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ORIGINAL ARTICLE

Natural history of incomplete atypical femoral fractures in patients after a prolonged and variable course of bisphosphonate therapy—a long-term radiological follow-up

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Abstract

Summary Understanding the natural history of lateral femoral stress fractures helps to guide their management. Improvement in their radiographic characteristics is rare. Progression was generally sequential, most developing an incomplete fracture line before fracture displacement. Stopping bisphosphonates decreased the fracture rate, a feasible management option for lesions without incomplete fracture lines.

Introduction Retrospective study evaluating the natural history of lateral femoral stress fractures (FSF) by serial radiography over a variable period of time in a cohort of patients treated for some time with bisphosphonates for osteoporosis, whilst also identifying the fracture response in cases where bisphosphonates were discontinued.

Methods The radiographs of 76 consecutive patients (92 femurs) with 161 FSF were reviewed to document their change over time. Femurs were classified into the following: A—normal, B—focal cortical thickening, C—dreaded black line and D—displaced fracture. Bisphosphonate history was recorded.

Results 66.5% FSF showed group stability between the first and last radiographs: group B (79.1%), group C (45.7%). 28.6% progressed, mostly following an ordered sequence starting from group A, progressing to B, then C, before culminating in D. Progression rate was as follows: A—100% (11/11), B—18.3% (21/115), C—40% (14/35). Regression in FSF was uncommon—5.6% (8/161). 34.8% (32/92) sustained displaced fractures. Kaplan-Meier analysis showed statistically significant difference between the groups; median survival (95% CI): A—4189 (-), B—3383.0 (-), C—1807 (0.0–3788.6) and progression to displaced fracture when bisphosphonate had been stopped for at least 6 months. The group without recent bisphosphonates had a lower group progression rate (17.1%, 12/70). Nevertheless, 10.9% (5/46) progressed to displaced fracture. This group also had the highest proportion of stable (77.1%, 54/70) and regressive lesions (5.7%, 4/70).

Conclusions In FSF, there is natural progression from normal bone, to focal cortical thickening, to dreaded black line and eventually to displaced fracture. Most lesions persist, remaining static or progressing, especially if a dreaded black line is present and bisphosphonates are continued. Regression is uncommon and more frequent when bisphosphonates are discontinued. Despite stopping bisphosphonates, there remains a 10.9% risk of progression to displaced fracture.

Keywords Atypical femoral fracture management · Bisphosphonate · Conservative management · Insufficiency fracture · Osteoporosis treatment · Prophylactic surgery

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Introduction

Atypical femoral fracture (AFF) is a rare type of femoral stress fracture, affecting mainly middle aged to elderly females, first described by Odvina et al. in 1995 [1]. Its pathogenesis has been attributed to severe suppression of bone marrow turnover [1] coupled with stress due to tensile forces present along the lateral cortex of the femur [2]. There is a known association between prolonged bisphosphonate (BP) therapy and AFF [3–7]. In order to reduce the incidence of AFF, it is important to understand their natural history, identify at risk femurs and manage them appropriately.

Lateral femoral cortical stress fractures (FSF) are known to precede complete or displaced atypical femoral fractures. They characteristically occur along the lateral cortex of the femur from the subtrochanteric to the supracondylar region. FSF demonstrate focal cortical thickening which can be endosteal, periosteal or both (present in most cases) or a transverse radiolucent line (dreaded black line (DBL)) or both. When associated with a fracture line, they are also referred to as incomplete AFF [5]. However, studies of these precursor lesions are few. Our earlier smaller cohort studies showed that the presence of a transverse radiolucent line DBL) on radiographs was found to be a predictor of stress lesions that went onto complete AFF [8, 9], particularly when associated with focal symptoms of pain, discomfort or "weakness". Presence of a DBL also appears to be a predictor of poor response to conservative treatment [10]. Min et al. [11] have proposed a scoring system with fracture risk increased for lesions in a subtrochanteric location, intact contralateral femur, diameter extent of radiolucent line and presence of pain.

FSF have been detected on the contralateral side in patients with history of atypical femoral fractures and also in patients on long-term BP therapy without prior AFF. Contralateral AFF has been reported in 28 to 41% of cases [5] (Dell R et al., presented at the 2012 annual meeting of the American Academy of Orthopedic Surgeons). Although these stress reactions have been identified as precursors to AFF, there are few or no reports that have tracked a large cohort of FSF and documented how they progress over time.

This retrospective study evaluates the natural history of femoral stress fractures by serial radiography over a variable period of time in a cohort of patients treated for some time with bisphosphonates mostly for osteoporosis and a few for cancer management, whilst also identifying the fracture response in cases where bisphosphonates were discontinued.

Hypothesis:

1. In susceptible patients with a history of bisphosphonate treatment for at least 1 year, the femur shows a natural progression from normal bone, with the absence of any deformity (A), to FSF and that it begins with a bump (B) which represents reactive bone formation around a microscopic crack. This bump may be endosteal (B1), periosteal (B2) or both (B3). As tensile forces prevent bone healing a crack develops (C), which represents a chronic non-union state. If not aborted, this process results in a displaced or complete fracture (D).
2. Lesions with DBL have a higher risk of progression to complete or displaced fracture.
3. Discontinuation of bisphosphonates alters the natural history of FSF.

Methods

The retrospective cohort study was approved by our institutional review board with waiver of informed consent. Consecutive cases were obtained from the Orthopedic department database of AFF and known FSF of patients who first presented between January 1, 2002, and March 31, 2017. Follow-up duration was calculated from the date of initial radiographs to the date of final radiographs for the non-fractured femurs. For cases of complete AFF, follow-up duration was taken from the initial radiographs to the date of displaced fracture. For prophylactically operated cases, follow-up duration was taken from the initial radiographs to the last radiograph prior to surgery. Follow-up duration varied, ranging from 1 to 4189 days (11 years 5 months), mean 1022 days, median 730 days (refer to Table 1). Age of patients ranged from 47 to 92 years, mean 68.6 years. The majority of cases were aged between the 50–59 years and 80–89 years age groups (refer to Table 1).

