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Factors that increase the risk of fracture in people with proximal femoral fibrous dysplasia

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Abstract

Objective: The main goal of this retrospective observational clinical study was to investigate the risk factors for fracture in individuals with proximal femoral fibrous dysplasia (FD).

Methods: In individuals with FD of the proximal femur according to whether or not they had experienced a hip fracture, we looked at body mass index, bilateral radiographs on both sides, femoral neck shaft angle measures, and markers of bone metabolism. Age, sex, clinical classification, anatomic classification, femoral neck shaft angle, pro-collagen type I N-terminal pro-peptide, type I collagen C-terminal telopeptide, and osteocalcin levels were the nine clinical variables used for univariate analysis. Multivariate logistic analysis was then applied to factors that showed out in the univariate study.

Results: In univariate analysis, the clinical classification, anatomic classification, femoral neck shaft angle, and osteocalcin level were found to be statistically significant risk variables for fracture. Multivariate analysis revealed that the osteocalcin level, femoral neck shaft angle, and anatomic classification were still important risk variables.

Conclusion: In patients with FD of the proximal femur, the osteocalcin level, the femoral neck shaft angle, and other key risk variables for fracture could be used to direct the execution of a fracture prevention strategy.

Keywords: Fracture; Proximal; Femoral; Fibrous dysplasia; Femur

1. Introduction

Fibrous dysplasia (FD), is a rare, non-hereditary, benign intramedullary fibro-osseous lesion that makes up 7% of benign bone tumours and 2.5% of all bone injuries, was initially identified by Lichtenstein in 1938. 1 The majority of FD cases are discovered in children. Both sexes are equally affected by the condition, which essentially ceases advancing in maturity but may do so in a few people. 2 Currently, it is thought that FD is brought on by spontaneous post-zygotic activating mutations in GNAS, which cause the G-S protein signalling in afflicted tissues to be dysregulated. 3 As a result, osteoblast development is impaired, and fibrous tissue replaces healthy bone. 4 Monostotic fibrous dysplasia (MFD), polyostotic fibrous dysplasia (PFD), and McCune-Albright syndrome, which is PFD worsened by endocrine disorders, are the three categories under which the condition can be classified. While patients with McCune-Albright syndrome appear with endocrine disorders and café au lait spots, the primary clinical signs of this condition are discomfort,

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deformity, and fractures. 5,6 Imaging studies and clinical symptoms are the two key factors in FD diagnosis. A uniform diffuse radiopacity with a ground glass look in continuity is the disease's radiological hallmark. 7 Puncture biopsy can be carried out on patients for whom imaging-based diagnosis is not possible with the aid of pathological evidence. Any bone in the body might develop FD. The maxilla, proximal femur, tibia, humerus, ribs, cranium, radius, and iliac bone are the most frequent locations for MFD, whereas the proximal femur is the most frequent site for PFD. 8 One of the most frequent side effects of FD in this location is pathological fracture. The proximal femur has a unique anatomic structure that concentrates stress there. So the area most likely to fracture is the proximal femur. Currently, it is challenging to forecast the likelihood of fracture in patients with FD of the proximal femur, which has an impact on treatment strategy. In this investigation, risk variables for fracture in individuals with FD of the proximal femur were to be found.

2. Material and methods

2.1. Study Design and Patient Selection

Between January 2016 and January 2021, individuals who were diagnosed with FD of the proximal femur in the Department of Orthopaedics at Kyiv City Clinical Hospital No14 were included in this retrospective observational clinical study. Following radiological or pathological confirmation of FD, a lesion area involving the proximal femur, and a follow-up period longer than 12 months were required for inclusion. Patients with concurrent neoplastic bone disease, those with insufficient case information, smokers, and alcohol consumers were eliminated. Our institutional ethics committee gave the study its blessing (approval number 2023-134 date of approval, 15 January 2023). The World Medical Association's 2013 amendment to the Declaration of Helsinki as well as the Health Insurance Portability and Accountability Act were followed in all experimental operations. Given the retrospective nature of the study and the lack of an effect on patients' financial or health state, written informed permission was not required. The identities of any patients have all been removed. The study's reporting complies with STROBE recommendations. 9 Information on body mass index (BMI), findings on bilateral hip radiographs, femoral neck shaft angle, and biomarkers of bone metabolism at the time of diagnosis was collected. The patients were divided into a fracture group and non-fracture group based on findings on bilateral hip radiographs and compared for age, sex, BMI, and clinical classification (MFD or PFD).

