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Potential bone fragility of mid-shaft atypical femoral fracture: Biomechanical analysis by a CT-based nonlinear finite element method

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ABSTRACT

Introduction: The authors previously reported a CT-based nonlinear finite element analysis (nonlinear CT/FEA) model to investigate loading stress distribution in the femoral shaft of patients with atypical femoral fractures (AFFs). This showed that stress distribution, influenced primarily by femoral bowing, may determine the location of AFF. Here, we demonstrate the locational characteristics associated with AFFs in an Asian, specifically Japanese, population regarding bone strength. This is the second report from our multicentre research project suggesting a possible new concept of diagnostic criteria or treatment according to AFF subtype.

Patients and methods: A multicentre prospective study was conducted at 12 hospitals in Japan from August 2015 through June 2018. We recruited three study groups composed of elderly females over the age of 60 years—the mid-shaft AFF group ($n = 14$; 80.0 ± 6.5 years), the subtrochanteric AFF group ($n = 15$; 73.9 ± 6.8 years), and the control group who had sustained unilateral hip fracture ($n = 21$; 82.1 ± 7.1 years)—and analysed femoral neck bone density and strength. Bone strength of the femoral neck was predicted with an evaluation method using nonlinear CT/FEA in both standing and falling configuration.

Results: Femoral neck bone density and strength were significantly higher in the subtrochanteric AFF group compared with the mid-shaft AFF and control groups ($p < 0.0001$). No significant difference was seen in bone strength between the mid-shaft AFF and control groups (standing, $p = 0.7616$; falling, $p = 0.3803$).

Conclusions: AFF has different features, in terms of bone strength, depending on fracture location. At the very least, Japanese patients with mid-shaft AFF could be at high risk of hip fracture because of bone fragility, in contrast to the firm bone of subtrochanteric AFF. For internal fixation of mid-shaft AFF using an IM nail, cervical screw insertion toward the femoral head might be recommended to prevent possible hip fracture.

Introduction

Atypical femoral fractures (AFFs) are short oblique or transverse fractures resulting from minor injury, or incomplete fractures without any preceding trauma, associated with focal thickening of the lateral cortex of the femoral shaft [1]. Although it has been reported that severely suppressed bone turnover (SSBT) due to prolonged bisphosphonates (BPs) use increases the risk of AFF [2], these fractures can occur also in patients with no BP exposure [3]. Consistent with this, some studies have indicated that AFF could be associated with other drugs, such as denosumab, proton pump inhibitors (PPIs), and glucocorticoids [4–6]. Furthermore, other reports describe the pathogenesis of AFFs as evolving from factors such as specific diseases like rheumatoid arthritis and chronic renal failure [7,8], ethnicity, geometry of the hip, and body mass index (BMI) [9,10]. On these bases, the American Society for Bone and Mineral Research (ASBMR) Task Force revised the diagnostic criteria for AFF in 2013, excluding implicated drugs and diseases from the minor features [3]. At present, the case definition of AFF, which must be located along the femoral diaphysis extending from just distal to the lesser trochanter to just proximal to the supracondylar flare, requires that at least 4 of the following 5 major features must be present—1. association with minimal or no trauma, as in a fall from a

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standing height or less; 2. transverse or oblique fracture line originating at the lateral cortex; 3. complete fracture extending through both cortices associated with a medial spike, or incomplete fracture involving only the lateral cortex; 4. noncomminuted or minimally comminuted; and 5. localised periosteal or endosteal thickening of the lateral cortex ("beaking" or "flaring") [3].

To investigate the features of AFF, the authors had previously developed a CT-based nonlinear finite element analysis (nonlinear CT/FEA) model to assess the distribution of loading stress in the femoral shaft, and demonstrated that stress distribution influenced primarily by femoral bowing may determine the location of AFF injury [11]. To aid analysis, we classified AFF, based on location, as subtrochanteric or mid-shaft. The subtrochanteric AFF group suggested smaller femoral neck-shaft angles and was associated with long-term use of specific drugs which can cause SSBT (e.g., BPs, PPIs, or glucocorticoids) [11]. On the other hand, mid-shaft AFFs in our previous reports showed bowing deformity of the femoral shaft, with less of a relationship to those drugs [11–13]. Thus, we concluded that stress fractures of the bowed femoral shaft (SBFs) in elderly Asian females should be distinguished from typical AFFs caused by SSBT, which generally occur in the subtrochanteric region [11].