Patient records were reviewed on our picture archival and communications system (PACS) to identify cases with pre-fracture radiographs of the ipsilateral or contralateral femur.

Selection criteria

There were in total 151 cases (patients) with a history of displaced AFF or FSF in the database. Those with pre-fracture radiographs of AFF or FSF were selected (109 cases).

Femoral and pelvic radiographs were reviewed for presence of FSF. A lesion was classified as an FSF if it met the ASBMR definition [5] for FSF. To qualify, the lesion must be located along the lateral cortex of the femur from the subtrochanteric to the supracondylar region and have one the following features: focal cortical thickening (periosteal and/or endosteal) and/or a transverse radiolucent cortical fracture line (DBL). Similarly, to qualify as a displaced or complete AFF, lesions needed to meet the ASBMR definition.

Exclusion criteria included the following: peri-prosthetic fractures (2 cases), FSF cases with no follow-up review (18 cases), non-displaced AFF cases with FSF radiographic follow-up duration less than 3 months (4 cases), fixation without a trial of conservative management (4 cases), stress fractures associated underlying tumour (1 case) and femurs with normal femoral radiographs prior to developing displaced AFF (4 cases). Altogether, 33 patients were excluded. The final study cohort comprised 76 patients with 92 affected femurs, 32 of which eventually sustained complete or displaced fractures.

Table 1 Demographics, cohort information, lesion summary, follow-up duration and bisphosphonate history of the study cohort

	Study cohort		
Patients	76		
Age (years)	47–92 (68.6)		
Number of cases by age group	40–49 years: 3	60–69 years: 27	80–89 years: 15
	50–59 years: 17	70–79 years: 29	90–99 years: 1
Sex	75 female:1 male (98.7%:1.3%)		
Race/nationality	Chinese 69, Malay 2, Indian 1, Filipina 1, Indonesian 1, Vietnamese 1, Arab 1		
Number of lesions studied	161 FSF		
	16 cases had bilateral lesions		
	23 femurs (5 bilateral, 13 cases unilateral) had multifocal lesions		
	Multifocal lesions or MFL (number of femurs affected):		
	2 MFL (7), 3 MFL (6), 4 MFL (2), 5 MFL (2), 6 MFL (2), 7 MFL (2), 8 MFL (2)		
	Group: A = 11 (6.8%), B 115 (71.4%), C 35 (21.7%)		
	32 fractured—34.8% of femurs with FSF; 19.9% of FSF studied		
Femurs	92		
	Group: A = 8 (8.7%), B 53 (57.6%), C 31 (33.7%)		
Radiographic follow-up duration in days: range (mean, median)	All femurs (92): 1–4189 or 11 years 5 months (1022, 730)		
	Non-fractured/non-operated femurs (48): 100–3233 (1249, 1131)		
	Fractured femurs (32): 1–4189 (825, 322)		
	Prophylactically fixed femurs: 5–3194 (642, 155)		
Side			
Lesions studied	Right 62:left 99		
Femurs studied	Right 36:left 56		
Bisphosphonate history			
Yes	71 patients (86 femurs with 147 FSF) had a history of bisphosphonate use; 5 were on long-term treatment but duration was not recorded		
	66 patients had bisphosphonates for >6 months: Treatment duration ranged from 7 months to 11 year 4 months (mean 5 years 5 months, median 4 years 7 months)		
No	1 patients (1 femur with 1 FSF)		
Unknown	4 patients, 5 femurs (13 FSF)		

The femurs were categorized as follows: normal (group A); focal lateral cortical thickening present (group B); transverse lateral cortical fracture (DBL) present with or without focal cortical thickening (group C) and complete, i.e. displaced, fracture (group D). A dreaded black line refers to presence of a transverse black line of any length involving the lateral cortex of the femur, which is seen at the epicentre of the focal cortical thickening when present. Group B was subdivided based on the pattern of focal cortical thickening: endosteal thickening (type B1), periosteal thickening (type B2), both endosteal and periosteal thickening (type B3). Group C was similarly further categorised based on the presence or absence and type of associated focal cortical thickening into types: C (no associated focal cortical thickening), B1C, B2C and B3C.

Bilateral lesions and multiple lesions in a single femur were documented separately. All lesions were tracked by serial radiographs until complete fracture, prophylactic fixation, last follow-up radiograph or patient demise.

Radiographs of those that went on to displaced fracture were checked to confirm that they met the ASBMR criteria for AFF including lack of high energy trauma in the fracture mechanism [5].

BP history of the study cohort and relevant medical history were obtained from electronic medication records and by reviewing the hospital admission and discharge notes.

Review technique

All images were double read, un-blinded, by a musculoskeletal radiologist and Orthopedic surgeon pair (PMA, KSBJ, TSH, PCM), all with more than 15 years' experience in their respective fields. Any disagreement was resolved by consensus between the reading pair.

Images were viewed on our hospital picture archival and communication system (PACS). Radiographic images were magnified in order to detect and accurately classify the stress fractures.

Results and statistical analysis

In order to chart lesion progression, the following assumptions were made:

1. Lesions with DBL are more severe than those without—This is based on prior studies that have shown that progression to displaced fracture is greater for this group [8, 9, 11, 12].
2. B2 and B3 lesions are more severe than B1 lesions—This was presumed because from our previous study, focal periosteal reaction was more commonly seen in displaced AFF than focal endosteal thickening [9, 13].
3. B3 lesions are more severe than B2 lesions—This was an empirical assumption that more extensive findings indicate more severe stress fractures.
4. For the *Y* axis of the graph, each lesion group and subgroup was attributed a value in order to create an ordinal scale: A—0, B1—1, B2—2, B3—3, C—4, B1C—5, B2C—6, B3C—7, D—8.

For femurs with multiple lesions, the lesion with the worst outcome was used to compute the results.