2.2. Anatomical Classifications

All patients' bilateral anteroposterior hip radiographs taken at the time of hospital admission were examined. The lesions were categorized according to Guille's classification10 as type A lesions (Figure 1a), type B lesions (Figure 1b), type C lesions (Figure 1c), or type D lesions (Figure 1d). Type A lesions cover the whole proximal femur (lesion involving only the intertrochanteric area, Figure 1d). We separated the patients into two groups based on anatomic classification to enable observation and due to the rarity of type B, C, and D lesions.Patients with type A lesions (involving the whole proximal femur) were designated as type 1 and those with type B, C, or D lesions (involving only part of the proximal femur) were designated as type 2.

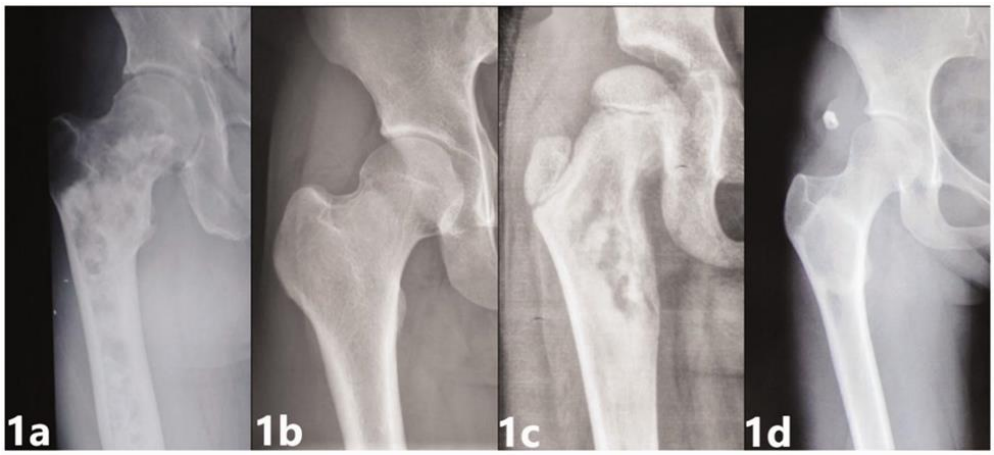

Figure 1 Anatomic classification of fibrous dysplasia of the proximal femur based on findings on radiographs. (a) Type A: the lesion covers the entire proximal femur. (b) Type B: the lesion only involves the femoral neck. (c) Type C: the lesion involves the femoral neck and intertrochanteric region and (d) Type D: the lesion involves only the intertrochanteric area

2.3. Femoral Neck Shaft Angles Measurement

Two radiologists with five and ten years of experience in radiology, operating independently and blinded to all clinical information, evaluated the femoral neck shaft angle retrospectively for all patients on bilateral anteroposterior plain radiographs of the hip joint. In adults, the usual range of femoral neck shaft angles is between 120° and 140°, while in children, it is between 135° and 145°.