In our clinical experience with Japanese SBFs (bowed mid-shaft AFFs), some SBF cases were complicated by hip fracture (Fig. 1). Oh et al. reported their experience of 2 cases of hip fracture during follow-up of 13 Japanese female patients with mid-shaft AFF [13]. In a retrospective cross-sectional study in another East Asian, specifically Korean, population, the diaphyseal AFF group had lower bone mineral density (BMD) than the subtrochanteric AFF group [14]. There has also been a report of mid-shaft AFF patients who sustained ipsilateral femoral neck fracture after IM nailing surgery in a European population [15]. For these reasons, we hypothesised that AFF has different features, including variations in bone strength, depending on the fracture location. Using our developed CT/FEA loading model of the whole femur [11], we demonstrated the possibility of bone fragility in Japanese patients

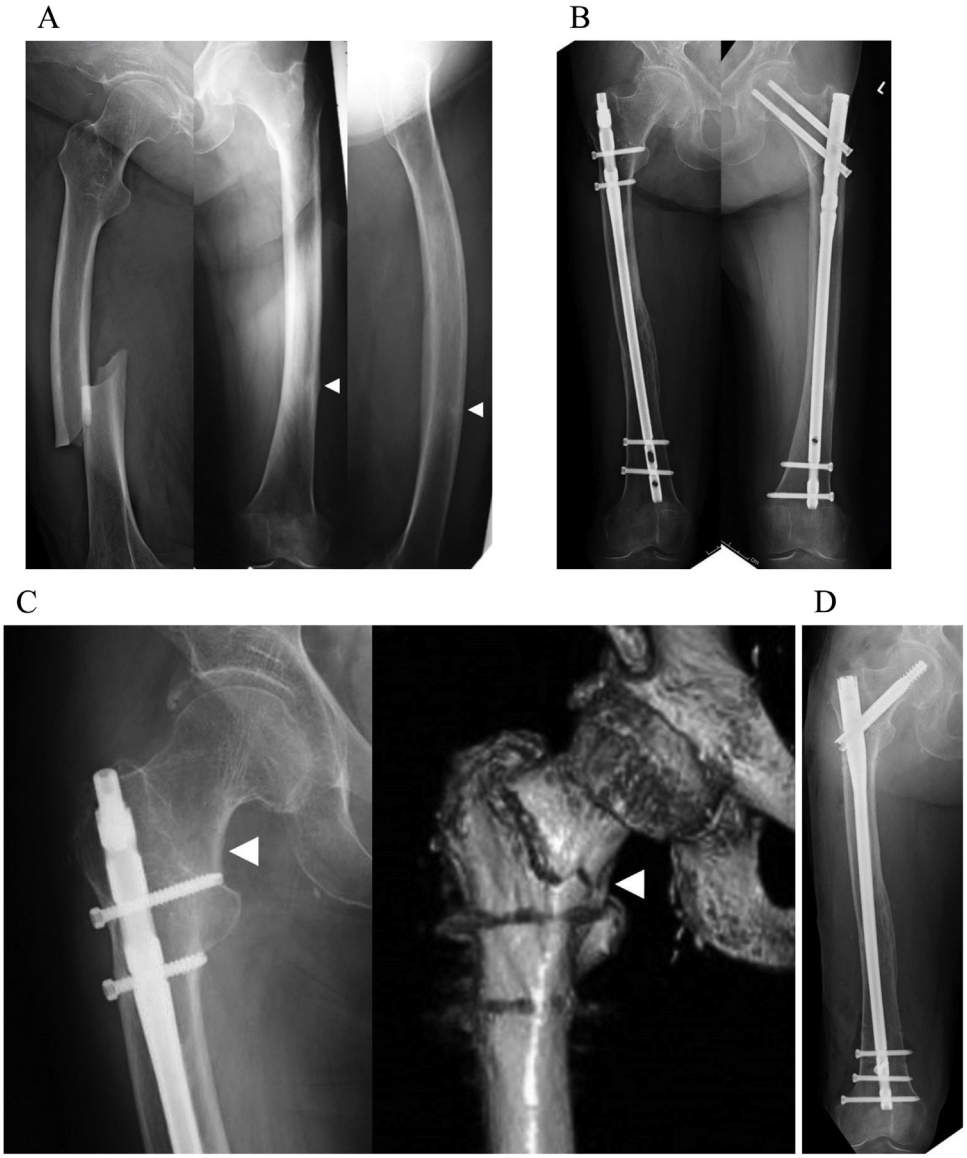

Fig. 1. Representative images from an 83-year-old female with a past history of bilateral atypical femoral fracture (AFF) in the middle-third. (A) At age 73 years, she suffered a displaced fracture of the right femoral shaft (AO/OTA 32-A2) satisfying the diagnostic criteria of AFF. At that time, the contralateral left femur showed an apparent bowing deformity and an incomplete AFF with a thickened lateral cortex (white arrowheads). (B) Both femurs were treated with IM nails. Firm bony union of the right side was achieved, and the left side did not develop a complete fracture. (C) Ten years after the first diagnosis of the AFF, she sustained a low-energy fracture of the right femoral neck. White arrowheads indicate fracture line in the basal neck. (D) Postoperative XR taken after revision nailing of the right femur.

with SBFs, which generally occur in the mid-shaft region [16]. However, our previously reported CT/FEA model was aimed at evaluating loading stress distribution in the femoral shaft [11], and would not be appropriate for quantifying bone strength. In the present study, we used a precisely confirmed nonlinear CT/FEA model [17] to analyse bone strength of the femoral neck in AFF patients.