For determination of progression, regression and stability rates, the last qualifying radiograph was taken as the end point. For lesion progression, examples of lesion type progression include B2 to B3, B2C to B3C and B3C to D, and examples of lesion group progression include B3 to B3C, A to B2 and B2C to D. For FSF regression or improvement, lesion type regression examples are B3 to B2 and B1 to B2C to B2 to A, and examples of lesion group improvement include B3C to B3 and B2 to A. Examples of stable lesion type include B1 to B1 and B2 to B2 or B3 to B3C to B3 (termed as variable stable), and stable lesion group examples include B2 to B3, B2C to B3C and B3C to B3C.

IBM SPSS Statistics 20.0 was used to obtain descriptive statistics and plot Kaplan-Meier survival analysis. Additional calculations and graphs of change in lesion type over time were performed using Microsoft Excel 2010. For Kaplan-Meier analysis of group progression and regression, end point was taken as the time to the first event.

Results

The study cohort comprised 76 patients and a total of 92 femurs with radiographs which met the inclusion criteria. Most were being treated with bisphosphonate for osteoporosis. Ten patients, 4 with bilateral FSF, had underlying malignancy: 9 with breast cancer, 1 patient with multiple myeloma. In total, there were 161 FSF. Bilateral lesions were seen in 16 cases. Multifocal lesions were seen in 23 femurs (5 bilateral, 13 unilateral), further details given in Table 1. At presentation, the FSF comprised the following: group A—11, group B—115 (B1—58, B2—45, B3—12) and group C—35 (C—1, B1C—4, B2C—10 and B3C—20).

The case demographics, lesion summary, follow-up duration and BP history of the study cohort are shown in Table 1.

Of the 161 FSF in 92 femurs that were studied, 11 (6.8%) were normal (group A) at initial presentation whilst 150 had stress lesions: 115 (71.4%) group B and 35 (21.7%) group C. Of the femurs studied, recording the FSF with the worst outcome for those with multifocal lesions, at presentation, there were 8 (8.7%) group A, 53 (57.6%) group B and 31 group C (33.7%) femurs.

Radiographic follow-up duration of affected femurs ranged from 1 day to about 11 years 5 months (mean 33.5 months, median 24 months). For the group managed conservatively, follow-up duration ranged from at least 3 months to about 8 years 10 months (mean 41 months, median 37 month).

As this was a retrospective study, bisphosphonate history was variable. One patient was specified to have no prior bisphosphonates. In four patients, there was no mention in the history whether patient had been on bisphosphonate—labelled as bisphosphonate uncertain. For patients with bisphosphonate exposure for at least 6 months (71 cases), treatment duration ranged from 7 months to 11 years 4 months (mean 5 years 5 months, median 4 years 7 months). For cases taken off bisphosphonates, duration of discontinuation (in days) for the non-fractured, non-fixed femur group ranged from 0 to 2557 (mean 436) compared with the displaced AFF group which ranged from 0 to 1826 (mean 187).

Natural history

FSF progression sequence

The complete results showing the change in lesion type are displayed in the line graph (Fig. 1). Between the first and last X-rays, the majority of lesions were either stable (orange lines or grey dashed-dotted line in black and white figure) or progressed (red lines or thin black line in black and white figure). Progression of FSF mostly followed in an ordered sequence: normal bone (A) to focal cortical thickening (B), transverse radiolucent line or DBL (C) to displaced atypical femoral fracture (D) as hypothesised. Figure 2 shows an example of a case that progressed from a B2 to a B3C lesion before converting to a displaced fracture.

The trend to follow a sequence from group A → B → C → D is also reflected in Table 2, which charts the different lesion types and their pattern of change over time based on whether BP treatment was received in the 6 months preceding the last X-ray. Tendency for B1 and B2 lesions to progress into B3 lesions is also confirmed.

FSF lesion change during the follow-up period (calculated from Table 2)

Between the first and last radiographs, the majority of lesions were stable by lesion type, 60.9% (98/161), and by lesion group, 66.5% (107/161). Stable lesion types were seen in 74.8% (86/115) of group B and 34.3% (12/35) of group C lesions, and lesions with stable grouping comprised 79.1% (91/115) of group B and 45.7% (16/35) group C lesions.

Overall lesion type progression was 33.5% (54/161) and lesion group progression was 28.6% (46/161). Progression rate was higher for group C with lesion type progression seen in 51.4% (18/35) of group C lesions as compared with 21.7% (25/115) group B lesions and lesion group progression seen in 40% (14/35) of group C and 18.3% (21/115) of group B lesions.

Nine of 161 FSF (5.6%) regressed, i.e. improvement in lesion type, of which one had a variable course. Eight of 161 (5%) showed improvement in the lesion group: 2.6% (3/115) of group B and 14.3% (5/35) group C.

