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ORIGINAL ARTICLE

Incidence, risk factors, and fracture healing of atypical femoral fractures: a multicenter case-control study

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Abstract

Summary The incidence of atypical femoral fractures (AFFs) was 2.95% among 6644 hip and femoral fractures. Independent risk factors included the use of bisphosphonates (BPs), osteopenia or osteoporosis, rheumatoid arthritis, increased femoral curvatures, and thicker femoral cortices. Patients with AFFs and BP treatment were more likely to have problematic healing than those with typical femoral fractures (TFFs) and no BP treatment.

Introduction To determine the incidence and risk factors of atypical femoral fractures (AFFs), we performed a multicenter case-control study. We also investigated the effects of bisphosphonates (BPs) on AFF healing.

Methods We retrospectively reviewed the medical records and radiographs of 6644 hip and femoral fractures of patients from eight tertiary referral hospitals. All the radiographs were reviewed to distinguish AFFs from TFFs. Univariate and multivariate logistic regression analyses were performed to identify risk factors, and interaction analyses were used to investigate the effects of BPs on fracture healing.

Results The incidence of AFFs among 6644 hip and femoral fractures was 2.95% (90 subtrochanter and 106 femoral shaft fractures). All patients were females with a mean age of 72 years, and 75.5% were exposed to BPs for an average duration of 5.2 years (range, 1–17 years). The use of BPs was significantly associated with AFFs ($p < 0.001$, odds ratio = 25.65; 95% confidence interval = 10.74–61.28). Other independent risk factors for AFFs included osteopenia or osteoporosis, rheumatoid arthritis, increased anterior and lateral femoral curvatures, and thicker lateral femoral cortex at the shaft level. Interaction analyses showed that patients with AFFs using BPs had a significantly higher risk of problematic fracture healing than those with TFFs and no BP treatment.

Conclusions The incidence of AFFs among 6644 hip and femoral fractures was 2.95%. Osteopenia or osteoporosis, use of BPs, rheumatoid arthritis, increased anterior and lateral femoral curvatures, and thicker lateral femoral cortex were independent risk factors for the development of AFFs. Patients with AFFs and BP treatment were more likely to have problematic fracture healing than those with TFFs and no BP treatment.

Seung-Jae Lim and Ingwon Yeo equally contributed to this work and share first authorship.

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Keywords Atypical femoral fracture · Bisphosphonates · Fracture healing · Incidence · Risk factors

Introduction

Bisphosphonates (BPs) are the most commonly used medications for osteoporosis worldwide [1]. Although they effectively reduce the risk of osteoporotic fractures, within the past decade, atypical femoral fractures (AFFs) have emerged as a potential complication of long-term BP treatment [2]. Although AFFs may occur independent of BP use, an increasing number of AFFs have been reported in epidemiological studies. For example, Odvina et al. (2005) described severe reductions of bone turnover after long-term use of the BP alendronate [3–11]. However, the causal association between prolonged use of BPs and AFF remains a subject of debate.

The role of BPs in the pathogenesis of AFFs has not been fully elucidated, although several mechanisms have been proposed [2, 12, 13]. In 2013, the American Society for Bone and Mineral Research (ASBMR) used major radiographic features to distinguish AFFs from ordinary osteoporotic femoral diaphyseal fractures, which suggests that AFFs may develop over time from stress or insufficiency fractures [2]. The authors also suggested that the lower limb geometry of Asian patients may increase the risk of AFFs, [2, 7], and several recent studies have reported the proximal femoral geometry of Asian women with the development of AFFs [10, 14–16]. Several studies have also raised concern that BPs delay fracture healing [17–22].

Although the epidemiology and risk factors of Asian women with AFFs have been researched [9–11, 16, 20], there have been no case-control studies determining the risk factors of AFFs among postmenopausal Asian women. This study was a multicenter-based case-control study that identified risk factors associated with AFFs, investigated the incidence of AFFs among hip and femoral fractures, and described the effects of BPs on AFF healing.

Materials and methods

Study design

We conducted a multicenter case-control study to determine the incidence and risk factors of AFFs using diagnoses according to the 10th revision of the International Classification of Disease (ICD-10). A total of 6644 hip and femoral fractures (ICD-10 codes S72.0–S72.9) were investigated at eight tertiary referral hospitals between January 2010 and December 2014. All of the medical records and radiographs were reviewed to distinguish AFFs from typical femoral fractures (TFFs) [2, 23]. Approval from the ethics committee of each institute was obtained.