2.4. Measurement of Bone Biomarker Levels

Pro collagen type 1 N-terminal pro-peptide (P1NP), C-terminal telopeptide of type I collagen (β-CTx), and osteocalcin levels were measured by an electrochemiluminescence method using a Cobas e601 analyzer (Roche, Berlin, Germany). The following normal reference values were used:

- P1NP: premenopausal women, 8.53 to 64.32 µg/L; postmenopausal women, 21.32 to 112.8 µg/L; men, 9.06 to 72.24 µg/L
- β-CTx: premenopausal women, 0.068 to 0.68 µg/L; postmenopausal women, 0.131 to 0.9 µg/L; men, 0.043 to 0.783 µg/L
- OST: premenopausal women, 11 to 43 µg/L; postmenopausal women, 15 to 46 µg/L; men aged 18 to 30 years, 24 to 70 µg/L; men aged 31 to 50 years, 14 to 42 µg/L; men aged 51 to 70 years, 14 to 46 µg/L.

2.5. Statistical Analysis

The Student's t-test and the Chi-squared test were used to compare categorical and continuous variables between groups. First, univariate analysis was used to examine potential risk factors. Multivariate logistic analysis was then used to investigate the factors that stood out in the univariate study. The statistical analysis software SPSS version 26.0 was used for all calculations (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a P-value 0.05.

3. Results

3.1. Demographic and Clinical Interpretations of the Patient

FD of the proximal femur was identified in 49 patients (27 male, 22 female) during the period of the study. The median age of the patients was 30.8 ± 14.7 years (range 12 to 74). 22 patients had PFD, while 27 patients had MFD. The average amount of time that patients were followed up with after their most recent fracture was 32.41 ± 15.81 months (range 10–60). Table 1 displays the clinical and demographic features of the patients. In contrast to age, sex, and BMI, there was no statistically significant difference in the clinical classification between the fracture group and the non-fracture group (P > 0.01).

Table 1 Demographic and clinical variables according to fracture status

Variable	Fracture group	Non-fracture group	t or $\chi 2$	*P*-value
N	17	32		
Age (years)	29.88 ± 13.85	31.40 ± 15.10	t = 3.39	0.736
Sex (male, %)	9 (52.94%)	18 (56.25%)	$\chi 2 = 0.49$	0.852
BMI (kg/m2)	23.98 ± 3.89	22.04 ± 3.04	t = 1.89	0.93
Clinical classification (MFD, %)	12 (70.59%)	15 (46.88%)	$\chi 2 = 4.59$	0.014
Anatomic classification (type 1, %)	14 (82.35%)	12 (37.5%)	$\chi 2 = 7.257$	0.007
Femoral neck shaft angle (normal, %)	23.98 ± 3.89	22.04 ± 3.04	t = 4.121	0.009
P1NP (normal, %)	3 (17.65%)	10 (31.25%)	t = 1.054	0.305
β-CTx (normal, %)	3 (17.65%)	11 (34.38%)	t = 1.522	0.217
Osteocalcin (normal, %)	1 (5.88%)	14 (43.75%)	t = 7.495	0.006

β-CTx, C-terminal telopeptide of type I collagen; BMI, body mass index; MFD, monostotic fibrous dysplasia; P1NP, pro-collagen type 1 N-terminal pro-peptide.

Anatomic classification, femoral neck shaft angle, and bone biomarker levels are shown according to fracture status in Table 1 and Table 2. The between-group difference in anatomic classification was statistically significant (odds ratio 8.622, P < 0.05), as was the femoral neck shaft angle (odds ratio 0.961, P < 0.05). There was no statistically significant between-group difference in the P1NP or β-CTx level; however, there was a significant difference in the osteocalcin level between the groups (odds ratio 0.006, P < 0.05).

Table 2 Variables identified to be significant risk factors for fracture according to sex and BMI