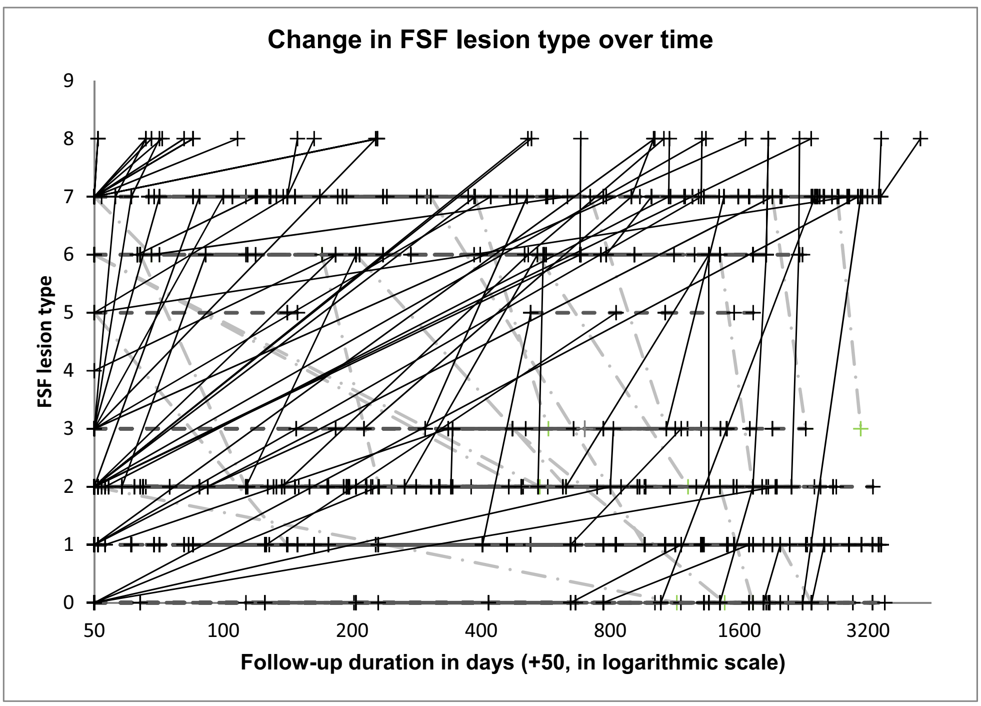

Fig. 1 Line graph plot showing pattern of change of each lesion based on initial and final lesion type against time

Key:

Y axis: 0 – Normal (A), 1 – Endosteal thickening alone (B1), 2 – Periosteal thickening alone (B2), 3 – Endosteal and periosteal thickening (B3), 4 – DBL alone (C), 5 - Endosteal thickening and DBL (B1C), 6 – Periosteal thickening and DBL ((B2C), 7 –Endosteal and periosteal thickening and DBL (B3C), 8 – Complete AFF (D)

Line colour: Getting worse – thin black line, stable – thick dashed line, getting better – light grey thick dashed-dotted line

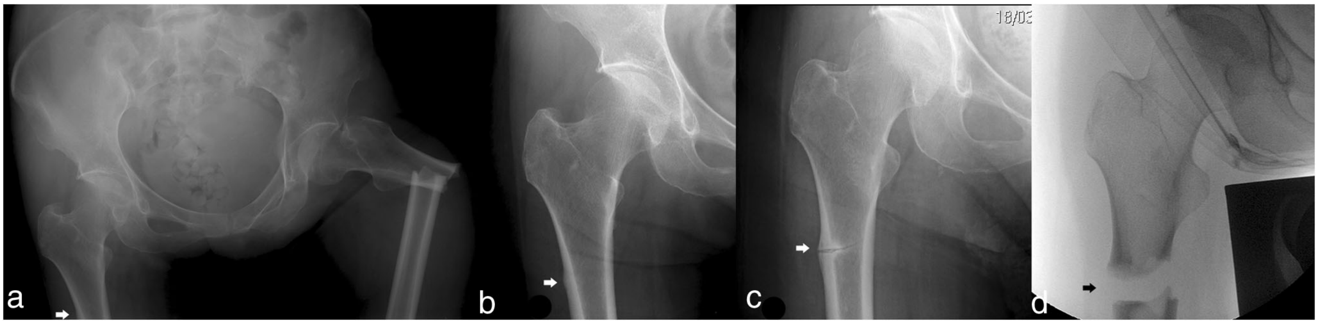

Fig. 2 A 57-year-old Chinese lady with a history of systemic lupus erythematosus and previous renal failure with renal transplantation done, on long-term treatment with oral prednisolone. She had been on alendronate since June 2005 for osteoporosis after sustaining a fracture of the distal humerus. **a** Slipped and fell in May 2007. Pelvic X-ray showed a transverse subtrochanteric fracture of the left femur with focal thickening of the lateral cortex, an undiagnosed atypical femoral fracture. At the edge of the film, there is a contralateral FSF in partial view (white arrow). **b** Postoperative check pelvic X-ray showed focal periosteal thickening of the lateral cortex (white arrow) in the subtrochanteric region of the right femur (B2 lesion). This went undetected. Her medication was switched to Raloxifene for 1.5 years and swapped again in November 2008 to risedronate. **c** In March 2010 at age 60 years, after about 1 year 4 months on BP, she tripped on 2 steps and fell, landing on her buttocks. Consequently, she developed right hip pain and was unable to walk. X-ray done showed FSF progression into an incomplete atypical femoral fracture (B3C) (white arrow) with a fracture line involving about 80% of the circumference. She was admitted and scheduled for prophylactic fixation. **d** However, 4 days later, upon transfer to the operating table, the fracture displaced. Image intensifier image shows a displaced AFF (black arrow)

FSF lesion group change over time (Table 3)

Overall group change was analysed using Kaplan-Meier survival.

Kaplan-Meier analysis showed statistically significant difference ($p < .01$) in time to progression with mean (95% CI) in days for B 2230.3 (1913.7–2546.8) compared with 1644.5 (1136.8–2152.3). Initial survival curve for group C showed steep decline (Fig. 3a) with the last two fractures recorded at 159 days (5.9 months) and this is also reflected in the low p value for the Breslow test.

FSF group regression was not analysed for group A as regression is not possible for this group. Group regression (Fig. 3b) was rare. Mean (95% CI) time to regression from Kaplan-Meier analysis for group C was 1969 (1346.4–2591.9) days and for group B was 2874.5 (2629.1–3119.9) days. The difference was statistically significant ($p = .001$). The results suggest that regression of lesions from group B to group A (normal femurs) is uncommon and time taken for regression is prolonged compared with regression of group C lesions.

Progression to displaced fracture (refer to Tables 2 and 3)

Thirty-two FSF progressed to complete or displaced atypical femoral fracture (AFF) representing 34.8% of the 92 femurs studied and 19.9% of the 161 lesions. Of these, 24 (75%) had passed through a DBL stage prior to fracture displacement and time to fracture from appearance of DBL ranged from 1 day to 8 years 3 months (mean 10.0 months, SD 23.5 months). 45.2% (14/31) of femurs with an initial group C lesion sustained a displaced fracture; 64.3% (9/14) of these had been exposed to BPs within the last 6 months.

