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Etiological, clinical characteristics, and treatment of atypical femur fracture

A retrospective study

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Abstract

This study aims to determine the etiology, clinical characteristics, and treatment of atypical femur fractures (AFFs). Clinical data from patients with an AFF who were treated in our hospital from January 2017 to June 2021 were retrospectively reviewed. The data were analyzed and summarized. Twenty-one patients (17 females and 4 males; average age, 66.59 ± 13.52 years; age range, 32–85 years) with AFFs (27 femurs [6 bilateral femurs]) were included in the current study. Based on relative risk analysis it was determined that the long-term use of bisphosphonates was a risk factor for AFFs. Using principal components analysis, severe osteoporosis, hip joint dysfunction, and structural abnormalities of the femur were shown to be risk factors for AFFs. Four femurs received non-surgical treatment, of which 2 were cured and the remaining 2 underwent surgical treatment. Twenty-five femurs received surgical treatment, of which 21 had intramedullary nail fixation and 4 had plate fixation. All fractures healed. The etiologic factors for AFFs are complex. Severe osteoporosis, hip joint dysfunction, and structural abnormalities of the femur were shown to be risk factors for AFFs based on principal components analysis. The appropriate treatment will be determined according to the characteristics of the fracture.

Abbreviations: AFF = atypical femur fracture, ASBMR = American Society of Bone and Mineral Research, BMD = bone mineral density, BPs = bisphosphonates, CF = complete fracture, CT = conservative treatment, F = female, FBA = femur bowing angle, FSA = femur structural abnormality, GCs = glucocorticoids, HJD = hip joint dysfunction, ICF = incomplete fracture, IM = Intramedullary nail, Ist = isthmus, L = left, M = male, PF = plate fixation, PPIs = proton pump inhibitors, R = right, SO = severe osteoporosis, Sub = subtrochanteric.

Keywords: atypical femur fracture, bisphosphonates, coxa vara, lateral femur bowing angle, severe osteoporosis

1. Introduction

Atypical femur fractures (AFFs) are rare and are defined as stress fractures of the subtrochanteric and shaft regions of the femur.[1] In a systematic review of 14 studies, the AFF incidence ranged from 3.0 to 9.8 cases per 100,000 patient-years.[2] AFFs are stress or insufficiency fractures,[3] or low-energy injuries with periosteal reactions in the lateral cortex.[4]

BPs are the main drugs for treating osteoporosis and reduce the risk of hip, spine, and other fractures by 50% to 70%.[4,5] However, the longer BPs are used, the higher the risk of AFFs.[3–6] In fact, the long-term use of BPs (>5 years) has been shown to be an independent risk factor for AFFs.[7] Multinational guidelines recommend that after oral BPs for 5 years or intravenous BPs for 3 years, drug holidays should be considered.[8–10] Other studies have also reported that proton pump inhibitors (PPIs) and glucocorticoids (GCs) may cause AFFs.[3,11,12] The common risk factors for AFFs include short stature, Asian ancestry, overweight, and glucocorticoid use.[13,14] BPs, PPIs, and glucocorticoids can suppress bone turnover and initiate the pathogenesis leading to AFFs.[15]

For AFF, the popular view is that BPs cause AFF. However, in clinical work and previous research, some AFF patients did not have a history of BPs and the underlying causes are

HW and ZZ contributed to this article equally.

System construction on the treatment and green guarantee of severe and multiple injuries in winter sports (awarded to Zhishan Zhang).

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was conducted according to the Declaration of Helsinki and approved by the Medical Science Research Ethics Committee of Peking University Third Hospital (No. 2021-R-819). The written informed consent was waived by the Medical Science Research Ethics Committee of Peking University Third Hospital due to the retrospective nature of the review. Oral informed consent was achieved from each patient vie telephone. All the data was anonymized.

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complex.[4–15] The potential mechanisms underlying AFFs are not clear. Few reports have summarized the etiologic factors and clinical characteristics of AFFs. Therefore, we retrospectively collected the clinical data from patients with AFF in our medical institution and summarized the etiology, clinical characteristics, and treatment results of these patients. This study attempted to further explain the etiology and clinical features of AFF.

2. Methods

2.1. Patients

This retrospective study was conducted according to the Declaration of Helsinki and approved by our hospital Medical Science Research Ethics Committee. Written informed consent was waived by our hospital Medical Science Research Ethics Committee due to the retrospective nature of the review. Oral informed consent was obtained from each patient vie telephone. All the data were anonymized.

The complete clinical data of patients with femoral fractures treated in our hospital from January 2017 to June 2021 were output from the electronic information system of our hospital. These data were blinded and reviewed by 2 physicians. Patients who met the AFF diagnostic criteria[3] were included in the AFF group. A third physician double-checked the eligible patients under the blinded way to confirm that the AFF diagnostic criteria had been met[3]; specifically, the fracture must be located along the femoral diaphysis distal to the lesser trochanter and proximal to the supracondylar flare. In addition, at least four of five major features must be present, as follows: no trauma-related fractures or minor trauma-related fractures, such as falling from a standing position or a low position; the fracture line originates from the lateral cortex and is generally transverse in its orientation but when extending to the medial femur, the fracture line may become oblique; complete fractures pass through both cortices and may be associated with a medial spike, while incomplete fractures only involve the lateral cortex; the fracture is non-comminuted or minimally comminuted; and local periosteal reaction or endosteal thickening ("beaking" or "flaring") in the lateral cortex is present at the fracture site. None of the minor features are required but are sometimes associated with these fractures. The minor features are as follows: generalized 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 complete or incomplete femoral shaft fractures; and delayed fracture healing.