Patient inclusion and exclusion criteria

We defined atypical fractures using all five major criteria described by the 2013 ASBMR task force [2]. Patients with the following cases were excluded: femoral neck fractures ($n = 2583$); intertrochanteric femoral fractures ($n = 2945$); distal femoral fracture ($n = 291$); high-energy injury fractures ($n = 328$); fractures around a prosthesis ($n = 163$); and pathologic fractures related to hematologic, epilepsy, celiac disease, Paget disease, renal osteodystrophy, or gastric surgery ($n = 119$). After these 6238 cases were excluded, 406 femoral subtrochanter and shaft fractures remained. Because all of the AAF patients were females older than 50 years of age, we excluded males ($n = 44$) and patients younger than 50 years ($n = 72$) from the control group. The final study group included 196 AFF patients and 94 TFF control patients, all of who were females over 50 years of age (Fig. 1). Menopausal status was self-reported, but we assumed postmenopausal status in women > 50 years of age in whom this information was missing. According to the Korea National Health and Nutrition Examination Survey (KNHANES), the mean age at natural menopause is 50.2 ± 3.7 years [24]. Furthermore, the 2008–2010 KNHANES indicates that bone mineral density (BMD) is significantly decreased in women older than 45 years [25]. Therefore, we assumed that all women older than 50 years in the study sample were postmenopausal. Radiologic images of AFFs were reviewed for anatomic classification; fractures located within 5 cm of the lower border of the lesser trochanter were considered subtrochanteric fractures, and fractures located distal to the 5 cm below the lesser trochanter and up to, but not including, the distal metaphyseal flare of femur were considered femoral shaft fractures [26].

Demographics and baseline characteristics

We collected patient data including demographics, fracture risk factors (use of BPs, smoking history, alcohol consumption, fragility fracture history, and diagnoses of osteopenia, osteoporosis, or rheumatoid arthritis), blood test results (serum levels of calcium, phosphate, albumin, and creatinine), medical histories (diabetes, chronic liver disease, chronic pulmonary disease, cardiovascular disease, or cerebrovascular disease), and fracture histories (prodromal symptoms, right or left femur, and subtrochanteric or shaft fracture). The duration of BP use was considered the length of time that patients were prescribed alendronate, risedronate, ibandronate, pamidronate, or zoledronate. Smoking history was determined by whether the patient smoked tobacco at the time of fracture [27]. Alcohol consumption was based on whether the patient