Kaplan-Meier survival analysis showed that group C FSF (with DBL) on initial radiographs ($p \leq .005$) showed a shorter time to fracture compared with group B and group A lesions. Mean (95% CI) and median (95% CI) survival analysis results (in days) for the different groups were as follows: A—3310.2 (2148.9–4471.5) and 4189 (-), B—2345.9 (1904–2787.7) and 3383 (-), C—1356.0 (808.8–1903.3) and 1807 (0–3788.6).

Effect of stopping bisphosphonate

As this was a retrospective study, BPs had been stopped for a variable length of time. Those with no recent BP refer to cases where BP had been stopped for at least 6 months.

Effect on lesion change over time based on original group

The group without recent BP exposure showed better stability and lower progression rates compared with those with recent BP exposure (BP exposure between 1 day and 6 months prior to the event) based on lesion group change between the first and last visits (derived from Table 2). Comparing FSF with no recent BP with those with recent BP exposure, the group progression rate was 17.1% (12/70): 37.1% (26/61), stability rate was 77.1% (54/70): 52.5% (32/61) and improvement rate was 5.7% (4/70): 4.9% (3/61).

Kaplan-Meier survival analysis (Table 3, Fig. 3c) showed that bisphosphonate usage had a statistically significant difference ($p < .001$) in time to progression of group status with median (95% CI) in days for group

Table 2 Lesion change in relation to recent bisphosphonate use

Change by lesion grouping		Change by lesion type	Bisphosphonate in last 6 months						
			No		Unknown		Yes		
			Count	Percent	Count	Percent	Count	Percent	
Stable	B→B	B1 B1	20	28.6	8	26.7	25	41.0	
		B1 B3 [#]	1	1.4					
		B2 B2	15	21.4	10	33.3	3	4.9	
		B2 B3 [#]	1	1.4					
		B3 B3	2	2.9					
	C→C	B1C B1C	1	1.4					
		B1C B3C [#]			1	3.3			
		B2C B2C	2	2.9			1	1.6	
		B2C B3C [#]	2	2.9					
		B3C B3C	2	2.9	2	6.7	3	4.9	
		C B2C [#]	1	1.4					
		B3C B2C B3C	1	1.4					
Worse	A→B	A B1	1	1.4	2	6.7			
		A B2					1	1.6	
		A B2 B3	1	1.4					
	A→C	A B3C	2	2.9					
	A→B→C→D	A B2 B2C D			1	3.3			
	A→C→D	A B2C D					1	1.6	
		A B3C D					1	1.6	
	B→C	B1 B1C	1	1.4			1	1.6	
		B2 B2C	1	1.4			1	1.6	
		B3 B3C	1	1.4					
		B2 B3 B3C					1	1.6	
	B→C→D	B1 B3C D					1	1.6	
		B2 B2C D	1	1.4			1	1.6	
		B2 B3C D					1	1.6	
		B3 B3C D			1^	3.3	2	3.3	
	B→D	B1 D					1	1.6	
		B2 D	1[@]	1.4			3	4.9	
		B3 D			1	3.3	2	3.3	
	C→D	B1C B3C D	1	1.4					
		B3C D	2	2.9	2	6.7	8	13.1	
Better	B→A	B2 A	1	1.4			1*	1.6	
		B3 A	1	1.4					
	C→B	B1C B1	1	1.4					
		B2C B2	1	1.4	1	3.3	1*	1.6	
Variable—worse	A→B→A→B	A B1 A B1			1	3.3			
	B→C→B	B1 B3C B3	1	1.4					
		B2 B3C B3	1	1.4					
	C→B→C→D	B2C B2 B2C D					1*	1.6	
Variable—better	B→C→B	B2 B3 B3C B1	1	1.4					
	C→B→C→B	B2C B2 B2C B2					1*	1.6	
Variable—stable	B→C→B	B2 B2C B2	2	2.9					
	B→C→B→C→B	B3 B3C B3 B3C B3	1	1.4					
		Total (lesions)	70	100	30	100	61	100	Total (percent)
		Overall better	5	7.7	1	3.3	3	4.6	9 (5.6%)
		Overall stable	46	70.8	20	66.7	32	49.2	98 (60.9%)
		Overall worse	19	29.2	9	30.0	26	40.0	54 (33.6%)
		Total (users)	70	108	30	100	61	93.8	161

[#] Lesion type change differs from lesion group change

Stress lesions with variable change are divided into subgroups based on feature change between the last two X-rays

1*—A case with bilateral multifocal endosteal thickening. Bisphosphonates were stopped for 5 years then re-started

1[@] —A case that fractured 5 years after stopping bisphosphonates

1^—A case with a long standing DBL which developed a displaced fracture more than 9 years after the FSF was diagnosed

with no recent BP use—3024 (-) and for the group with recent BP use—966 (282.1–1649.9). Kaplan-Meier analysis for group status regression (Table 3) was not statistically significant.

Effect on healing of DBL

Healing of DBL was seen in 12 out of 59 DBL (20.8%) at some point during the study course (although 8 subsequently recurred). Ten (83.3%) had discontinued BPs for at least 6 months prior to DBL healing, including 1 patient (case 1*) with bilateral multifocal FSF had 3 lesions which healed during the course of follow-up. This patient had been taken off BP when DBLs were discovered and subsequently two DBLs healed. However, one recurred during the drug holiday; 6 months after re-starting BP, the contralateral femur showed a new stress lesion with DBL and healing of two existing stress lesions, one of which had a DBL. In 1 case, it was unclear whether BPs had been stopped. Duration from stopping BP to radiographic DBL healing ranged from 0 days (case 1*) (i.e. still on bisphosphonates) to 6 years 5.5 months (mean 2 years 6.5 months, median 2 years 7 months).

Effect on fracture risk

Better outcome was also seen in those taken off BP accounting for a lower displaced fracture rate: 10.9% with no recent BP and 68.8% with recent BP usage (Table 2). In the remaining 5 fractures, three cases had unknown BP history, and in two cases, it was unclear whether BP had been stopped, as there was no mention in the records and medication records were not available.