This is the second report from our research project [11], in which we intended to establish a novel concept of diagnostic criteria or treatment based on the subtype of AFF. It is pertinent to clarify that there is some overlap of patient data with data reported in our earlier report [11]; however, this present study contains a myriad of different analyses and proposes innovative facts regarding bone fragility in patients with mid-shaft AFF.

This study was approved by the institutional review boards of the participating institutions. All procedures involving human participants were performed in accordance with the ethical standards of the relevant institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Our reporting of patients was completely anonymous, protecting their privacy and dignity.

Patients and methods

Study design and patients

This prospective multicentre study of patients with AFFs was conducted by Tokyo Medical and Dental University (TMDU) Orthopaedic Study Team comprising TMDU Medical Hospital and 11 other associated hospitals in Japan, from August 2015 through June 2018. The project was designated “TMDU Orthopaedics Multicentre AFF Study (TOMAS)”. Inclusion criteria were as follows: fulfilling the diagnostic criteria of AFF as revised by the ASBMR Task Force [3], Japanese nationality, female sex, age > 60 years old, and capable of providing consent to participate in the study. Exclusion criteria were a history of fracture of the lower extremity excluding AFF or surgery involving the lower extremity (excluding AFF), or bilateral femoral internal fixation. Participants were then classified into mid-shaft (i.e., the middle-third of the femoral shaft) and subtrochanteric (i.e., the proximal-third of the femoral shaft) AFF groups. In total, 29 elderly women with AFF were enrolled and classified into the mid-shaft AFF group ($n = 14$; age 80.0 ± 6.5 years) and subtrochanteric AFF group ($n = 15$; age 73.9 ± 6.8 years) according to the location of injury (Table 1). No patients in this study period suffered an AFF located in the distal third of the femoral shaft.

For comparison, we also included a control group of Japanese women also over the age of 60 years ($n = 21$; age 82.1 ± 7.1 years), who had sustained a unilateral hip fracture that was treated at Saku Central Hospital (Nagano, Japan) during the study period.

We evaluated age, height, body weight, BMI, long-term (≥ 5 years) history of use of specific drugs (BPs, PPIs, or glucocorticoids) that can cause SSBT and bone density and strength of the femoral neck.

Bone density

BMD of the femoral neck was examined using dual-energy XR absorptiometry (DEXA). We assessed the femoral neck of the predominantly painful side in AFF patients with no internal fixation of both femurs, and in the contralateral side in AFF patients with internal fixation of one femur. In the control group, the femoral neck contralateral to the fracture side was examined.

Bone strength using CT/FEA

CT imaging was performed using the regular equipment at each institution and de-identified CT data were collected at the primary research facility and blinded by the project leader (Y. O.); all cases were analysed by another contributing author (A. T.). Predicting bone strength was evaluated based on a nonlinear CT/FEA method, which had been approved as an advanced medical technology in Japan (1 June 2007 – 1 April 2018) [17]. CT-Digital Imaging and Communications in Medicine (CT-DICOM) data were obtained from the femoral bone on the same side, on which BMD of the femoral neck was assessed using DEXA, at 2-mm slice intervals, and analysed using MECHANICAL FINDER Software (Research Center of Computational Mechanics, Inc., Tokyo, Japan). The region of interest (ROI) was extracted from the femoral head to 6 cm below the lesser trochanter, and this was used for creating the three-dimensional imaging model, which was then converted to the finite element model. This model consisted of 3-mm regular tetrahedral solid elements and 3-mm equilateral shell elements with a 0.4-mm thickness that covered the entire surface of the model. A calibration phantom could not be used for CT imaging because some institutions did not have access to one. Thus, instead of a phantom, the standard calibration curve was adapted to convert Hounsfield units into the bone material density value (g/cm^2). Using the equations proposed by Keyak et al. [18], material properties were set for each element, conforming to Young’s modulus, Poisson’s ratio, and Drucker-Prager’s yield stress.

In this study, standing and falling configurations were designed for use when evaluating femoral neck bone strength. Loading and constraint conditions for the breaking analysis in each configuration were set as follows. In the standing configuration, the loading direction was set at 20° to the femoral long axis in the frontal plane and 0° to the femoral neck axis in the horizontal plane; the constraint condition was defined as a completely restrained lesion extending from 2 cm to 6 cm below the top of the lesser trochanter (Fig. 2A). In the falling configuration, the loading direction was set at 120° to the long axis of the femur in the frontal plane and 15° anterior to the axis of the horizontal plane; the constraint condition was then defined as a completely restrained lesion, as

Table 1
Summary of subjects.