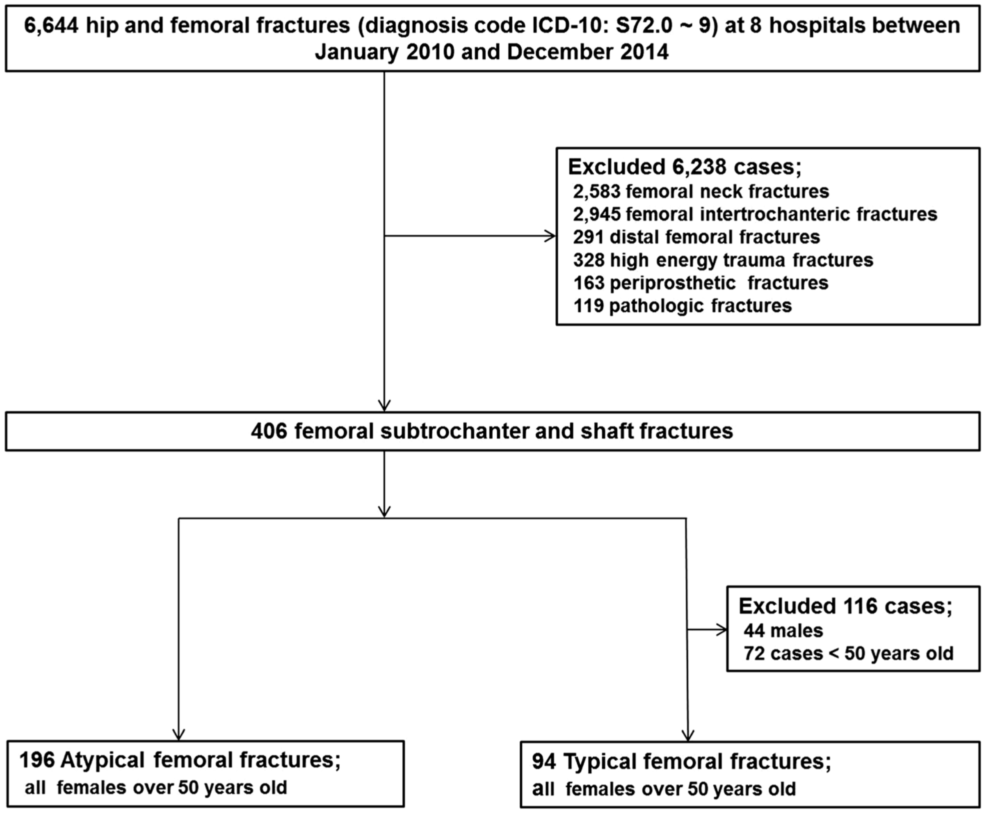

Fig. 1 Flowchart of the study population

consumed three or more units of alcohol daily [27]. The documented presence of thigh pain, a prodromal symptom, was identified. In accordance with the World Health Organization criteria, a normal BMD was defined as < 1 standard deviation (SD) below the young adult peak BMD (T-score), osteopenia was defined as 1.0–2.5 SDs below the young adult peak BMD, and osteoporosis was defined as ≥ 2.5 SDs below the young adult peak BMD [28]. The site and reference was determined using dual-energy x-ray absorptiometry (DXA) at the femoral neck.

Radiographic assessment

Radiographs were assessed by two orthopedic surgeons blinded to all patient characteristics. Digital Imaging and Communications in Medicine files of hip, femur, and knee radiographs were used to measure the respective picture archiving and communication system. To identify geometric risk factors, we used simple radiographs to compare geometric parameters of femurs with different types of AFFs (Fig. 2). The average of the two observers' measurements was calculated and used for each geometric parameter. Fracture healing was assessed using plain radiographs. Radiographic healing was defined as a bony bridge of three of four cortices on anteroposterior and lateral radiographs, as well as painless weight bearing on the affected extremity [29]. Fractures that showed osseous unions within 6 months of the index surgery were considered successfully healed, whereas fractures without osseous unions were considered problematically healed [6].

Statistical analyses

Subjects, study site personnel, and sponsors were all blinded to the data. For data verification, the investigators entered a randomized number on the electronic case report form, and data were reviewed by a member of the Biostatistics Quality Assurance Group and locked after approval. A database quality check specified the total error rate of 0.063% from the study sample (6644 cases), which indicated a properly maintained database with a total error rate within than the upper limit (0.1%) of acceptable error. All continuous data are presented as means ± SDs. The risk factors for AFFs were evaluated by univariate and multivariate logistic regression analyses. Univariate logistic regressions were performed with each variable to determine differences between the two experimental groups. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Variables with $p < 0.05$ were incorporated into a stepwise multivariate logistic regression to calculate the adjusted ORs. We also performed interaction analyses to investigate the effects of BP use on AFF healing. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA). P values < 0.05 were considered statistically significant.