The exclusion criteria were as follows: age under 18 years old; incomplete data; fractures of the femoral neck; intertrochanteric fractures with spiral subtrochanteric extension; peri-prosthetic fractures; and pathologic fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (e.g., Paget disease and fibrous dysplasia).

2.2. Measurements

Two physicians independently analyzed and evaluated the clinical records and preoperative X-ray images (frontal and lateral X-ray projections of the hip joint) according to the AFF diagnostic criteria[3] published by the American Society of Bone and Mineral Research in 2014. The femoral neck shaft angle was measured to evaluate hip joint function. The lateral femur bowing angle (FBA)[16] was measured, the femoral deformity was evaluated, and the bone mineral density (BMD) was recorded to evaluate the severity of osteoporosis. When the two physicians disagreed with the measurements, a third physician made a measurement judgment.

The femoral neck shaft angle was measured based on the technique proposed by Boese et al.[16] FBA[17] is defined as the angle made by the mid-diaphyseal lines of the proximal and distal parts of the femur. In a standing anteroposterior (AP) radiograph of the entire femur, the lateral FBA was calculated as follows: a line that best described the midpoint of the endosteal canal of the femoral diaphysis was drawn in the proximal and distal quarters. The degree of bowing was defined as the angulation between the two lines. BMD is an important indicator of bone strength and is expressed in grams per cubic centimeter. BMD was measured using dual-energy X-ray.[18] BMD was typically measured at three points: the spine; and the bilateral proximal femurs. The FBA and BMD were measured and analyzed based on the clinical records of the patients by two radiologists. When the two radiologists disagreed with the measurements, a third physician made a measurement judgment.

2.3. Clinical follow-up

Our hospital has a well-established follow-up system and the follow-up staff was comprised of the same group of physicians and radiologists mentioned above. The follow-up medical staff made appointments according to the follow-up time of each patient. If the follow-up data was incomplete, the patient was excluded based on the above exclusion criteria.

Patients were reevaluated by the same group of physicians and radiologists mentioned above at 3, 6, and 12 months and every 12 months thereafter. Evaluation included radiographic imaging of the fracture site (AP and lateral views) and assessment of complications, if any. BMD was reexamined every 6 months to guide the application of anti-osteoporosis drugs (BP, calcium and calcitriol) where necessary. Adequate nutrition, regular weight-bearing exercise, and avoiding smoking and excessive alcohol were suggested to the patients and asked their family members to monitor and remind the patients. Follow-up evaluations were continued until June 2023. The data generated during each follow-up evaluation were double-checked by the same third physician.

2.4. Statistical analysis

Statistical analyses were performed using SPSS software (SPSS statistics 25; IBM, Armonk). The measurement data are expressed as the mean ± SD. Relative risk analysis was used to determine risk factors for the occurrence of AFFs. Principal component analysis was used to determine several principal components of AFFs. Through the principal component analysis, the main factors (general characteristics and particularity) of patients are found out, so as to summarize the characteristics of the patients. A $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline data

After retrospective screening of the data, 4135 patients with femoral fractures were treated in 2021, among whom only 22 met the inclusion criteria for an AFF. The detailed information for each patient is shown in Table 1.

Except for one patient who was lost to follow-up after conservative treatment, 21 AFF patients (27 femurs [6 bilateral femurs]) were included. Among these patients, 17 were female with an average age of 66.59 ± 13.52 years (age range, 32–85 years). Nine of 21 patients had prodromal symptoms, mainly manifesting as pain and weakness during movement or an inability to stand on one leg. The fractures were diagnosed by a physician, and AFFs occurred with no trauma or minor trauma.

Based on fracture location, AFFs were divided into subtrochanteric (13 femurs) and femoral isthmus fractures (14 femurs). According to the fracture degree, AFFs were divided into complete (22 femurs) and incomplete fractures (5 femurs).

Table 1

The detailed information of 21 AFFs (27 femurs).