By Kaplan-Meier analysis, recent bisphosphonate usage ($p < .001$) was predictive of time to fracture (Table 2, Fig. 3d). Mean (95% CI) survival (in days) was as follows: no recent bisphosphonates—2851.1 (2539.2–3163.0) and recent bisphosphonates—2314.1 (1356.6–3271.5).

Discussion

FSF are recognised precursors of complete or displaced AFF. They may be symptomatic or asymptomatic. As the natural history of these lesions is unknown, decisions on when and whether or not to intervene surgically are difficult and not based on scientific evidence.

We looked at 161 discrete lesions in 92 femurs in an attempt to determine the natural history of FSF. If our hypothesis is correct, serial radiographs should show a logical sequence of progression starting from a normal femur (A), appearance of a stress reaction featured as focal thickening at the lateral cortex due to tension forces (B), developing a "crack" or DBL (C) and culminating in a frank AFF (D). X-rays being snapshots in the development of the FSF may miss certain stages of the progression but nevertheless we should see a logical progression along this continuum, i.e. we should not see regressive sequences like C → A → B → D or A → C → B; although steps may be missing, the sequence should seldom reverse. Exceptions would include healing of the "crack", i.e. C → B if BPs is stopped or possible reading errors in very small bumps or very fine cracks.

Results from our study showed that the majority of FSF remained stable or progressed. As hypothesised, when FSF developed in normal bone, it progressed in sequence starting with focal cortical thickening, developing a DBL before frank fracture. Displaced AFF occurred in 34.8% of femurs with FSF detected. FSF with DBL were more likely to progress to displaced AFF (45.2% of group C FSF) and fracture displacement occurred more frequently in femurs with recent BP exposure (68.8% were on BPs).

According to the literature, between 15 and 62.9% of all FSF progress to displaced fracture when managed conservatively [14–17]. Conservative treatment in these retrospective studies varied, including restricted weight-bearing until pain and radiologic improvement as assessed by radiographs, MRI or bone scan, and discontinuation of bisphosphonates with or without treatment with teriparatide. In the presence of an incomplete fracture line, risk of displaced fracture is higher, seen in 57.1% in our smaller cohort study of 35 FSF [9] and down to 34.8% in this current larger cohort study which includes a larger number of cases where BP treatment was discontinued.

Thus, in the earlier literature, prophylactic fixation was advocated to manage FSF, particularly when a transverse radiolucent fracture line was present. However, more recent published literature has suggested that conservative management with cessation of BP therapy, in some cases supplemented by a course of teriparatide, and restricted weight-bearing has good results, with stress fracture healing and symptom resolution, avoiding need for prophylactic surgery [15, 18].

Knowing the natural history of FSF and the effect of stopping BPs as well as ability to identify lesions at risk are essential information required to guide the decision between conservative management and prophylactic surgery.

Schilcher et al. observed that the risk of AFF fell by 70% per year after discontinuation of BPs [19]. Similarly, Adams et al. at Kaiser Permanente Southern California reported a 44% reduction in the risk in the first year after discontinuing BP therapy and from 1 to 4 years after discontinuation, the risk decreased by 80% per year and after 4 years, the risk decrease was 78% [20]. Although these studies have observed decreased fracture risk after stopping BPs, this did not refer to a cohort that had already developed an FSF.

Studies looking at FSF and risk of displaced fracture are few. Besides a dreaded black line, other reported predictors of fracture progression include pain [8, 11], focal cortical radiolucency [9] and extent of the incomplete fracture line and subtrochanteric location [11]. Scoring systems to predict fracture risk have been proposed by Png et al. (2012) based on FSF morphology [9] and Min et al. (2017) based on a combination of FSF morphology, site, status of the contralateral femur and presence of pain [11].

Table 3 Results of Kaplan-Meier survival analysis

Kaplan-Meier survival analysis	Group	Total N	N (percent) of events	Mean for survival time			Median for survival time			Chi-square (Mantel-Cox, Breslow, Tarone-Ware)	Log rank p value (Mantel-Cox, Breslow, Tarone-Ware)
				Estimate	95% confidence interval		Estimate	95% confidence interval			
					Lower bound	Upper bound		Lower bound	Upper bound		
Time to FSF group progression by initial FSF group	A	11	11	1751.8	1190.4	2313.2	1909	1019.9	2798.1	10.3	.006
	B	115	26	2230.3	1913.7	2546.8	.	.	.	14.3	.001
	C	35	13	1644.5	1136.8	2152.3	.	.	.	11.4	.003
	Overall	161	50	1958.2	1699	2217.4	2307	1710.2	2903.8		
Time to FSF group regression by initial FSF group (group A excluded)	B	115	3	3039.9	2823.6	3256.3	–	–	–	12.3	.000
	C	35	5	1969.1	1346.4	2591.9	–	–	–	15.5	.000
	Overall	150	8	2874.5	2629.1	3119.9	–	–	–	15.0	.000
Time to FSF group regression by recent BP (excludes BP history uncertain)	No recent BP	78	4	3045.1	2867.5	3222.7	.	.	.	2.2	.139
	Recent BP	55	3	1762.2	1661.4	1863.0	1807.0	.	.	.2	.653
	Overall	133	7	2936.5	2721.4	3151.5	.	.	.	.6	.432
Time to FSF group progression by recent BP (excludes BP history uncertain)	No recent BP	78	18	2453.4	2148.8	2758.0	3024.0	.	.	24.0	.000
										13.9	.000
	Recent BP	55	25	932.7	705.3	1160.1	966.0	282.1	1649.9	18.3	.000
	Overall	133	43	2006.8	1729.8	2283.7	2307.0	1396.5	3217.5		
Time to displaced fracture by initial FSF group	A	8	3 (37.5%)	3310.2	2148.9	4471.5	4189	.	.	10.5	.005
	B	53	15 (28.3%)	2345.9	1904	2787.7	3383	.	.	16.7	.000
	C	31	14 (45.2%)	1356	808.8	1903.3	1807	0	3788.6	14.3	.001
	Overall	92	32 (34.8%)	2327	1838.1	2815.9	2307	1536.1	3077.9		
Time to displaced fracture by recent BP use (BP use within the last 6 months)	No recent BP	46	5 (10.9%)	2851.1	2539.2	3163	.	.	.	30.0	.000
	Recent BP	32	22 (68.8%)	2314.1	1356.6	3271.5	3383	.	.	18.9	.000
	BP uncertain	14	5 (35.7%)	1015.5	542.8	1488.2	961	321.1	1600.9	24.7	.000
	Overall	92	32 (34.8%)	2327	1838.1	2815.9	2307	1536.1	3077.9		
Time to displaced fracture by presence of DBL phase	Absent	37	8 (21.6)	2094.7	1513.2	2676.1	1821	730.3	2911.7	3.5	.063
	Present	55	24 (43.6)	2356.8	1872.8	2840.9	.	.	.	6.5	.011
	Overall	92	32 (34.8)	2327	1838.1	2815.9	2307	1536.1	3077.9	5.2	.022