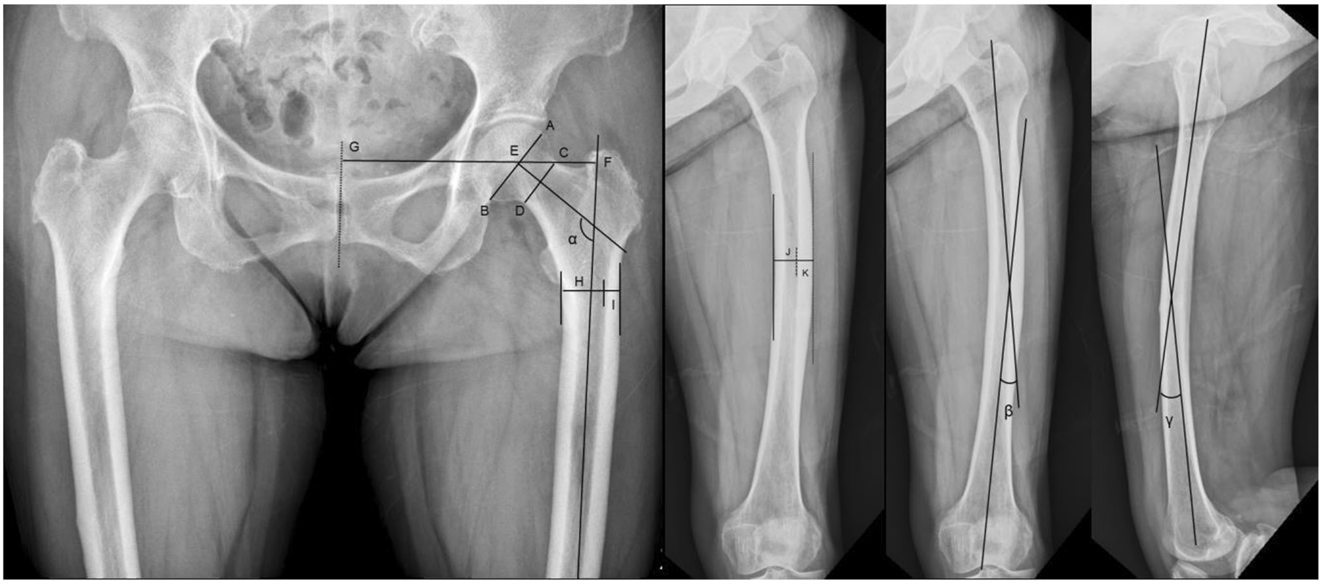

Fig. 2 Radiographic parameters of femoral geometries measured on digital X-ray images. Femoral head-neck offset ratio: the ratio of femoral neck to femoral head. Longest femoral neck diameter (lines C–D); femoral head diameter drawn from center of femoral head (line A–B). Neck-shaft angle (α): angle (°) between the femoral shaft axis and the femoral neck axis. Lever-arm ratio: the ratio of femoral offset to distance between a line bisecting the long axis of the femur and pelvic center. Femoral offset: the distance along the mediolateral direction from the center of the femoral head rotation to a line bisecting the long axis of the femur (lines E–F). Distance between a line bisecting the long axis of the femur and pelvic center: the distance in the mediolateral direction from a line bisecting the long axis of the femur to a line bisecting the long axis of the pelvis and spine (lines F–G). Lateral cortical thickness index at the subtrochanter level: thickness of the lateral femoral cortex at the most distal point of the lesser trochanter (I) divided by thickness of the outer cortical diameter at the same level (H). Lateral cortical thickness index at the femoral shaft level: thickness of the lateral femoral cortex at the thickest point of the femoral shaft (K) divided by thickness of the outer cortical diameter at the same level (J). Coronal curvature (β): angle (°) between the axial lines of proximal and distal part of femur on anterolateral radiographic view. Sagittal curvature (γ): angle (°) between the axial lines of proximal and distal part of femur on lateral radiographic view

Results

Incidence, demographic data, clinical risk factors, and femoral geometries

The incidence of AFFs was 2.95% ($n = 196$) among the 6644 hip and femoral fractures (ICD-10 codes S72.0–S72.9) that occurred between January 2010 and December 2014. There were 90 subtrochanteric femoral fractures and 106 femoral shaft fractures. All AFF patients were females with a mean age of 72.0 ± 7.88 years (range, 51–95 years). The mean patient height was 152.5 ± 6.66 cm (range, 132–179 cm), and the mean patient body weight was 54.0 ± 8.76 kg (range, 35–90 kg). The mean BMI was 23.2 ± 3.60 kg/m^2 (range, 16.5–40.7 kg/m^2). Of the 196 AFFs, 148 (75.5%) underwent BP treatment (AFF + BP), with a mean treatment duration of 5.2 years (range, 1–17 years). Alendronate was prescribed to 84 patients (56.8%), risedronate to 34 patients (23.0%), ibandronate to 20 (13.5%), pamidronate to 8 (5.4%), and zoledronate to 2 (1.3%). No patient had taken a drug holiday from BPs at the time of fracture. Fifty-six patients (29%) had bilateral lesions and 31% had prodromal symptoms. For all of the measured radiographic variables, the intraclass correlation coefficient was 0.9 or higher, which indicates high interobserver precision (Supplemental Table 1). Comparisons of demographic data, clinical risk factors, and femoral geometries between the two groups are summarized in Table 1. There were significant differences in osteopenia or osteoporosis, BP use, rheumatoid arthritis, diabetes, cerebrovascular disease, femoral head-neck offset, lever-arm ratio, coronal and sagittal femoral curvatures, and lateral cortical thickness index at the shaft level between patients with AFFs and TFFs.