	Variable	**Fracture group**	**Non-fracture group**	***P*-value**
n		9	18	
Male	P1NP (μg/L)	546.72 ± 140.73	401.02 ± 106.37	0.649
	β-CTx (μg/L)	1.30 ± 0.28	1.46 ± 0.25	0.704
	OST (μg/L)	102.14 ± 11.17	85.46 ± 15.68	0.047
	Femoral neck shaft angle (°)	109.67 ± 8.27	136.11 ± 1.57	0.000
n		8	14	
Female	P1NP (μg/L)	454.76 ± 155.78	331.63 ± 93.92	0.479
	β-CTx (μg/L)	1.39 ± 0.71	1.12 ± 0.18	0.399
	Osteocalcin (μg/L)	129.91 ± 30.16	97.01 ± 23.59	0.045
	Femoral neck shaft angle (°)	105.13 ± 5.84	127.36 ± 7.63	0.031
n		6	23	
Normal BMI*	P1NP (μg/L)	388.86 ± 153.92	382.20 ± 83.87	0.971
	β-CTx (μg/L)	1.12 ± 0.27	1.40 ± 0.20	0.507
	Osteocalcin (μg/L)	95.32 ±2 2.69	96.14 ± 16.16	0.024
	Femoral neck shaft angle (°)	101.67 ± 5.36	132.13 ± 4.85	0.005
n		11	9	
Abnormal BMI	P1NP (μg/L)	565.95 ± 134.45	341.19 ± 146.03	0.273
	β-CTx (μg/L)	1.46 ± 0.25	1.09 ± 0.28	0.331
	Osteocalcin (μg/L)	126.05 ± 20.24	76.44 ± 24.39	0.036
	Femoral neck shaft angle (°)	110.73 ± 7.23	132.67 ± 0.67	0.014

*Normal BMI in China is defined as 18.5–23.9.

β-CTx, C-terminal telopeptide of type I collagen; BMI, body mass index; P1NP, pro-collagen type 1 N-terminal pro-peptide.

3.2. Multivariate Logistic Analysis of Possible Predictors of Fracture

Table 3 Multivariate logistic analysis of risk factors for fracture in patients with fibrous dysplasia of the proximal femur

Variable	**B**	**SE**	**World**	**P-value**	**OR**	**95%Cl**
Clinical classification	−0.919	1.099	0.699	0.403	0.399	0.046–3.438
Anatomical classification	2.154	0.925	5.423	0.020	8.622	1.407–52.854
Femoral neck shaft angle	−0.40	0.18	2.525	0.026	0.961	0.928–0.995
Osteocalcin	−2.499	1.266	4.157	0.041	0.082	0.007–0.908

CI, confidence interval; OR, odds ratio

The osteocalcin level, femoral neck shaft angle, clinical classification, anatomic classification, and femoral neck angle were all statistically significant prognostic factors in the univariate analysis and were included in the multivariate logistic analysis. According to Table 3, multivariate logistic analysis revealed that osteocalcin level, femoral neck shaft angle, and anatomic classification all maintained statistical significance ($P< 0.05$).

3.3. Two Representative Cases

Figure 2 depicts the imaging results at the proximal femur for a 22-year-old woman who was admitted to the hospital due to right thigh pain that had been present for three years. Her osteocalcin level was within the normal range, the lesions only affected a small portion of the proximal femur, and the anatomic classification was type 2. The pathological findings and imaging tests showed FD of the proximal femur. In the next year of follow-up, the patient experienced no fractures.

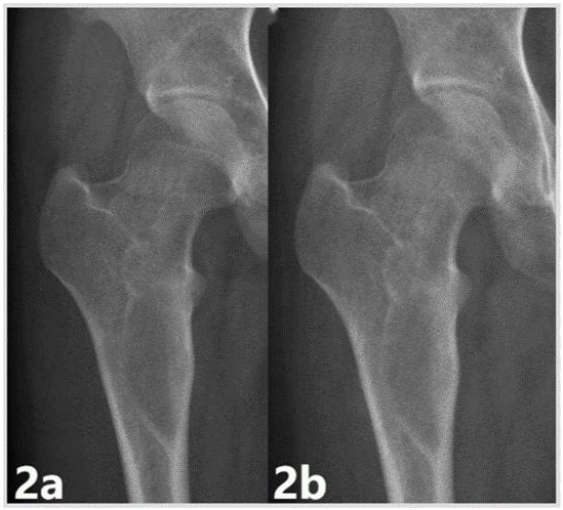

Figure 2 Radiographs for a patient with fibrous dysplasia of the proximal femur who did not develop a fracture. Radiographs obtained (a) at the time of diagnosis and (b) when the patient was rechecked. There was no fracture of the proximal femur