	Mid-shaft AFF (n = 14)	Subtrochanteric AFF (n = 15)	Control (n = 21)	*p* value
Age (years)	80.0 ± 6.5	73.9 ± 6.8	82.1 ± 7.1	< 0.01
Height (cm)	145.3 ± 8.0	150.3 ± 4.3	147.6 ± 5.2	0.1760
Body weight (kg)	48.5 ± 8.2	52.3 ± 7.8	47.1 ± 8.9	0.1684
BMI (kg/m^2)	23.0 ± 3.4	23.2 ± 3.2	21.5 ± 3.4	0.1844
BMD (g/cm^2)	0.530 ± 0.131	0.781 ± 0.109	0.421 ± 0.068	< 0.0001
Predicted bone strength by CT/FEA (N) standing configuration	3393 ± 1007	4837 ± 857	3352 ± 489	< 0.0001
Predicted bone strength by CT/FEA (N) falling configuration	1393 ± 263	1810 ± 410	1452 ± 255	< 0.01

Statistical analysis was performed with the Kruskal-Wallis test for comparison of all three groups.
AFF, atypical femoral fracture; BMD, bone mineral density; BMI, body mass index; CT/FEA, CT-based finite element analysis.

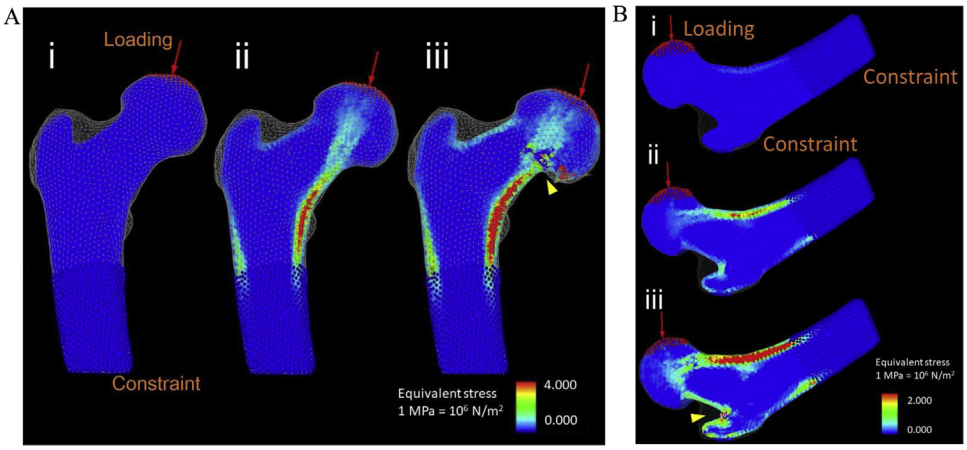

Fig. 2. CT-based finite element analysis model of the proximal femur. The contour figures of the proximal femoral coronal section of the proximal femur describe the changing equivalent stress loaded to the solid elements. Color bar shows stress volume (1 MPa = 10^6 N/m^2). Red arrows show loading direction, and red dots and blue dots show loading and constraint range, respectively. (A) Standing configuration: As load increases, compressive stress becomes highly concentrated in the medial femoral neck, and finally, the model starts breaking at the medial femoral neck (yellow arrowhead) (i, no loading; ii, stress loading; iii, breaking point). (B) Falling configuration: As load increases, tensile stress becomes highly concentrated in the medial femoral neck and compressive stress becomes highly concentrated in the piriform fossa, where breaking occurs (yellow arrowhead) (i, no loading; ii, stress loading; iii, breaking point).

with the standing configuration, but occupying the lateral side of greater trochanter (Fig. 2B). Loading stress was gradually increased in intervals of 50 N.

Bone strength was defined as fracture load (N), which was the load when ≥ 1 shell element failed (Fig. 3). If the shell element failed around the constraint area in the falling configuration, the constraint condition was modified manually and then the analysis was repeated.

Statistical analysis

Data were analysed with GraphPad Prism 5 software (GraphPad Software Inc., La, Jolla, CA), and values are expressed as means and standard deviation. The Kruskal-Wallis test was used to perform non-parametric two-tailed tests to compare the three groups; the Mann-Whitney U test was used to compare each pair of groups directly. A p value of < 0.05 was considered statistically significant.

Results

Patients background

Mean age was significantly lowest in the subtrochanteric AFF group ($p < 0.01$), and no significant difference was seen in age between the mid-shaft AFF and control groups ($p = 0.5327$). Physically, there were no significant differences in height, body weight, and BMI among the three groups. Thirteen of the 15 patients in the subtrochanteric AFF group, 4 of the 14 patients in the mid-shaft AFF group, and 2 of the 21 patients in the control group had a history of prolonged (≥ 5 years) exposure to specific AFF-related drugs. However, 2 patients with shorter durations (< 5 years) of use of such drugs in the subtrochanteric AFF group had been exposed to alendronate or denosumab for over 4 years.

Bone density

Mean BMD of the femoral neck was 0.530 ± 0.131 g/cm^2, 0.781 ± 0.109 g/cm^2, and 0.421 ± 0.068 g/cm^2 in the mid-shaft AFF, subtrochanteric AFF, and control groups, respectively. The subtrochanteric AFF group had significantly higher BMD than the other groups both overall ($p < 0.0001$) and in the direct comparisons (mid-shaft AFF group, $p < 0.0001$; control group, $p < 0.0001$), whereas BMD was also significantly lower in the control group than in the mid-shaft AFF in the direct comparison ($p < 0.05$) (Fig. 4A).