Multivariate analyses of factors associated with AFFs

Multivariate analyses indicated that the use of BPs was significantly associated with AFF development ($p < 0.001$, OR = 25.65; 95% CI = 10.74–61.28). In addition, patients with AFFs were more likely to have osteopenia or osteoporosis, rheumatoid arthritis, increased anterior and lateral femoral curvatures, and thicker lateral cortex at the femoral shaft level and were less likely to have diabetes compared to patients with TFFs (Table 2).

Effects of BPs on fracture healing

Of the 290 cases of AFFs and TFFs, 15 (5.2%) did not attend follow-up appointments before osseous union. The final cohort included 275 cases, with a mean follow-up of 25.3 ± 8.18 months (range, 12–60 months). There were 225 patients (81.87%) with successful healing, and 20 patients (18.2%)

Table 1 Demographics, clinical risk factors, and femoral geometries

		All fractures ($n = 290$)			AFFs ($n = 196$)			TFFs ($n = 94$)			*P*
		N	% or mean	SD	N	% or mean	SD	N	% or mean	SD	
Demographics											
Age (years)		290	71.77	8.31	196	72.05	7.88	94	71.20	9.16	0.418
Body mass index (kg/m^2)		290	23.26	3.72	196	23.21	3.57	94	23.36	4.02	0.760
Fracture risk factors											
Smoking	Yes	3	1.04		3	1.54		0	0.00		0.986
	No	287	98.96		193	98.47		94	100.00		
Alcohol	Yes	24	8.33		18	9.23		6	6.45		0.427
	No	266	91.72		178	90.82		88	93.62		
Osteopenia or osteoporosis[a]	Yes	184	63.45		167	85.20		17	18.09		<.001
	No	106	36.55		29	14.80		77	81.91		
Bisphosphonates use	Yes	158	54.48		148	75.51		10	10.64		<.001
	No	132	45.52		48	24.49		84	89.36		
Rheumatoid arthritis	Yes	21	7.24		20	10.20		1	1.06		0.022
	No	269	92.76		176	89.80		93	98.94		
Fragility fracture history	Yes	42	14.53		32	16.33		10	10.75		0.212
	No	248	85.51		164	83.67		84	89.36		
Medical history											
Diabetes	Yes	58	20.00		32	16.33		26	27.66		0.025
	No	232	80.00		164	83.67		68	72.34		
Chronic liver disease	Yes	2	0.69		2	1.02		0	0.00		0.988
	No	288	99.31		194	98.98		94	100.00		
Chronic pulmonary disease	Yes	9	3.10		6	3.06		3	3.19		0.952
	No	281	96.90		190	96.94		91	96.81		
Cardiovascular disease	Yes	30	10.34		25	12.76		5	5.32		0.059
	No	260	89.66		171	87.24		89	94.68		
Cerebrovascular disease	Yes	18	6.21		8	4.08		10	10.64		0.037
	No	272	93.79		188	95.92		84	89.36		
Serum levels											
Calcium (mg/dL)		290	9.13	5.10	196	9.29	6.11	94	8.80	1.48	0.614
Phosphorus(mg/dL)		290	3.21	0.54	196	3.23	0.54	94	3.18	0.53	0.415
Albumin(g/dL)		290	3.89	0.46	196	3.92	0.41	94	3.81	0.54	0.052
Creatinine(mg/dL)		290	0.73	0.42	196	0.69	0.18	94	0.79	0.69	0.108
Fracture history											
Affected side	Left	144	51.06		98	52.13		46	48.94		0.613
	Right	138	48.94		90	47.87		48	51.06		
Location	Subtrochanter	135	46.55		90	45.92		45	47.87		0.755
	Femoral shaft	155	53.45		106	54.08		49	52.13		
Femoral geometries on radiographs											
Femoral head-neck offset ratio		290	0.62	0.10	196	0.61	0.11	94	0.65	0.08	0.0018
Neck-shaft angle		290	134.31	8.14	196	133.92	7.57	94	135.11	9.21	0.2450
Lever-arm ratio		290	0.34	0.09	196	0.34	0.10	94	0.32	0.09	0.0277
Coronal femoral curvature		290	4.34	3.13	196	4.93	3.36	94	3.10	2.12	<.0001
Sagittal femoral curvature		290	7.64	3.50	196	8.46	3.52	94	5.94	2.79	<.0001
Lateral cortical thickness index (LT level)		290	0.17	0.06	196	0.17	0.06	94	0.17	0.06	0.9443
Lateral cortical thickness index (shaft level)		290	0.31	0.07	193	0.32	0.04	94	0.27	0.04	<.0001