In this study, disruption of the natural history of FSF was not common. The majority of group B lesions (79.1%) remained stable. A large proportion of group C lesions (40%) progressed although progression ceased after 6-month follow-up (Fig. 3a) likely due to the positive effect of conservative management. Altogether, 34.8% of affected femurs sustained displaced fractures. Discontinuation of BPs was associated with higher rates of lesion group stability (77.1% versus 52.5%), slower progression, healing of DBL and a lower fracture rate (10.9% versus 68.8%). Nevertheless, despite stopping BPs, 5 progressed to displaced fracture, 4 of which had a DBL.

These findings support previous studies of the utility of a BP drug holiday as a preventive measure for FSF progression to displaced AFF but only for group B. A drug holiday would entail stopping BP use when FSF is detected. Conservatively, managed cases should be closely monitored for thigh or hip symptoms and reviewed regularly. Although there are currently no clear guidelines for optimal follow-up interval for these lesions, one study recommended routine follow-up every 2 to 3 months until healing of the FSF and annually thereafter [14]. However, we suggest follow-up radiographs initially at 1 month for symptomatic patients and group C, and subsequently at 6 months and 12 months for group B and 3 months, 6 months and 12 months for group C, with shorter intervals if

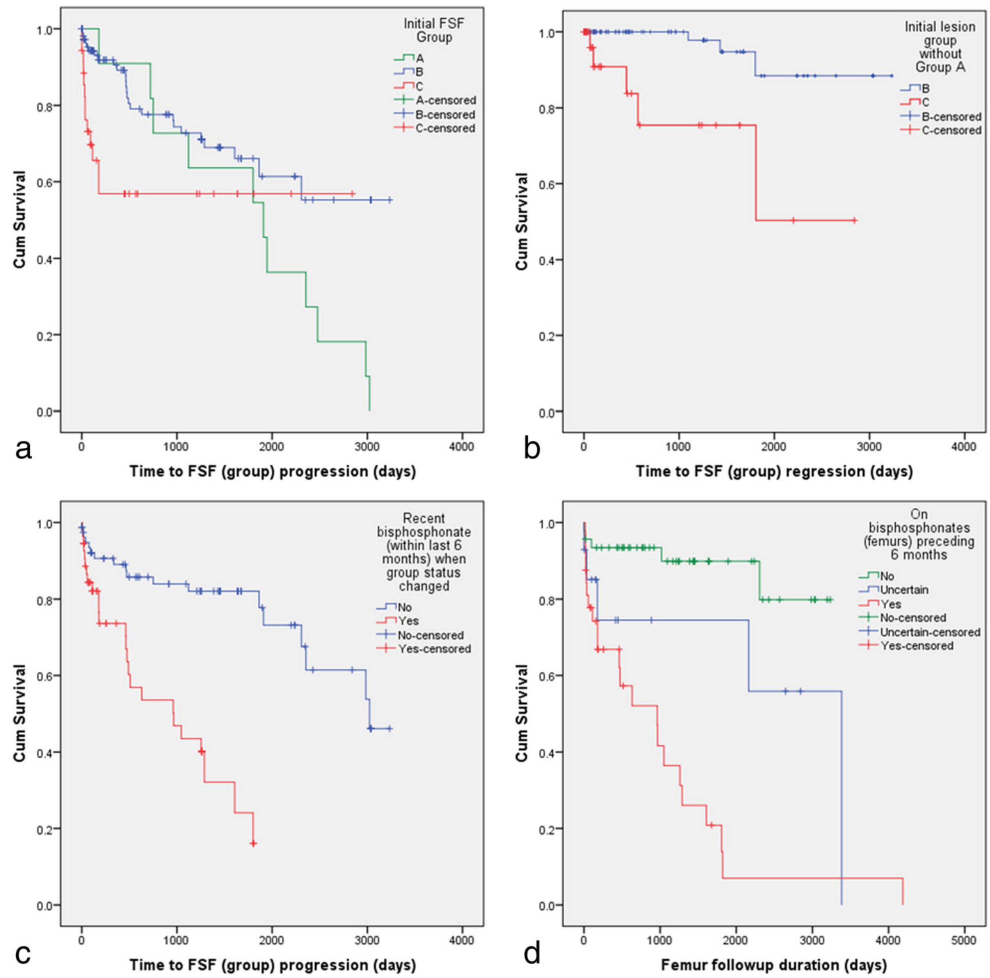

Fig. 3 Kaplan-Meier survival curves. Figures plot the results of Kaplan-Meier survival analysis. **a** Time to FSF group regression by initial lesion group shows group C lesions progress early during the follow-up period but after 6 months they stabilised whereas this was not seen with group B or A lesions. This may be attributed to vigilant monitoring and effective conservative management in group C lesions whereas group B lesions and normal femurs may not be as closely monitored. **b** Time to FSF group regression by initial lesion group shows more rapid regression of group C lesions compared with group B lesions. **c** Time to group status progression by recent BP use shows slower progression in the group without recent BP but progression continues for a longer period of time. **d** Survival curve for time to fracture by recent BP use suggests a faster time to fracture for femurs recently exposed to bisphosphonates

symptoms persist or recur, thereafter, if there is no radiographic progression and no symptoms, follow-up annually.