The imaging results at the proximal femur for a 36-year-old lady with a 10-month history of left femoral discomfort are shown in Figure 3. Her osteocalcin level was above the normal range, the anatomic classification was type 1, and examination results showed that the lesions spanned the whole proximal femur. The pathological findings and imaging tests showed FD of the proximal femur. The third month of follow-up saw the patient suffer a proximal femur fracture.

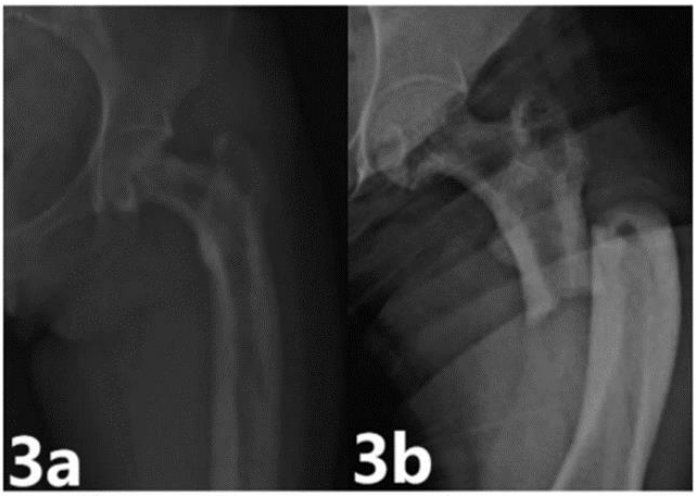

Figure 3 Radiographs for a patient with fibrous dysplasia of the proximal femur who sustained a fracture. (a) Radiograph showing that the lesion covered the entire proximal femur at the time of diagnosis. (b) Radiograph obtained when the patient was rechecked showing a fracture of the proximal femur

4. Discussion

One major FD consequence is fracture. Due to its unique anatomic position, the proximal femur is prone to abnormalities and fractures. 11 Patients with FD have a difficult time predicting fractures, and they frequently aren't admitted to the hospital until a fracture has already occurred, missing the optimum window of opportunity for treatment. In order to develop the optimal treatment plan and lower the incidence of fractures that do occur, early prediction of fractures in patients with FD involving the proximal femur is essential. Several researchers have developed treatment plans for people who have proximal femur fractures with FD. The lack of studies on the risk factors for fracture in these patients with FD, however, means that there are no clear guidelines for prevention. Majoor et al. assessed the surgical procedures performed on 32 patients who had FD of the proximal femur and their effectiveness, although they did not go over any of the patients' risk factors for fractures. 12 Bian et al. examined 26 children with FD of the proximal femur retrospectively, looking at surgical procedures employed, clinical results, and reasons for revision; however, they did not look into any potential risk factors for fracture in these patients. 13 In order to predict the risk of fracture and create preventative measures, it is necessary to determine the risk factors for fracture in these patients. FD of the proximal femur has been classified by a number of researchers. There are now three such classification systems: those created by Guille et al. (10), Ippolito et al. (14), and Zhang et al. (15). We used the straightforward Guille's classification in this investigation. We discovered that type A patients made up the majority of the patients we considered, while cases of types B, C, and D were infrequent.

