European Journal of Medical Research

RESEARCH

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Long-term bisphosphonate use and femoral morphological changes in osteoporosis patients: a retrospective cohort study

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Abstract

Objectives We examined the association between long-term bisphosphonates use and morphological change in the femur.

Methods 140 patients (97.1% female, 70.8 ± 8.7 years) with over 5-year BP use (8.1 ± 2.4 years) were matched 1:1 for age (± 3), same BMD status with patients as a control group. The primary outcome was femoral lateral bowing (FLB). The hip–knee–shaft angle (HKSA) and femoral neck shaft angle (FNSA) were secondary outcomes.

Results Compared with the Control group, the femoral lateral bowing and hip–knee–shaft angle (5.9 ± 4.3° vs. 3.7 ± 1.7°; 6.6 ± 2.6° vs. 5.1 ± 1.5°, respectively) were significantly larger, while the femoral neck shaft angle was significantly lower (128.1 ± 3.4° vs. 129.3 ± 2.5°) in the BP group. The correlation analysis shows there is a positive correlation between the BP therapy time and FLB ($r = 0.2566$, $P < 0.01$), HKSA ($r = 0.1353$, $P = 0.1325$), while negative correlation between the BP therapy time and FNSA ($r = -0.1637$, $P = 0.0681$) without significance, indicating that the longer BP therapy, the larger the lateral bowing of the femur.

Conclusions Patients who took bisphosphonates over 5 years have a larger femoral lateral bowing, hip–knee–shaft angle and a smaller femoral neck shaft angle than control patients.

Introduction

Antiresorptives such as bisphosphonates (BP) are commonly used osteoporosis treatments that are effective in preventing osteoporotic fractures by suppressing bone turnover [1]. Although bisphosphonates are effective in reducing hip and osteoporotic fractures, their long-term use is reported to be associated with atypical femoral fracture (AFF), a rare potential side effect [1]; incidence increasing from three to more than 50 cases per 100,000 person-years between 1 and 10 years of exposure [2]. Macroscale femoral geometry is considered as one of the potential contributors to AFF risk, because the whole bone geometry influences the stresses and strains generated in the femur under loading. AFF patients were found to have larger lateral bowing angle than patients with no fracture history (mean: 3.2°vs. 0.8°) [3]. Yoon et al.

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reported incomplete diaphyseal AFF is associated with increased anterolateral bowing [4]. Jang et al. reported that AFF patients had larger anterior (mean: 12.39° vs. 3.97°) and lateral (mean: 15.71°vs. 10.72°) bowing angles [5]. These retrospective case–control studies highlight potential femoral geometrical features that may increase AFF risk. However, no studies have answered whether bisphosphonate usage influences femoral geometry.

Bone modeling and bone remodeling are two different processes related to the physiological metabolism of the human skeleton. In the skeletal lexicon, "modeling" means sculpting or shaping gross architecture. After birth it establishes the transverse and longitudinal macrogeometry, except for features due to cartilage phenomena, such as the length of most bones and epiphyseal, articular, and apophyseal size and shape [6]. The architectural activities and effects of bone modeling occur primarily during growth. Since Hattner et al. first reported bone modeling phenomenon at 1965, most literature has suggested that the osteogenic and osteoclastic activities that cause bone modeling usually ceases when the bone matures, as we only see strong bone shaping ability in angulated long bone malunions in children. However, studies have shown that bone modeling can occur throughout life and is not only active during infancy and early childhood [7, 8]. Studies have shown some bone medication can have a significant effect on the process of bone modeling. Ma et al. reported that teriparatide increases bone formation both in modeling and remodeling osteons in postmenopausal women with osteoporosis [9]. Denosumab also shows the ability to contribute to continuous bone mineral density (BMD) gains by modeling-based bone formation histologically during adulthood [10, 11]. In clinical practice, we observed that patients with atypical femur fracture seem to have a bigger femur lateral bowing and more varus alignment in standing radiographs of the lower limbs. Based on the theory that bone modeling can be persistent throughout human life, we asked if long-term usage of bisphosphonate changes femoral geometrical features.