Bone strength using CT/FEA

In the standing configuration, mean bone strength was 3393 ± 1007 N, 4837 ± 857 N, and 3352 ± 489 N in the mid-shaft

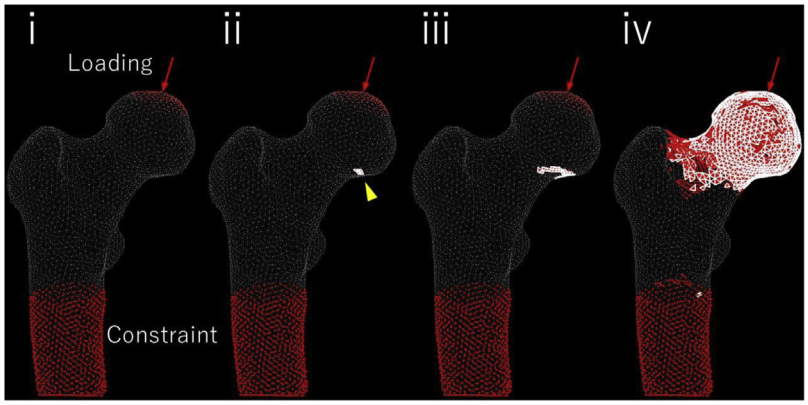

Fig. 3. Representative images of breaking analysis of the proximal femur in standing configuration. The load is gradually increased in 50 N increments. Red arrow shows loading direction, and red dots show loading and constraint ranges. (i) No loading. (ii) Shell elements start to break in the medial femoral neck at 2950 N (yellow arrowhead). (iii) Broken shell elements (white colour) spread around the femoral neck at 3000 N. (iv) Complete breaking at 3100 N.

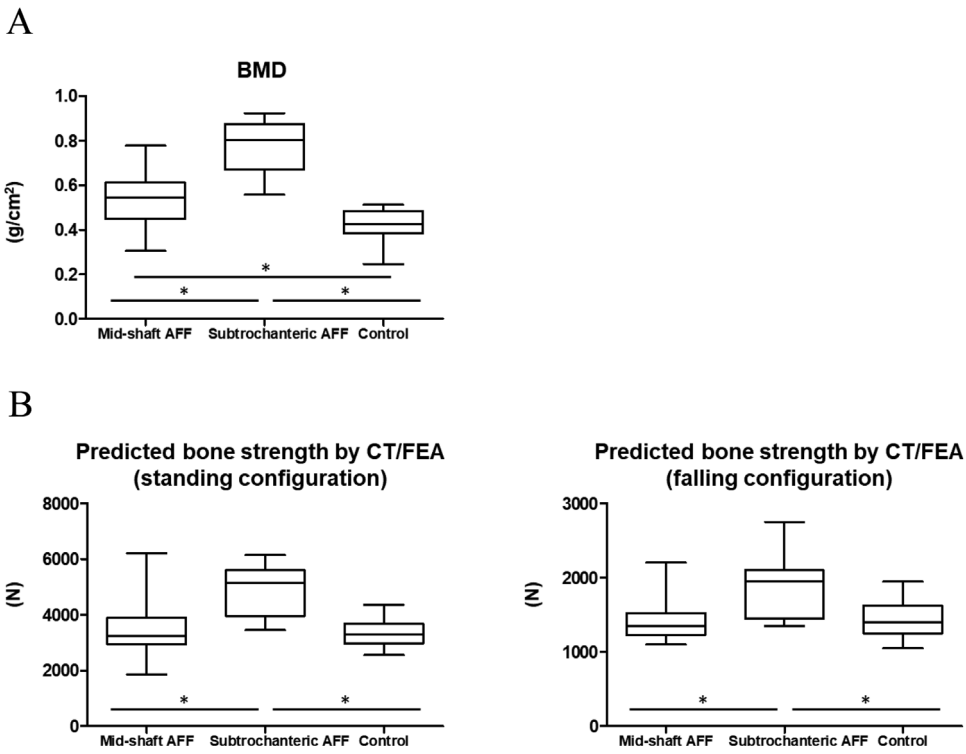

Fig. 4. Box-and-whisker plot for each group. The Mann-Whitney U test was used to compare each pair of groups directly (*$p < 0.05$). (A) BMD of the femoral neck examined using dual-energy XR absorptiometry. (B) Predicted bone strength of the femoral neck quantified using CT/FEA in both standing and falling configuration.
AFF, atypical femoral fracture; BMD, bone mineral density; CT/FEA, CT-based finite element analysis.

AFF, subtrochanteric AFF, and control groups, respectively. The subtrochanteric AFF group had significantly higher bone strength than the other groups both overall ($p < 0.0001$) and in the direct comparisons (mid-shaft AFF group, $p < 0.001$; control group, $p < 0.0001$) (Fig. 4B). However, there was no significant difference between the mid-shaft AFF group and the control group in the direct comparison ($p = 0.7616$).