NO.	Etiological factors	Gender	Age	Prodromal symptoms	GCs	BMD	Location		Type		Treatment		Healing (mo)	
							L	R	L	R	L	R	L	R
1	SO	F	80	No	Yes	–4.7	Sub	-	ICF	-	CT/IM	-	10	-
2	SO	M	74	No	No	–4.1	-	Sub	-	CF	-	IM	-	8
3	SO	F	76	No	Yes	–4.4	-	Ist	-	CF	-	IM	-	5
4	BPs	F	70	Yes	No	–0.3	-	Sub	-	CF	-	IM	-	4
5	BPs	F	68	Yes	No	–1.5	Sub	-	ICF	-	CT/IM	-	3	-
6	HJD	M	33	No	No	1.2	Sub		CF	-	PF	-	-	8
7	HJD	F	53	Yes	No	–2.1	-	Sub	-	CF	-	IM	-	4
8	HJD	F	54	Yes	No	–1.4	Sub	-	CF	-	CT/IM	-	6	-
9	SO	F	61	No	Yes	–4.5	-	Ist	-	CF	-	IM	-	8
10	FSA	M	32	Yes	No	–1.3	-	Ist	-	CF	-	IM	-	4
11	HJD	F	64	Yes	No	–2.7	Ist	-	CF	-	IM	-	9	-
12	HJD	F	72	Yes	No	–2.7	-	Sub	-	CF	-	IM	-	8
13	FSA	F	76	Yes	No	–5.2	Sub	-	ICF	-	PF	-	6	-
14	FSA	F	76	Yes	No	–5.2	-	Ist	-	CF	-	PF	-	6
15	BPs	F	74	No	No	–1.1	-	Sub	-	CF	-	IM	-	8
16	BPs	F	77	No	No	–1.9	-	Ist	-	CF	-	IM	-	7
17	BPs	F	53	No	No	–3.1	Ist	-	CF	-	IM	-	8	-
18	BPs	F	53	No	No	–3.1	-	Ist		ICF	-	CT	-	6
19	BPs	M	63	No	No	–3.4	-	Ist		ICF	-	CT	-	6
20	BPs	F	81	No	No	–0.3	Ist	-	CF	-	IM	-	6	-
21	FSA	F	67	No	No	–4.4	-	ist	-	CF	-	PF	-	8
22	SO	F	78	No	No	–5.2	Sub	-	CF	-	IM	-	4	-
23	BPs	F	64	No	Yes	–2.7	-	Ist	-	CF	-	IM	-	5
24	SO	F	83	No	No	–4.6	-	Ist	-	CF	-	IM	-	6
25	HJD	F	85	No	No	–1.8	Sub	-	CF	-	IM	-	4	-
26	BPs	F	65	No	No	–2.4	-	Ist	-	CF	-	IM	-	5
27	SO	F	66	No	No	–4.2	-	Sub	-	CF	-	IM	-	6

No. 4: 5; No. 7: 8; No. 11: 12; No. 24, 25 are the bilateral femoral fractures occurred in 4 patients at different times. No. 13: 14; No. 17: 18 are the bilateral femoral fractures occurred in 2 patients at the same times.

Abbreviations: Etiological factors: BPs = bisphosphonates, FSA = femur structural abnormality (which is defined as excessive anterolateral curvature of the femur accompanied by a subacromial fracture of the femur, or a fracture of the femoral stem), HJD = hip joint dysfunction, SO = severe osteoporosis. Sex: F = female, M = male. BMD = bone mineral density. Location: L = left, R = right, Sub = subtrochanteric, Ist = isthmus. Type: CF = complete fracture, ICF = incomplete fracture, Treatment: IM = intramedullary nail, PF = plate fixation, CT = conservative treatment.

In total, 23 femurs were treated surgically. Four femurs with complete fractures underwent plate fixation, and 19 femurs with complete fractures and 2 AFFs were received intramedullary nail treatment. Four femurs with incomplete fractures were treated conservatively (for AFF without displacement or with slight displacement). Two fractures healed and two fractures did not heal after 3 months of conservative treatment, but healed following surgical treatment.

The average duration of follow-up was 20.59 ± 3.85 months (range, 12–25 months). There were no re-operations or revisions during the follow-up period and all femurs healed.

3.2. Etiologic analysis

There were 8 patients (10 femurs [2 bilateral and 6 unilateral femurs]) with AFFs and long-term administration of BPs, including 7 females and 1 male with an average age of 66.8 ± 9.28 years (age range, 53–81 years). The reasons for long-term administration of BPs were as follows: long-term administration of zoledronic acid was used for treating tumors. The hip BMD was generally not decreased in patient nos. 4 and 15. It may be possible to misdiagnose the early periosteal reaction of AFFs as tumor bone metastasis (Fig. 1A–D). Long-term application of BPs for prevention of osteoporosis caused by glucocorticoids in patient nos. 17, 18, and 23. Long-term oral BPs for the treatment of osteoporosis in patient nos. 16, 19, 20, and 25. In this group, two femurs showed incomplete fractures and were treated conservatively. The fractures healed after 6 months in patient nos. 18 and 19.

There were 7 patients with AFFs (7 femurs) who had severe osteoporosis and no history of BP use. There were 6 females with an average age of 74 ± 7.85 years (age range, 61-83 years) and the T values for hip BMD were –4.53 ± 0.36 SD. There were two patients with severe osteoporosis who had long-term use of glucocorticoids before the AFFs occurred (patient nos. 1 and 9). Patient no.1 was treated regularly with anti-osteoporosis drugs lasting for 3 months when the AFF occurred, then the incomplete fracture progressed into a complete fracture which required intramedullary nail surgery (Fig. 2A–D). Other patients in this group had primary osteoporosis and no long-term history of using various anti-osteoporosis drugs (patient nos. 2, 3, 22, 26, and 34. The characteristic of this group was long-term primary or secondary severe osteoporosis.

There were four patients with AFFs who had hip joint dysfunction (6 femurs [nos. 24 and 25] were the same patient; no. 24 had an isthmus fracture 2 years ago). The hip joint dysfunction symptoms included hip joint pain and limited movement. The average cervical shaft angle was 100.93 ± 2.01° on plain radiographs (Fig. 3A–M).

There were three patients with AFFs (4 femurs) who had increased lateral FBA. Patient nos. 13 and 14 were the same patient, and bilateral femoral isthmus fractures occurred at the same time. The average angle of this group was 35.4 ± 2.41°. One young patient (no. 10) underwent internal fixation with intramedullary nails after osteotomy at the fracture end to correct the deformity because the bending angle of the lateral FBA was out of the normal range. The other two patients (nos.13 and 14) underwent total knee arthroplasty. To avoid affecting the knee prosthesis, the patients were treated with plate fixation (Fig. 4A–N).