AFFs atypical femoral fractures, *TFFs* typical femoral fractures, *SD* standard deviation, *LT* lessor trochanter

[a] Femoral neck BMD T-score < − 2.0

with delayed union or nonunion (problematic healing). The probability of successful healing was significantly higher in TFF patients ($n = 77$, 90.6%) than in AFF patients ($n = 146$, 77.9%; $p = 0.014$). Our interaction analyses indicated that the

Table 2 Multivariate analyses of factors associated with atypical femoral fractures

Variable	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Osteopenia or osteoporosis[a]	26.08(13.52–50.30)	< 0.001	15.46(3.54–67.46)	< 0.001
Bisphosphonates use	25.90 (12.45–53.85)	< 0.001	25.65 (10.74–61.28)	< 0.001
Rheumatoid arthritis	10.56 (1.40–79.88)	0.022	21.01 (1.78–250.10)	0.016
Diabetes	0.51 (0.28–0.92)	0.025	0.36 (0.14–0.94)	0.037
Cerebrovascular disease	0.36 (0.14–0.94)	0.037	0.33 (0.08–1.29)	0.111
Femoral head-neck offset ratio	0.01 (0.01–0.17)	0.002	0.12 (0.01–4.41)	0.249
Lever-arm ratio	21.83 (1.40–340.19)	0.028	2.02 (0.03–143.35)	0.745
Coronal femoral curvature	1.27 (1.14–1.41)	< 0.001	1.23 (1.04–1.45)	0.015
Sagittal femoral curvature	1.31 (1.19–1.45)	< 0.001	1.25 (1.09–1.44)	0.001
Lateral cortical thickness index at shaft level	3.23 (1.78–5.88)	< 0.001	1.08 (1.03–1.13)	0.001

OR odds ratio, *CI* confidence interval

[a] Femoral neck BMD T-score < − 2.0

AFF + BP group had a significantly higher risk of problematic healing (22.1%) than TFF patients who did not use BPs (TFF group; 9.4%, $p = 0.015$, OR = 2.94; 95% CI = 1.23–7.01). There were no significant differences in fracture healing rates between the AFF + BP and TFF + BP ($p = 0.336$), AFF + BP and AFF ($p = 0.335$), AFF and TFF + BP ($p = 0.585$), AFF and TFFs ($p = 0.235$), or TFF + BP and TFF ($p = 0.967$) groups (Table 3).

Discussion

Our study is the first to describe the incidence and risk factors for AFF development in postmenopausal Korean women using a large multicenter-based case-control study with radiological correlates. Among the 6644 hip and femoral fractures, there was a 2.95% incidence rate of AFFs according to the 2013 ASBMR criteria [2]. We also found that BP treatment, osteopenia or osteoporosis, rheumatoid arthritis, increased anterior and lateral femoral curvature, and thicker lateral femoral cortex were independent risk factors for developing AFFs.