In the falling configuration, mean bone strength was 1393 ± 263 N, 1810 ± 410 N, and 1452 ± 255 N in the mid-shaft AFF group, subtrochanteric AFF, and control groups, respectively. The subtrochanteric AFF group had significantly higher bone strength than the other groups both overall ($p < 0.01$) and in the direct comparisons (mid-shaft AFF group, $p < 0.01$; control group, $p < 0.01$). However, there was no significant difference between the mid-shaft AFF group and the control group in the direct comparison ($p = 0.3803$).

Discussion

Previous studies have suggested that AFFs located in the middle-third are associated with osteoporosis [14,16]. In these studies, bone fragility was investigated using two-dimensional BMD measurement methods such as DEXA. However, it has been reported that DEXA is not readily reproducible because of the influence of calcification or lower limb rotation, and that femoral bone strength is better predicted by FEA [19]. CT/FEA enabled quantitative evaluation of bone strength in a virtual biomechanical model that was constructed using patient-originated CT-DICOM data, considering bone morphology, structure, mechanical properties, and three-dimensional bone density, and developed as an evaluation tool for osteoporosis. Bessho et al. examined fracture mechanics in fresh cadaveric bones using a biomechanical compressor with their finite element model of the proximal femur, and reported a strong correlation between CT/FEA and their biomechanical model in terms of predictive bone fracture loading, breaking stress, and surface strain of the femur [20]. In addition, they developed a modified nonlinear CT/FEA model and set loading parameters and lesions in the virtual proximal femoral bone in both standing and falling load configurations [17]. The Japanese Ministry of Health, Labour and Welfare had approved this evaluation method for predicting bone strength using quantitative CT imaging as an advanced medical technology between June 2007 and April 2018. Kaneko et al. investigated the predicted bone strength of the proximal femur in a Japanese population (552 men and 273 women) using the same CT/FEA model as in the present study, and reported a simple mathematical formula of predicted bone strength (N) of the femoral neck in Japanese women (standing configuration, $-61.378 \times$ years + 9476.4; falling configuration, $-17.329 \times$ years + 3096) [21]. According to these equations, predicted age-adjusted femoral neck bone strength (standing/falling configurations) in the present study were calculated as 4566/1710 N in the mid-shaft AFF group, 4941/1815 N in the subtrochanteric AFF group, and 4437/1673 N in the control group. Compared with the actual measurement values in the present report, the mid-shaft AFF and the control group suggest bone fragility in terms of bone strength. Therefore, in an Asian, specifically Japanese, population, mid-shaft AFF could be associated with not only bowing deformity but also with low bone strength, and these patients could be at high risk of femoral neck fracture because of bone fragility. Based on these results, for internal fixation of mid-shaft AFF using an IM nail, cervical screw insertion toward the femoral head [13] might be recommended to prevent possible hip fracture.

In contrast, bone density and strength of the femoral neck in the subtrochanteric AFF group were indicated to be significantly higher and stronger than that in both the mid-shaft AFF and control groups. Although the rather younger age in the subtrochanteric AFF group might have affected these results, BMD in the

subtrochanteric AFF group was clearly higher than the average of Japanese women in the same age group [22]. According to a paper from the 1960s, stress fractures can be classified into 3 types: fatigue fracture from overuse, insufficiency fracture from bone fragility, and pathologic fracture [23]. Fatigue fracture develops in normal or rather strong bone of athletes and soldiers due to overuse. On the other hand, insufficiency fracture occurs due to bone fragility despite a low stress level of daily physiological activity. Although SBF (bowed mid-shaft AFF) is conceptually the same as the classical concept of insufficiency fracture, described first in 1975 but overlooked in recent years [24], the bone in "typical" subtrochanteric AFF might not be fragile. We think this is a contradiction of AFF, and thus a fourth concept of stress fracture might be necessary to comprehend AFF.