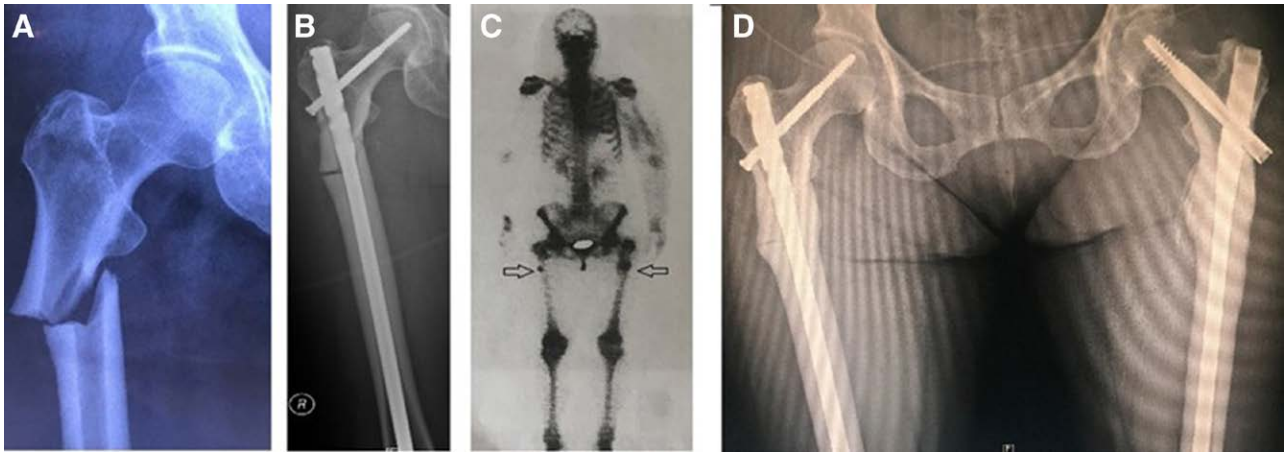

Figure 1. Patient no.4 was a 70-yr-old female who was treated with zoledronic acid for 10 yr after bone metastases secondary to breast cancer. A subtrochanteric AFF occurred after a fall from a standing height and was treated with an intramedullary nail (A and B). A radionuclide bone scan showed a right subtrochanteric nuclide abnormal concentration that was misdiagnosed as a bone metastasis (C). The right leg fracture healed 4 mo postoperatively. Two years ago the left subtrochanteric AFF was completely healed after intramedullary nailing (D). AFF = atypical femur fracture.