Our findings were consistent with several previous studies reporting that Asian women have a greater risk of developing AFFs [7, 26]. Some researchers hypothesize that Asians have a higher risk of femoral bowing, which contributes to increased tensile stress on the lateral aspect of the femoral shaft [14–16]. In our study, AFFs occurred more frequently at the femoral shaft (56%) than at the subtrochanter (44%), which corroborates the findings of Kim et al. [10] and Hyodo et al. [16]. Moreover, patients with AFFs had more anterior and lateral femoral curvatures compared to patients with TFFs, corroborating the findings of Chen et al. [14] and Saita et al. [15]. We also found thicker lateral femoral cortices at the shaft level in patients with AFFs than with TFFs. Although the ASBMR task force defines localized periosteal or endosteal thickening of the lateral cortex as one of the major features of AFFs [2], Koeppen et al. [30] showed no significant difference in cortical thickness between patients with or without BP treatment. Napoli et al. [31] found that women with thicker cortices, particularly the medial femoral cortex, had a lower risk of subtrochanteric and diaphyseal femur fractures. Although the role of BPs in cortical thickening is unclear, Armamento-Villareal et al. [32] suggested that a subset of BP-treated individuals may be predisposed to cortical fractures, which in most cases are associated with suppressed bone remodeling. Long-term BP treatment may lead to the suppression of bone turnover and loss of toughness, reducing the tissue's intrinsic resistance to fracture [33]. Recently, Lee et al. [34] suggested that lateral cortical thickening and compositional heterogeneity of the lateral cortex of the subtrochanteric femur, measured on quantitative CT scans, might be indicators of the early detection of AFFs in long-term BP users. Because antifracture efficacy is retained after

Table 3 Interaction analyses of the effects of bisphosphonates use on fracture healing

Subgroup	Number of patients (%)	
AFF + BPs	140 (50.9)	
AFFs	50 (18.2)	
TFF + BPs	10 (3.6)	
TFFs	75 (27.3)	
Interaction analyses	Odds ratio (95% CI)	*P*
AFF + BP vs. TFF + BP	2.81 (0.34–22.96)	0.336
AFF + BP vs. TFF	2.94 (1.23–7.01)	0.015
AFF + BP vs. AFF	1.52 (0.65–3.58)	0.335
AFF + BP vs. TFF + BP	1.85 (0.20–16.69)	0.585
AFF + BP vs. TFF	0.52 (0.17–1.54)	0.235
TFF + BP vs. TFF	0.95 (0.10–.69)	0.967

AFFs atypical femoral fractures, *TFFs* typical femoral fractures, *BPs* bisphosphonates, *CI* confidence interval the discontinuation of BPs, it is reasonable to consider a drug holiday to balance the risks and benefits associated with long-term BP use [35–37].

Compared to our 2.95% rate of AFFs among 6644 hip and femoral fractures, a recent retrospective cohort study in Japan [38] reported a 0.63% rate of AFFs among 2238 hip and femoral fractures, which were similar to the findings in Caucasians. In Caucasian patients with hip and femoral fractures, the rates of AFFs were 0.26% in France [39], 0.46% in Sweden [40], and 0.77% in the UK [41] (Table 4). An alendronate dose of 10 mg/day is prescribed for the treatment of osteoporosis in Western countries and Korea, whereas Japan typically prescribes a 5 mg/day dose; this may partially explain the greater suppression of bone turnover with BPs in our patient population with low BMIs (mean 23.2 kg/m^2). In our study, 75.5% of patients underwent BP treatment with a mean duration of 5.2 years, and the use of BPs was identified as an independent risk factor for the development of AFFs. However, we also found 24.5% of AFF patients did not have a history of BP use. Our findings are consistent with another relatively large Korean study [10], which reported that 22% of patients with AFFs had no history of BP use. Although the pathogenesis of AFFs has not been fully elucidated, there is a general consensus that AFFs are stress or insufficiency fractures [2]. The lateral cortex of the femoral shaft sustains the highest level of tensile stress, particularly in a bowed femur. The suppression of intracortical remodeling following the administration of BPs is associated with impaired healing of stress fracture. Although the pathogenesis of increased femoral curvature in Asian women is unknown, this may contribute to the higher incidence of AFFs in Asian women or in patients with no history of BP treatment [14–16]. We believe that the increased rate of AFFs in our study is attributable to BP dosage and anterolateral bowing of the femur. Therefore, an abundance of precaution is essential when prescribing BPs for Asian women with high femoral curvature.