Materials and methods

Study design

To investigate if long-term use of bisphosphonate increases femoral lateral bowing, we conducted a retrospective cohort study. The data used were gathered from electronic health records including standing radiographs of the lower limbs, age, gender, height, weight, bone mineral density (BMD) and bisphosphonates use in the Second Affiliated Hospital of Zhejiang University School of Medicine. Figure 1 shows the flowchart of the study. First, the Information Technology Department screened 40,000 standing radiographs of the lower limbs from our hospital from 2020 to 2024. Among 40,000 cases, 162 patients have a history of over 5-year BP treatment history. 22 cases were excluded because of non-standard lower limbs X-ray (16), rheumatoid arthritis (4), tumor of the femur (1), and congenital anomalies of lower extremity (1). X-rays with extreme rotation of the femur were defined as non-standard and, therefore, excluded. For the control group (non-users of BPs), a total of 832 patients with lower limbs X-ray in August 2023 were placed into the age–sex list. Then the control patients were randomly selected and purposely selected to match the age, sex, and BMD status of treatment group on a 1:1 basis, by sex and age (± 3 years). If no corresponding BMD was available, another patient was randomly selected from the matched age–sex list. Control patients with diagnoses of non-standard lower limbs X-ray or other metabolic bone disorders were also excluded. The study was approved by the institutional review board at the Second Affiliated Hospital of Zhejiang University School of Medicine. Based on the results of a clinical study [12], we predicted a difference of 5 degrees in femoral lateral bowing between groups, each group will need to contain 40 patients to achieve a power of 80%, with an α value of 5% and standard deviation of 2.2 at least.

Data collection

Baseline characteristics of patients were recorded, including age, gender, body mass index (BMI), as well as characteristics of BMD by dual-energy X-ray absorptiometry (DXA), BP treatment (type of drugs, duration before baseline). The primary outcome was femoral lateral bowing (FLB), femoral neck shaft angle (FNSA), hip–knee–shaft angle (HKSA) from frontal plane in standing radiographs of the lower limbs [3]. The angles were measured manually using PACS software by two orthopedic surgeons that were blinded. The average of two measurements provided the final figure. Figure 2 shows the geometric parameters of the femur and definitions. In addition, the quality of standing radiographs should be carefully evaluated, since the geometric parameters on the femur coronal plane can be easily affected by internal or external rotation. The degree of femur rotation of both groups is semi-quantified and compared statistically as baseline. The neutral position of femur is defined "NE", while mild internal and external rotation are defined "IN" and "EX", respectively (Fig. 3). Figure 3 shows five different positions of femur (note that X-rays with extreme femur rotation are not included in the study). Overall, the rotation of femur is judged by the outline of greater trochanter. The greater the external rotation angle of the femur, the greater the trochanter [13, 14]. BMD by DXA was extracted from the closest examination to standing radiographs of the lower limbs. Osteoporotic status was