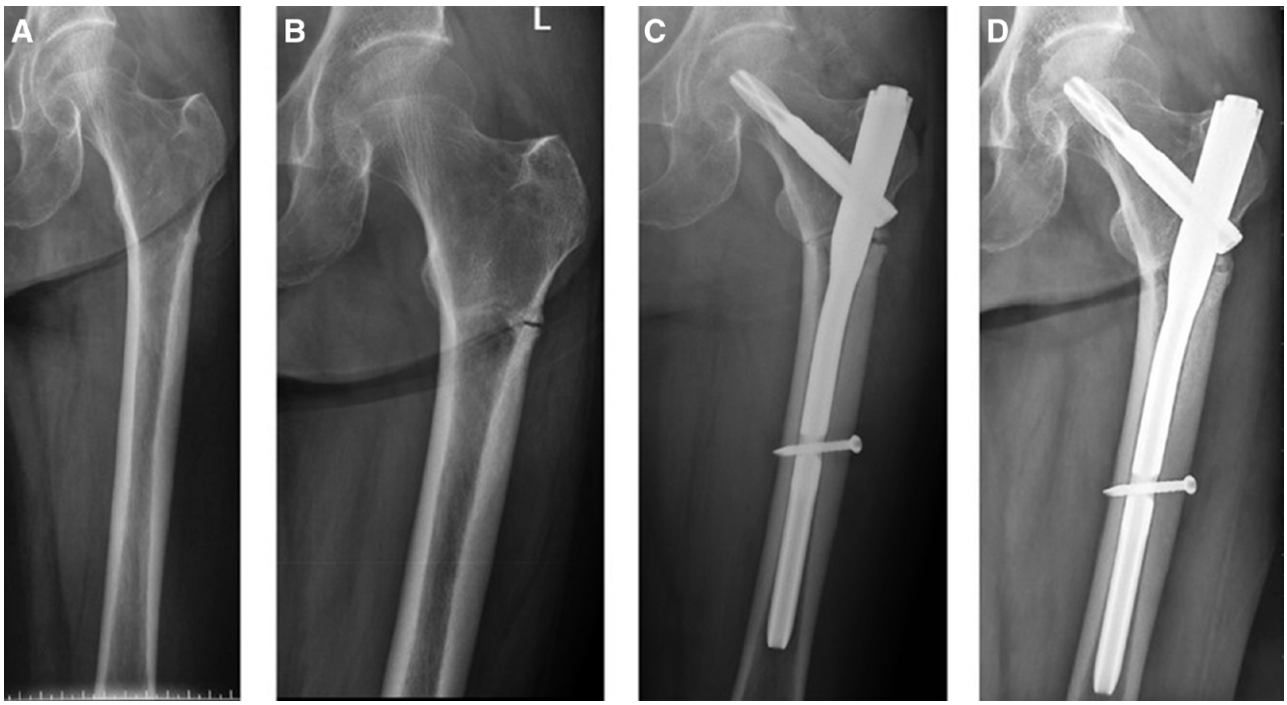

Figure 2. Patient no. 1 is an 80-yr-old female with chronic rheumatoid arthritis who took oral prednisone for 7 yr. She sought treatment for left anterolateral femoral pain. An X-ray showed local periosteum thickening at the left subtrochanteric region (A). After anti-osteoporosis treatment for 3 mo, an incomplete AFF was noted (B) and intramedullary nailing was performed (C). Ten months postoperatively fracture healing was observed at the fracture site (D). AFF = atypical femur fracture.

3.3. Relative risk analysis and principal component analysis

According to relative risk analysis, long-term administration of BPs is a risk factor for AFFs (Table 2). Principal component analysis was used to identify several principal components that were independent and closely related to AFFs (Table 3). Based on the literature[6,19–23] and the above statistical results, the main risk factors for AFFs are divided into four categories: the long-term administration of BPs; severe osteoporosis; hip joint dysfunction; and structural changes of the femus (excessive anterolateral curvature of the femur accompanied by a subacromial fracture of the femur or a fracture of the femoral stem).

3.4. Follow-up results

The follow-up results showed that the AFF healed 3 to 10 months after treatment among the patients (Table 1). All the patients recovered well through the last follow-up evaluation in June 2023.

4. Discussion

The etiologic factors for AFFs are complex. The main risk factors for AFFs are divided into four categories: the long-term administration of BPs; severe osteoporosis; hip joint dysfunction; and structural changes of the femus.