According to anatomic classification, we separated the patients into two groups for research and observational purposes: type A (affecting the complete proximal femur) was classified as type 1, while type B, C, and D (affecting a portion of the proximal femur) were labelled as type 2. There was a statistically significant difference in the anatomic classification between the fracture group and the non-fracture group in the multivariate logistic analysis. Due to the comprehensive extent of the lesions in Type 1, substantial bone degeneration occurred. As a result, it became harder to sustain the weight of the upper body, and the likelihood of fracture increased. Therefore, a type 1 anatomic classification is an important risk factor for fracture in patients with FD of the proximal femur. There are currently limited investigations on the association between fracture and the angle of the femoral neck shaft in patients with FD of the proximal femur. Additionally, proximal femur fractures are thought to be facilitated by hip varus. 16 The femoral neck shaft angle was found to be a predictor of the probability of stress fractures of the femoral head in a study of 37 cases of femoral neck fracture. 17 In our investigation, the hip joints were radiographically inspected on each patient, and the femoral neck shaft angle was calculated. We revealed that patients with FD of the proximal femur who had an abnormal femoral neck shaft angle were more likely to fracture than those who had an angle that was within the usual range. As a result, another significant risk factor for fractures in these patients is a femoral neck shaft angle that is outside of the usual range.

Indicators of bone metabolism are excellent indicators of the likelihood of fracture. The level of osteocalcin is frequently employed as a measure of bone resorption and creation. The most prevalent non-collagenous protein in bone, osteocalcin is only expressed by osteoblasts. 18 It is a new biomarker that may be utilised to analyse bone metabolism and has a significant role in controlling bone calcium metabolism. It can keep the mineralization of bone in equilibrium, prevent aberrant hydroxyapatite crystallization, and directly monitor osteoblast activity and bone production. 19 Osteocalcin is a crucial indicator of the risk of hip fracture and is closely associated to bone mineral density20. 21,22 While bone resorption causes the release of osteocalcin from the bone matrix, the substance is nonetheless a sign of bone development. As a result, the level of serum osteocalcin can also be used as a measure of bone turnover. 23 Ost-deficient animals were seen in a different study24 to grow robust bones. As a result, it is believed that low levels of osteocalcin are associated with better bone function, indicating that osteocalcin is a negative regulator of bone formation. Because osteocalcin is expressed more in FD than in other lesions, it may be inhibiting bone formation and causing poor fibres in the bone structure. Consequently, the lesser the bone quality and greater the risk of fracture, the higher the level of osteocalcin.

172 fractures were observed in a prior study that followed 35 patients with FD for 14.2 years. It also revealed that the peak age for fracture was between 6 and 10 years, with a decline after that. 25 Han et al. conducted a retrospective study in which they found that the peak age for fracture was bimodal, with the first peak occurring between the ages of 6 and 10 and the second peak occurring after the age of 36. 26 In a multicenter investigation, half of the 14 patients with MFD of the proximal femur subsequently fractured. 27 Low BMI has been linked to a higher risk of fracture in numerous studies. 28,29 However, our study did not find BMI to be a statistically significant risk factor. According to other studies, patients with endocrine diseases had a much higher risk of fracture. The breakdown of bone structure and loss of bone mass can both be accelerated by hyperthyroidism, which raises the risk of fracture. 30,31 This research has several restrictions. In the beginning, a small number of patients who smoked or drank alcohol were left out of the study. Yet, environmental and behavioural aspects of life can have an impact on the fracture rate. Further research will need to be

conducted on larger cohorts. Also, more research is required on the pathogenesis of FD of the proximal femur, and a thorough treatment plan must be developed for these patients to prevent fractures.

5. Conclusion

In individuals with FD of the proximal femur, the anatomic categorization, femoral neck shaft angle, and osteocalcin level are significant risk factors for fracture. In order to provide direction for these patients' fracture prevention methods, analysis of these indices would be beneficial.

Compliance with ethical standards

Acknowledgments

The authors are very thankful to the participants who showed interested to this research.

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

The study was approved by the Institutional Ethics Committee of The Department of Orthopaedics at Kyiv City Clinical Hospital No14 (approval number 2023-134 date of approval, 15 January 2023). All experimental procedures were conducted in accordance with the Declaration of Helsinki (World Medical Association, as amended 2013) and the Health Insurance Portability and Accountability Act. Written informed consent was not necessary in view of the retrospective design of the study and the lack of impact on the health and financial status of patients.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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