Currently, the role of MRI, CT or bone scan as a follow-up tool is unclear although at presentation, it may help to assess the risk of progression to complete fracture [5]. Literature suggests that MRI is the preferred imaging option allowing for detection of bone and marrow oedema as well as cortical fracture line. If not possible, CT followed by radionuclide bone scan may be used. Some authors also suggest follow-up MRI until resolution of bone oedema or bone scan until no increased activity is detected [21] although this is not our routine practice.

The optimum duration of a drug holiday is unclear. Watts et al. [22, 23] suggest 1 to 2 years in patients at high risk of osteoporotic fracture, 3 to 5 years in moderate-risk patients and indefinitely in low-risk patients ending, as recommended by American Association of Clinical Endocrinologists (AACE) guidelines, when there is a fracture, BMD declines or clinical fracture risk increases significantly. Bone turnover markers rising to pre-treatment levels may also end the drug holiday [23]. Duration of the drug holiday may also depend on the bisphosphonate group [24]. Patients on BP drug holidays who are at high risk of fracture based on bone mineral density, age, or other clinical risk factors warrant close follow-up, especially as the duration of the drug holiday lengthens [25]. Fracture risk analysis needs to be regularly assessed and treatment resumed accordingly.

On the other hand, group C should preferably undergo prophylactic fixation since if DBL is present, the natural history is not to heal, the majority of lesions either stayed static (28.6%) or progressed (40%) to group D (displaced AFF); 3 out of 14 (Table 2) developed a displaced fracture despite stopping BPs.

It would appear that conservative management has inherent dangers. FSF are seen to persist for years even after stopping bisphosphonates, with some lesions still present more than 10 years later, one new lesion developed more than 2.5 years later and the overall regression rate was low (less than 6%). In addition, displaced fractures occurring late were seen, with one case with a long-standing DBL (case 1^) which ultimately resulted in a displaced fracture occurring more than 9 years after the FSF was first diagnosed and another case fracturing 5 years after stopping BP treatment (case 1[@]).

Other studies of FSF have also shown that conservative treatment is inadequate [17, 26]. Saleh et al. [10] prospectively studied 10 patients with 14 FSF. All 5 incomplete fractures without a radiolucent fracture line were treated successfully by non-operative whereas only 2 of 8 incomplete fractures with a radiolucent fracture line were treated successfully with 3 months of the same non-operative treatment [10]. Egol et al. [27] retrospectively studied thirty-one patients with 43 incomplete fractures. Their results showed that a higher percentage of patients treated surgically became asymptomatic and demonstrated radiographic evidence of healing earlier than those treated non-surgically. Studies also show that surgery is easier before than after fracture completion, healing time is shorter and length of postoperative hospital stay is also shorter [26, 28]. The ASBMR AFF taskforce recommends prophylactic nail fixation for incomplete fractures (with cortical lucency) accompanied by pain [5].

Considering the poorer prognosis of FSF with DBL, technical challenges of AFF fixation [15, 28] and higher complication rates of operative fixation after frank fracture [5, 16, 29–31] as well as technically easier surgery, faster fracture healing, shorter hospital stay and better clinical outcome when operated before the fracture displacement, we advocate that group C FSF be surgically treated as risk of complete AFF is high and conservative management is less likely to succeed. If not operated upon, close follow-up is warranted even in the absence of pain or other symptoms. These patients should be warned to watch out for prodromal symptoms and have regular radiographic follow-up.

This study has several limitations. Firstly, there is selection bias since the cohort is from an Orthopedic database of AFF patients with history of displaced AFF or stress fractures. This cohort is also likely to see more severe or symptomatic patients and thus radiographs obtained are more likely to have stress lesions. Secondly, the retrospective design results in a number of limitations: (1) not all patients with prior AFF had radiographs of the contralateral femur and subsequent follow-up especially in the earlier years between 2003 and 2008 when there was little awareness of this entity. Follow-up radiographs were more likely to be done for symptomatic cases and more significant lesions which may influence the likelihood of lesion progression. (2) Cases with normal radiographs (type/group A) are less likely to have serial radiographs until they become symptomatic which results in a spuriously high rate of progression and displaced AFF developing after the initial radiograph in this group. (3) The follow-up interval and follow-up duration were variable. (4) Cases lost to follow-up may have had AFF but treated at other institutions, potentially causing underestimation of the true number of fractures or lesion progression. (5) Some cases had a long interval between last radiograph and progression to AFF. These may have had interval changes in their features prior to fracture. (6) Lastly, medication usage was not controlled and thus patients with normal radiographs were more likely to be continued on long-term BP treatment and some with stress lesions did not stop BP therapy. Also, some cases may have concomitant teriparatide or strontium ranelate given as part of the conservative regimen. BP history was also incomplete and the true number of patients still on BP therapy within the 6 months prior to complete AFF is not known. The duration of bisphosphonate and cessation of duration were also variable.

Conclusions

Our findings show that FSF tend to persist even after stopping BPs, either remaining stable or progressing. Progression follows an orderly sequence from normal femur to a lesion with focal cortical thickening, then DBL and eventually frank fracture. Displaced fractures were more frequent in lesions with DBL. Regression is uncommon and more frequent when bisphosphonates were discontinued. Nevertheless, 10.9% eventually sustained a displaced AFF. Based on the natural progression of FSF in patients on long-term BPs, when femurs have FSF restricted to focal cortical thickening, conservative management with cessation of BP and interval follow-up is feasible. However, when a transverse radiolucent line (DBL) is present or develops, prophylactic fixation should be the treatment of choice. If not possible, more aggressive conservative management with close interval follow-up is prudent.

Compliance with ethical standards

The retrospective cohort study was approved by our institutional review board with waiver of informed consent.

Conflicts of interest Meng Ai Png, P. Chandra Mohan, Choong Yin Howe and Tet Sen Howe declare that they have no conflict of interest.

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