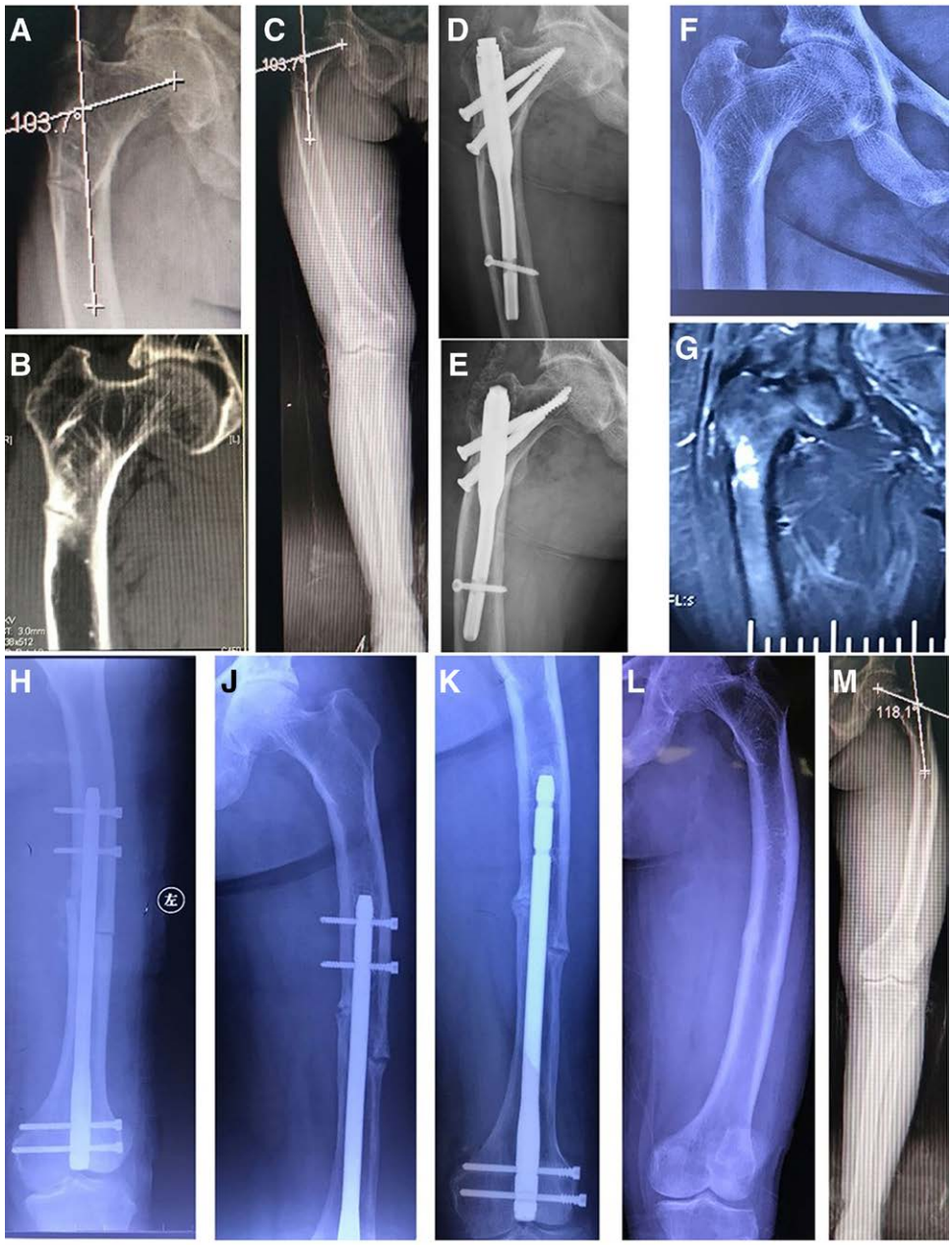

Figure 3. Patient no.12 is a 72-year-old female. An X-ray showed an incomplete right subtrochanteric AFF; the right cervical shaft angle was 103.7° (A–C). New interlocking intramedullary nail fixation was performed (D and E). Five years ago an X-ray showed a right lateral cortical periosteal reaction (F) and an MRI showed right subtrochanteric hyperintensity (G) but no treatment was provided. Eight years ago an AFF at the left isthmus was treated with intramedullary nailing (H). One year postoperatively the fracture had healed poorly (J). The intramedullary nail was dynamized (K). The nail was removed 2.5 yr after the operation (L). The left cervical shaft angle was 118.1° (M). AFF = atypical femur fracture.

AFFs are typically characterized by prodromal symptoms,[22,24] such as symptoms of pain, discomfort, and weakness in the groin area or on the thigh during weight bearing in the weeks or months prior to the fracture.[3,4,11] In the current study 9 of 21 patients had prodromal symptoms with no trauma or minor trauma. A simple transverse fracture line is revealed on radiographs of patients with AFFs. When the fracture line extends to the medial femur, the fracture line may become inclined. Complete AFFs pass through two layers of the cortex, potentially with small tips on the medial aspect. Local periosteal reactions or periosteal thickening of the lateral femoral cortex is often observed in patients with incomplete AFFs.[25,26] In the current study two patients were cured with conservative treatment. Radiographs were recommended at early diagnosis of AFFs.[25–28] Therefore, if there are prodromal symptoms or imaging findings indicating a "simple transverse" femur fracture, it is necessary to consider the possibility of an AFF in high-risk patients and determine if there is a contralateral AFF. The appropriate treatment will be determined according to the characteristics of the fracture.

Studies have shown that bilateral femoral fractures occur in 40% of patients with AFFs but in only 2% of patients with common fractures and 21% of patients with AFFs present with focal cortical thickening of the contralateral femur.[3,27,28] Probyn et al[28] reported a series of 124 patients with AFFs in whom 78 had bilateral AFFs, and the contralateral AFF diagnoses were made at an average of 10.3 months. Six of 21 patients in the current study also had bilateral AFFs. Therefore, bilateral femoral