The current evidence indicating that BP treatment delays AFF healing is controversial, likely compounded by differences in surgical techniques. Overall, recent studies have suggested that the risk of delayed healing and the need for further surgery is higher in AFFs than TFFs [18–22]. Weil et al. [18] found that 7 of 17 patients (46%) treated by intramedullary nailing needed revision surgery. Kang et al. [20] showed that delayed healing occurred in 43 of 76 patients (56.5%). Both studies attributed the high rate of delayed healing to prolonged BP therapy. Egol et al. [19] found that the healing time was longer in AFFs than TFFs, but that 40 of 41 (98%) AFFs treated by intramedullary nailing ultimately healed after an average of 8.3 months (range, 2–18 months). The authors also found that the healing time of anatomically reduced AFFs was faster than those fixed in varus. Lim et al. [21] suggested decreasing the anterior and lateral fracture gaps (avoidance of distraction) to reduce healing time of AFFs treated by intramedullary nailing. Cho et al. [22] found that the quality of fracture reduction is the most important factor in bony union of atypical subtrochanteric femur fractures treated by cephalomedullary nailing. In our study, patients with AFFs were significantly more likely to show problematic healing than those with TFFs. In our interaction analyses, patients with AFFs and BP treatment had a significantly higher risk of problematic fracture healing than those with TFFs and no BP treatment. Interestingly, there were no significant differences in fracture healing rates between AFF + BP and TFF + BP, AFF + BP and AFF, AFF and TFF + BPs, AFF and TFFs, or TFF + BP and TFF groups. To the best of our knowledge, no studies have investigated the role of BPs on the fracture healing of AFFs or TFFs. However, additional work is needed before establishing the role of BPs in the delayed healing of AFFs.

The limitations of this study include the retrospective design and medical record-based data collection, which may have increased bias. This study involved only Korean patients and had a cross-sectional design, which does not allow prospective AFF risk prediction. Some risk factors associated with AFFs, such as the long-term use of glucocorticoids or low serum levels of 25-hydroxyvitamin D, could not be included in our study due to incomplete medical records.

Table 4 Studies regarding incidence of atypical femoral fractures among hip and femoral fractures

Study	Number of cases	Country	Incidence of AFFs (%)	Mean age (year)	Mean BMI (kg/m^2)	BP use (%)	BP dose
Schilcher et al. [40]	12,777	Sweden	0.46	75.3	–	78	
Thompson et al. [41]	3515	UK	0.77	75.6	–	92	
Beaudouin-Bazire et al. [39]	4592	France	0.26	72.2	–	42	
Saita et al. [38]	2238	Japan	0.63	66.0	21.8	90	50% of standard dose in Western countries
Current study	6644	Korea	2.95	72.0	23.2	75	Same standard dose as in Western countries

AFFs atypical femoral fractures, *BMI* body mass index, *BPs* bisphosphonates

However, we minimized confounding factors by excluding patients with comorbidities that could affect bone metabolism. This study only included patients from a referral hospital, which might have influenced the rate of this unusual fracture. In this study, 1 in 40 patients from the Korean referral hospitals had an AFF. Although the incidence of AFFs was low, the rate of problematic healing was relatively high in AFFs compared to TFFs. Because the average Korean traumatologist treats more than 50 hip and femoral fractures a year, one or more patient per year would have these problem fractures. Great care should be taken in identifying these fractures and treating them appropriately. Finally, although we found that patients with AFFs and BP treatment had a significantly higher risk of problematic fracture healing than those with TFFs and no BP treatment, it is unclear whether this was due to delayed bone healing as a result of long-term BP use, or the nature of the fracture. The strengths of this study include its large sample size stemming from the multicenter collaboration. To the best of our knowledge, this is the largest multicenter case-control study with radiographic adjudication comparing AFFs with a control group of TFFs in Asian women.

In summary, the incidence of AFFs was 2.95% among 6644 hip and femoral fractures. Independent risk factors for the development of AFFs included osteopenia or osteoporosis, BP use, rheumatoid arthritis, increased anterior and lateral femoral curvatures, and thicker lateral cortices at the femoral shaft. We also found that patients with AFFs and BP treatment were more likely to have problematic healing than those with TFFs and no BP treatment.

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Compliance with ethical standards

Approval was obtained from the Ethics Committees of each institute.

Conflicts of interest None.

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