement. The indications for surgery are prodromal pain on the contralateral side, and prevention of secondary stress fracture displacement.[36-38] In this study, due to its retrospective nature, there were insufficient data on prodromal pain. The cases in which impending fractures (minor signs) were recognized were followed closely conservatively. The literature reports a high rate of secondary displacement of non-operated cases.[36,38] Ha et al.[37] reported that five of 14 cases had secondary displacement. Unfortunately, in this study, out of 24 recognized cases, 10 developed a contralateral complete fracture and needed fixation surgically.

In this retrospective study, the lack of coherence of standardized weight bearing scores in the patient groups led to insufficient information regarding patients achieving full-weight bearing. Information on prodromal pain was also missing. Pain on palpation at the site of injury is currently widely used among physicians to judge union; however, it is a highly subjective outcome, given individual and cultural differences in perception and tolerance level of pain among the population.[39]

Furthermore, this study reports no femoral neck fracture complications. Femoral neck fractures may occur, when gold-standard IM nails have been used and it is recommended to use cephalomedullary nails in AFFs.[18,28,30]

The retrospective nature, a relatively small sample size, and a low number of BP users in the control group are the other limitations of this study. The latter demonstrates that some of the statistics are not statistically significant. They are, however, supported by the literature. There were some overlaps between BP use and chronic diseases which both can cause AFFs. These cases cannot be divided due to small case numbers and complicated study design.

In conclusion, BP use is the most significant risk factor for developing AFF. Longer BP therapy

(>5 years) causes longer delayed bone union. The BP therapy must be suspended in case of impending fracture or AFF occurrence. The risk of developing atypical fracture and the incidence of bilateral fractures on BP is high. Other risk factors, besides BP use, should be also considered in case of atypical fractures. In case of an AFF, a contralateral femoral X-ray must be always performed for signs of an impending fracture. Prophylactic IM nailing can be beneficial for patients who have a risk of secondary stress fracture displacement.

Declaration of conflicting interests

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