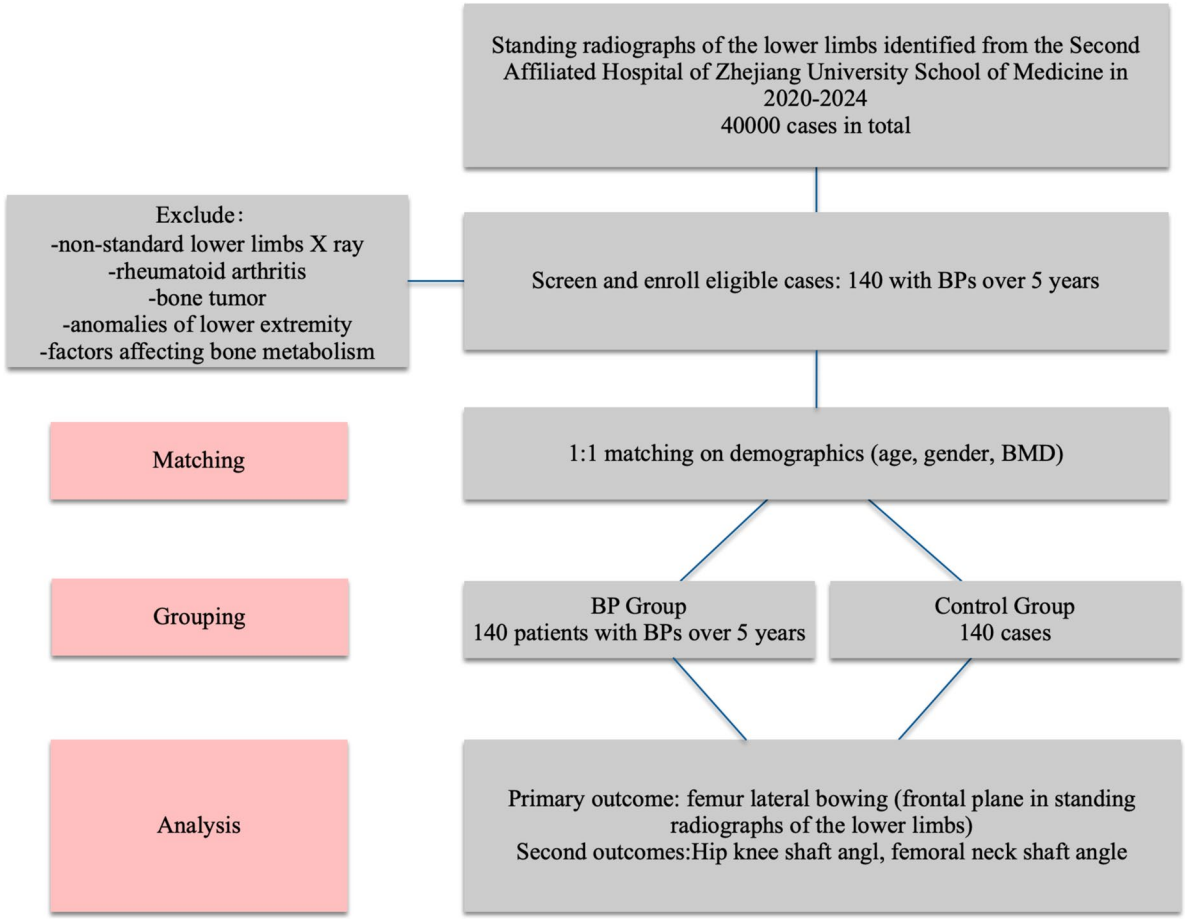

Fig. 1 Radiographs with different degree of femur rotation. X-rays with extreme internal/external rotation of femur are defined non-standard lower limbs photographs and not included in this study. The rotation of femur is judged by the outline of greater trochanter. The greater the external rotation angle of the femur, the greater the trochanter

defined as a T-score ≤ -2.5 SD at least at one site among lumbar spine, femoral neck, and total hip; osteopenia as at least one T-score between -1 and -2.5 SD with none ≤ -2.5 SD at the lumbar spine, total hip, or femoral neck; normal BMD as T-score over -1 [15].

Statistical analysis

Baseline characteristics were compared between groups with chi-square test for categorical variables and a Mann–Whitney test for continuous variables. Comparisons between means were assessed with a Student's *t* test. Spearman's correlation coefficient was used to examine the correlation between the geometric parameters of femur and duration of BP therapy. Statistical analyses were performed using SPSS software (version 20.0; IBM, Armonk, NY, USA). All tests were two-tailed and *P* values < 0.05 were considered significant.

Results

Among 40,000 patients, 162 cases were identified with over 5-year BP history between January 2020 and January 2024. 140 cases were included in this study. The main reason for exclusion is non-standard lower limbs X-ray (16), rheumatoid arthritis (4), tumor of femur (1), congenital anomalies of lower extremity (1). Patients were mostly women (97.1%), and mean age was 70.8 years (range, 55–85 years) (Table 1). 85% patients received Sodium Alendronate tablets and 15% patients received injection of Zoledronic acid. The mean duration of BP treatment in treated patients was 8.1 ± 2.4 years (range, 5 years to 13 years). BP therapies were all given for osteoporosis and the prevention of fragility fractures. The baseline characteristics of patients in the BP group and Control group are reported in Table 2. There was no difference in the degree of femur rotation between two groups.