Regarding the location of AFF injury, Schilcher et al. reported that subtrochanteric AFF was more likely in Asian populations and that mid-shaft AFF was more likely in European populations [25]. However, the Japanese Orthopaedic Association surveyed 230 AFFs in Japan and found that mid-shaft AFF was common in Japan, with rates of 30.4% for proximal third, 68.3% for middle third, and 1.3% for distal third [26]. Besides, relationships between AFF location and height, body weight, femoral bowing, and femoral bone density have been reported in several studies, especially from East Asian countries [14,27–29]. Yoo et al. reported mean lateral bowing angle of the femoral shaft as $10.10^\circ \pm 3.79^\circ$ in the diaphyseal AFF group and $3.33^\circ \pm 2.45^\circ$ in the subtrochanter AFF group [29]. Certainly, the present report states that in Japanese AFF patients, femoral bowing was significantly greater in the mid-shaft group than in the subtrochanteric AFF group, consistent with previous reports [11,16]. Maratt et al. reported that femoral bowing increased as length shortened and that femoral bowing was greater in Asian than in European or African populations [30]. In a study that reported femoral bowing analysis in elderly Japanese women, both lateral and anterior bowing of the femoral shaft showed a correlation with body height or bone density of the femoral neck [27]. The study also showed that elderly Japanese women with characteristics of short stature and low bone density could be at high risk of SBF, which is equivalent to mid-shaft AFF associated with femoral shaft bowing deformity [27]. Besides, various studies based on CT/FEA, including our previous report [11,12,16], support the notion that femoral morphology is key in AFF injury. Martelli et al. suggested that daily stress in the lateral side of the femoral shaft, which is influenced by lateral bowing, was associated with AFF risk [31]. Haider et al. reported that changes in femoral geometry can have an impact on strain in the femoral diaphysis using the CT/FEA model assuming the stance phase of gait [32]. The stress distribution of the two patterns of the representative cases in this article [32] is quite similar to the results of our CT/FEA loading model [11], and the femur, which shows a diffuse stress pattern, has obvious bowing deformity.

A previous article surmised that the femur in Europeans is longer and straighter than that of Asians [30], it was also reported that mid-shaft AFF is more common than subtrochanteric AFF in Sweden as well as in Japan [25,26]. Because femoral neck fracture associated with mid-shaft AFF occur not only in Japanese but also European patients [15], it is necessary to clarify the locational characteristics of AFF in each region of the world. As discussed based on the results in the present study, bone fragility in Western patients with mid-shaft AFF may be elucidated in the future, and it may become standard to keep in mind the risk of hip fracture complicated with mid-shaft AFF even in regions other than Asia.

Our study has several limitations. First, CT scans were performed using different CT scanners at different centres because this is a multicentre study. For the same reason, a calibration phantom could not be used and different bone densitometers were used for assessment of bone density at different participating hospitals, and this could have created some bias. Second, we did not confirm if bone density and strength of the femoral neck was similar for both femurs. Subject-specific finite element modelling of the strength of the bilateral femurs in post-menopausal women has shown some statistical significance but mechanically negligible differences between sides (the right femur was, on average, 4% stronger than the left) [33]. Third, only Asian, specifically Japanese, patients were enrolled in the study. Moreover, we were unable to enrol patients with AFF located in the distal third. Fourth, we used Keyak's model [18] in this study, which proposes material properties based on a cadaveric study of fresh frozen tibias from adult men. It is thus expected that differences in bone strength by sex or age might have affected the results. Moreover, we defined bone strength as the force (in newtons) required to start breaking only one shell element through compressive or tensile stress, but this was unstable and susceptible to error from the influence of manual processing (e.g., extracting the ROI and setting shell conditions). Thus, a new definition of bone strength is desired to be developed for this purpose.

Conclusions

AFF has different features, including bone density and strength, depending on the fracture location, at least in a Japanese population. The findings of this study indicated that SBF (AFF associated with femoral shaft bowing deformity), which mostly occur in the mid-shaft region, could be a fragility fracture. In contrast, subtrochanteric AFF is an unnatural fracture which differs vastly from a fragility fracture. East Asian, particularly Japanese, patients with mid-shaft AFFs are considered to be at high risk of hip fractures because of bone fragility.

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Declaration of Competing Interest

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References

[1] Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010;25:2267–94.

[2] Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005;90:1294–301.

[3] Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2014;29:1–23.

[4] Mahjoub Z, Jean S, Leclerc JT, Brown JP, Boulet D, Pelet S, et al. Incidence and characteristics of atypical femoral fractures: clinical and geometrical data. J Bone Miner Res 2016;31:767–76.

[5] Meier RP, Perneger TV, Stern R, Rizzoli R, Peter RE. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. Arch Intern Med 2012;172:930–6.

[6] Thompson RN, Armstrong CL, Heyburn G. Bilateral atypical femoral fractures in a patient prescribed denosumab - a case report. Bone 2014;61:44–7.

[7] Giusti A, Hamdy NA, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. Bone 2011;48:966–71.

[8] Lo JC, Huang SY, Lee GA, Khandelwal S, Provus J, Ettinger B, et al. Clinical correlates of atypical femoral fracture. Bone 2012;51:181–4.

[9] Adler RA. Duration of anti-resorptive therapy for osteoporosis. Endocrine 2016;51:222–4.

[10] Taormina DP, Marcano AI, Karia R, Egol KA, Tejwani NC. Symptomatic atypical femoral fractures are related to underlying hip geometry. Bone 2014;63:1–6.

[11] Oh Y, Fujita K, Wakabayashi Y, Kurosa Y, Okawa A. Location of atypical femoral fracture can be determined by tensile stress distribution influenced by femoral bowing and neck-shaft angle: a CT-based nonlinear finite element analysis model for the assessment of femoral shaft loading stress. Injury 2017;48:2736–43.