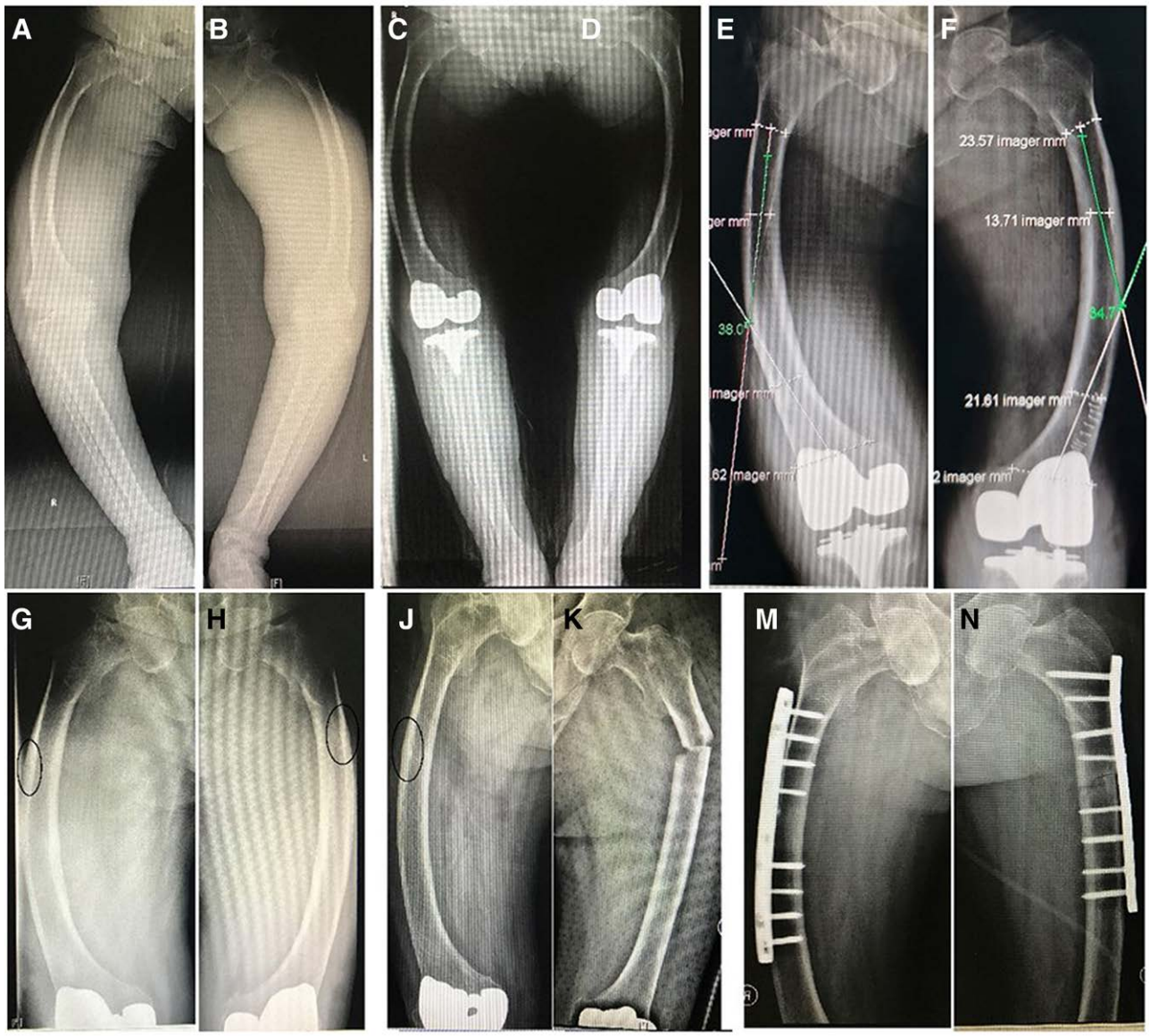

Figure 4. Patient no.13 was a 76-year-old female with severe "O-shaped legs" and bilateral severe osteoarthritis of the knee who was unable to walk properly for 5 years due to pain (A and B). A bilateral total knee arthroplasty was performed 2.5 yr ago (C and D). The left and right lateral FBAs were 34.7° and 38°, respectively (E and F). One year ago there was anterolateral pain in both thighs when ambulating and an X-ray showed that the periosteum of the lateral cortex of both femoral isthmuses were thickened (G and H). Three days ago the patient experienced severe pain in the middle and upper left thigh with limited movement when turning over in bed. An X-ray showed a left subtrochanteric fracture (K) and periosteum thickening in the isthmus of the right femur was more apparent than previously (J). Because the lateral FBAs were too large for intramedullary nailing, bilateral plates were used (M and N).

X-rays, an MRI, or bone scans are recommended in patients with a unilateral AFF to avoid missed diagnosis of AFFs.[27,28]

BPs mainly inhibit osteoclast function. The long-term administration of BPs increases bone fragility and decreases fracture resistance. Therefore, AFFs may occur even after no trauma or minor trauma as a complication of long-term BP use.[3,26] When bone turnover is severely inhibited, the mechanisms involved in fracture union may be dysfunctional, leading to delayed union.[29] Bone turnover markers, and iliac crest and fracture site biopsies have confirmed that bone remodeling is inhibited in typical BP-related AFFs.[3,29,30] After a fracture occurs, osteoclasts cannot participate in bone remodeling and delay fracture union. In the current study there were six patients with a history of BP use > 5 years, which is consistent with previous studies.[26,29,30]

The lowest *T* values for the hip BMD were not significantly reduced and an AFF occurred when a patient fell from a standing position. However, some patients had no definite history of trauma and only showed anterolateral pain in the thigh. AFFs were demonstrated during examinations. Patient no.17 took alendronate sodium tablets for 5.5 years and continued to take alendronate after surgical treatment of the left side AFF. There were no signs of fracture union 11 months after surgery. When alendronate sodium tablets were discontinued, teriparatide was administered and the intramedullary nail was dynamized and the fracture healed after 8 months. Therefore, attention should be paid to these patients to avoid missed diagnoses. Our recommendation is to monitor bone metabolism markers regularly and perform femoral bone image scans during BP treatment, which allows for the early detection and treatment of AFFs.[27,28,31,32]

Studies[9,27,33] have reported AFFs unrelated to BPs. Lim et al[21] studied 6644 hip fractures and reported an AFF incidence of 2.95%. Of the patients with hip fractures, 24.5% did not involve a history of BP administration. Kim et al[20] studied 147 patients with AFFs and found that 22% of the patients had no history of BP use. This study reported 7 patients with AFFs (7

Table 2

Relative risk analysis between long-term administration of BPs and AFFs.

Parameters	Value	df	Asymp. sig. (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)	95% Confidence interval	
						Lower	Upper
Pearson Chi-Square	13.25†	1	<0.001				
Continuity correction*	10.69	1	0.001				
Likelihood ratio	12.34	1	<0.001				
Fisher exact test				0.001	0.001		
Linear-by-linear association	13.07	1	<0.001				
N of valid cases	68						
Odds ratio for group (AFF)	13.85					2.61	73.40
For cohort BPs = administration	8.95					2.08	38.61
For cohort BPs = no administration	0.65					0.46	0.91

Abbreviations: AFFs = atypical femur fractures, BPs = bisphosphonates.

* Computed only for a 2 × 2 table.

† One cells (25.0%) have expected count <5. The minimum expected count is 3.09.

Table 3

The principal components closely related to AFFs among the independent factors were distinguished by principal component analysis.

Component	Initial Eigen values			Extraction sums of squared loadings		
	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
The cervical shaft angle	1.63	40.75	40.75	1.63	40.75	40.75
Lateral femur bowing angle	1.19	29.66	70.42	1.19	29.66	70.42
Bone mineral density	.64	16.03	86.45	.64	16.03	86.45
Body mass index	.54	13.55	100.00	.54	13.55	100.00

Note: In this group of data, the contribution rate of the cervical shaft angle is only 0.416. If the first three principal components are taken, the cumulative contribution rate has reached 0.901, so it is appropriate to take the first three principal components in this group of data.