[12] Oh Y, Wakabayashi Y, Kurosa Y, Fujita K, Okawa A. Potential pathogenic mechanism for stress fractures of the bowed femoral shaft in the elderly: mechanical analysis by the CT-based finite element method. Injury 2014;45:1764–71.

[13] Oh Y, Wakabayashi Y, Kurosa Y, Ishizuki M, Okawa A. Stress fracture of the bowed femoral shaft is another cause of atypical femoral fracture in elderly Japanese: a case series. J Orthop Sci 2014;19:579–86.

[14] Kim JW, Kim JJ, Byun YS, Shon OJ, Oh HK, Park KC, et al. Factors affecting fracture location in atypical femoral fractures: a cross-sectional study with 147 patients. Injury 2017;48:1570–4.

[15] Schilcher J. High revision rate but good healing capacity of atypical femoral fractures. A comparison with common shaft fractures. Injury 2015;46:2468–73.

[16] Oh Y, Wakabayashi Y, Kurosa Y, Fujita K, Okawa A. Validation of locational classification for atypical femoral fracture (in Japanese). Kossetsu (Journal of Japanese Society for Fracture Repair) 2018;40:6–9.

[17] Bessho M, Ohnishi I, Matsumoto T, Ohashi S, Matsuyama J, Tobita K, et al. Prediction of proximal femur strength using a CT-based nonlinear finite element method: differences in predicted fracture load and site with changing load and boundary conditions. Bone 2009;45:226–31.

[18] Keyak JH, Rossi SA, Jones KA, Skinner HB. Prediction of femoral fracture load using automated finite element modeling. J Biomech 1998;31:125–33.

[19] Cody DD, Gross GJ, Hou FJ, Spencer HJ, Goldstein SA, Fyhrie DP. Femoral strength is better predicted by finite element models than QCT and DXA. J Biomech 1999;32:1013–20.

[20] Bessho M, Ohnishi I, Matsuyama J, Matsumoto T, Imai K, Nakamura K. Prediction of strength and strain of the proximal femur by a CT-based finite element method. J Biomech 2007;40:1745–53.

[21] Kaneko M, Ohnishi I, Matsumoto T, Ohashi S, Bessho M, Hayashi N, et al. Prediction of proximal femur strength by a quantitative computed tomography-based finite element method: creation of predicted strength data of the proximal femur according to age range in a normal population. Mod Rheumatol 2016;26:151–5.

[22] Soen S, Fukunaga M, Sugimoto T, Sone T, Fujiwara S, Endo N, et al. Diagnostic criteria for primary osteoporosis: year 2012 revision. J Bone Miner Metab 2013;31:247–57.

[23] Pentecost RL, Murray RA, Brindley HH. Fatigue, insufficiency, and pathologic fractures. JAMA 1964;187:1001–4.

[24] Devas M. Stress fractures of the femur. Stress fractures. Edinburgh: Churchill Livingstone; 1975. p. 107–29.

[25] Schilcher J, Howe TS, Png MA, Aspenberg P, Koh JS. Atypical fractures are mainly subtrochanteric in Singapore and diaphyseal in Sweden: a cross-sectional study. J Bone Miner Res 2015;30:2127–32.

[26] Hagino H, Endo N, Yamamoto T, Harada A, Iwamoto J, Kondo N, et al. Treatment status and radiographic features of patients with atypical femoral fractures. J Orthop Sci 2018;23:316–20.

[27] Oh Y, Fujita K, Wakabayashi Y, Kurosa Y, Okawa A. Characteristics of patients at high risk of femoral neck fractures associated with atypical femoral fractures (in Japanese). J Eastern Japan Assoc Orthop Traumatol 2018;30:48–51, doi: http://dx.doi.org/10.24645/jejot.30.1_48.

[28] Chen LP, Chang TK, Huang TY, Kwok TG, Lu YC. The correlation between lateral bowing angle of the femur and the location of atypical femur fractures. Calcif Tissue Int 2014;95:240–7.

[29] Yoo H, Cho Y, Park Y, Ha S. Lateral femoral bowing and the location of atypical femoral fractures. Hip Pelvis 2017;29:127–32.

[30] Maratt J, Schilling PL, Holcombe S, Dougherty R, Murphy R, Wang SC, et al. Variation in the femoral bow: a novel high-throughput analysis of 3922 femurs on cross-sectional imaging. J Orthop Trauma 2014;28:6–9.

[31] Martelli S, Pivonka P, Ebeling PR. Femoral shaft strains during daily activities: implications for atypical femoral fractures. Clin Biomech (Bristol, Avon) 2014;29:869–76.

[32] Haider IT, Schneider P, Michalski A, Edwards WB. Influence of geometry on proximal femoral shaft strains: implications for atypical femoral fracture. Bone 2018;110:295–303.

[33] Taddei F, Falcinelli C, Balistreri L, Henys P, Baruffaldi F, Sigurdsson S, et al. Left-right differences in the proximal femur's strength of post-menopausal women: a multicentric finite element study. Osteoporos Int 2016;27:1519–28.