Abbreviation: AFFs = atypical femur fractures.

femurs) who had severe osteoporosis but no history of BP use, consistent with previous studies.[20,21] Lim et al[21] and Kim et al[20] concluded that severe osteoporosis is an independent risk factor for AFFs.[20,21]

The T value for hip BMD in the group of patients with severe osteoporosis was –4.1 to –5.2 SD and involved primary and secondary osteoporosis caused by long-term administration of glucocorticoids. Patient no.10 had an X-ray examination before the fracture. Local periosteal thickening under the left femoral trochanter was noted and conservative treatment revealed that the local periosteal thickening had progressed to complete AFF. Localized periosteal thickening, i.e., "beaking" or "flaring," is one of the characteristics of AFFs, often appearing 1 year before the onset of an AFF.[32,33] For the combined administration of glucocorticoids and BPs, 8% to 10% of patients with periosteal thickening may develop AFF within 2 years, thus indicating that "beaking" or "flaring" is an important predictor of AFFs.[32–34] Therefore, for patients with severe osteoporosis who receive glucocorticoids on a long-term basis for another disease, regular radiologic examinations of the femur should be performed to detect the occurrence of "beaking" or "flaring," especially for those who use BPs concurrently.

In the current study four patients with hip joint dysfunction were identified (6 femurs [2 patients developed contralateral fractures after 1 year]). These patients had long-term hip pain and X-ray examination of the hip showed that the hip joint had severely degenerated and the cervical shaft angle decreased significantly. At the same time, the most common location of the fracture was the subtrochanteric region of the femur (5/6). Abnormal hip structure affects the stress distribution in the proximal femur. Taormina et al[23] reported that there is a clear relationship between the cervical shaft angle and the development of AFFs. Oh et al[22] used a computed tomography-based non-linear finite element analysis model and showed that tensile stress in the lateral cortex of the subtrochanteric region increased as the cervical shaft angle decreased, eventually resulting in an AFF. At present there are few reports involving AFFs caused by hip joint dysfunction. Additional clinical cases are needed for analysis.

A review by Haider et al[35] suggested that AFF might be related to femoral neck geometry or hip alignment. Our study showed that AFFs can occur when combined with abnormal femoral structure (coxa vara or abnormal lateral FBA), which may validate the results by Haider et al[35] Several studies[3,36,37] have reported that AFF is a stress fracture related to tension failure of the lateral femoral cortex caused by biomechanical effects over time. Yoo et al[38] measured the femurs of 56 individuals and suggested that the lateral FBA threshold should be 5.25°. The average value of the lateral FBA in the current study was 35.4 ± 2.41°, which was much greater than that reported in the literature.[38] The patients in the current study often had no history of trauma. X-ray examinations showed local cortical thickening at the apex of the curvature. With time, osteoporosis gets worse and the tensile stress on the lateral femoral cortex and the compressive stress on the medial femoral cortex increase at the same time. Daily load can lead to a fracture and opening of the lateral cortex, then lead to a complete fracture. Such patients are often accompanied by knee degeneration. The treatment should be implemented according to the specific condition of the patient. Two patients (3 femurs) had previously undergone total knee arthroplasty. So as not to affect the function of the knee prosthesis, the patients were treated with plate internal fixation combined with bone-forming drugs to promote fracture healing and treat osteoporosis. Another young patient (32 years of age) underwent an osteotomy at the fracture end to correct the bending angle of the lateral FBA and was fixed with intramedullary nails. The fracture healed well postoperatively.

There were several limitations in the present study that must be appreciated when interpreting these findings. First, data collection was done in a retrospective manner with a small sample size, which might lead to some potential biases. In addition, this was a single-center study and there might be an element of bias due to the surgeons, such as the choice of surgical method, postoperative treatment regimen, and advice about anti-osteoporosis treatment. Third, there was no unified guide for reference. And the grouping was not completed in this study according to different underlying causes. We will endeavor to do the research by grouping different causes in a large sample scale.

5. Conclusions

The etiologic factors of AFFs are complex. The main risk factors for AFFs are divided into four categories: the long-term administration of BPs; severe osteoporosis; hip joint dysfunction; and structural changes of the femus. The appropriate treatment and comprehensive treatment plan should be chosen according to the characteristics of fractures.

Based on a comprehensive analysis of the 21 patients (27 femurs) with AFFs, the diagnosis and treatment suggestions in clinical practice were as follows: If prodromal symptoms occur, the possibility of an AFF should be considered and femoral imaging examinations (including X-ray, MRI, and bone scan) should be performed. When the patient has a prodrome or low-energy injury leading to a "simple transverse" fracture, it is necessary to be alert to the possibility of an AFF. It is necessary to carefully inquire about the use of BPs and the treatment history of osteoporosis, checking hip joint function, and evaluating femoral structure, especially whether the opposite side has an AFF at the same time. For the long-term administration of anti-osteoporosis drugs (BPs or denosumab) that inhibit bone resorption, attention should be paid to the possibility of an AFF. The recommended administration time for intravenous and oral BPs should not exceed 3 and 5 years, respectively. Bone metabolism markers in patients should be evaluated regularly. If bone scans show an abnormal concentration of local nuclide in the femur, care should be taken to distinguish between metastasis of local tumor foci and the AFF. AFF treatment should be analyzed according to patient condition. Anti-osteoporosis is the basis for the treatment of AFFs. For patients who are suitable for conservative treatment, the patient must be reexamined regularly. The main surgical treatment is intramedullary fixation and the influence of internal fixation on adjacent joints should be considered.

Author contributions

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