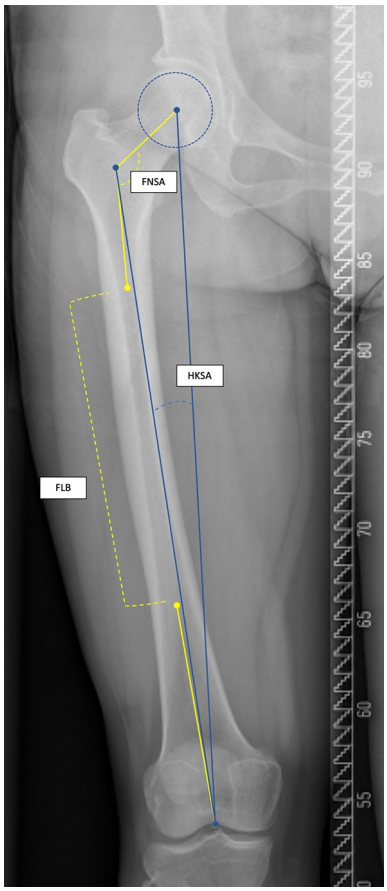

Fig. 2 Femur geometrical parameters on X-ray. Femoral lateral bowing: angle between axes of 20% proximal and distal sections of femur diaphysis; Femoral neck shaft angle: angle between the femoral neck axis and mechanical axis of the femur. Hip–knee–shaft angle: angle between mechanical and anatomical femoral axes

The mean femur lateral bowing and hip–knee–shaft angle were 5.9° ± 4.3° (range, 0.301° to 21.459°), 6.6° ± 2.6° (range, 1.433° to 17.572°) in the BP group, respectively, which are significant more than 3.7° ± 1.7° (range, 0.219° to 9.728°), 5.1° ± 1.5° (range, 0.112° to 11.556°) in the Control group (both $P < 0.001$). The mean femoral neck shaft angle was 128.1° ± 3.4° (range, 120.083° to 141.819°) significantly less in the BP group compared with 129.3° ± 2.5° (range, 121.048° to 137.696°) in the Control group ($P < 0.01$). The geometric parameter of femur of patients are reported in Table 2. Figure 4 shows the representative lower limbs X-ray of BP users and control patients. To further eliminate the bias of femoral rotation, a subgroup analysis with only neutral position of femur in each group was carried out. Among 140 cases in each group, 89 BP cases are included, while 76 Control cases are included with neutral position (NE) of femur. The mean femur lateral bowing and hip–knee–shaft angle was 6.0° ± 4.2°, 6.5° ± 2.5° in the BP–NE group, respectively, which was significantly larger than 3.2° ± 1.7°, 5.0° ± 1.5° in the Control–NE group (both $P < 0.001$). The mean femoral neck shaft angle was 128.2° ± 3.3° in the BP–NE group, while 129.1° ± 2.8°in the Control–NE group ($P = 0.0511$) as shown in Table 3.

To further examine the effect of BP treatment for morphological change of femur, the correlations between duration of BP treatment and geometric parameters were examined using Spearman's rank correlation coefficients. There is a weak positive correlation between the BP therapy time and FLB ($r = 0.2566$, $P < 0.01$), HKSA ($r = 0.1353$, $P = 0.1325$), as shown in Fig. 5A, B. A weak negative correlation is found between the BP therapy time and FNSA ($r = -0.1637$, $P = 0.0681$) with no significance, as shown in Fig. 5C.

Discussion

To our knowledge, this is the first study that shows that the morphological change in the femur is associated with long-term BPs exposure. This study provides macroscopic evidence that bone modeling plays a role in the adult skeleton. In addition, with previous reports, our results give a clue to the mechanism of AFF. There are several reasons we chose the femur as the object of this study. First, the femur is one of the main load bearing bone of lower limbs. Second, different to the straight tibia, the mechanical and anatomical femoral axes of femur are malaligned which results in more deforming forces on load bearing. Here we report long-term BP treatment increases femoral lateral bowing, hip–knee–shaft angle and decreases femoral neck shaft angle. The longer BP therapy lasts, the bigger lateral bowing in the femur are.

Bisphosphonates, a class of antiresorptive drugs that inhibit osteoclastic bones resorption, are widely used to prevent osteoporotic fractures and treat osteoporosis and other bone diseases [16, 17]. The successful application of BP originates from their high affinity to hydroxyapatite. At the cellular level, the mechanism of action of BPs is based on the inhibition of bone resorption by their selective binding and adsorption on the bone mineral surface. After BPs are internalized by bone-resorbing cells (osteoclasts), they interfere with the biochemical processes of these cells, inducing their apoptosis [18]. Although the therapeutic activity of BPs depends mainly upon their inhibitory effect on osteoclasts, increasing attention is paid to their effect on other bone cells, such as osteoblasts and osteocytes [19]. Because the half-life period of BPs could be years, BPs can have very long-lasting effects in reducing bone turnover which arises the concerns of side effects such as increased microdamage [20].

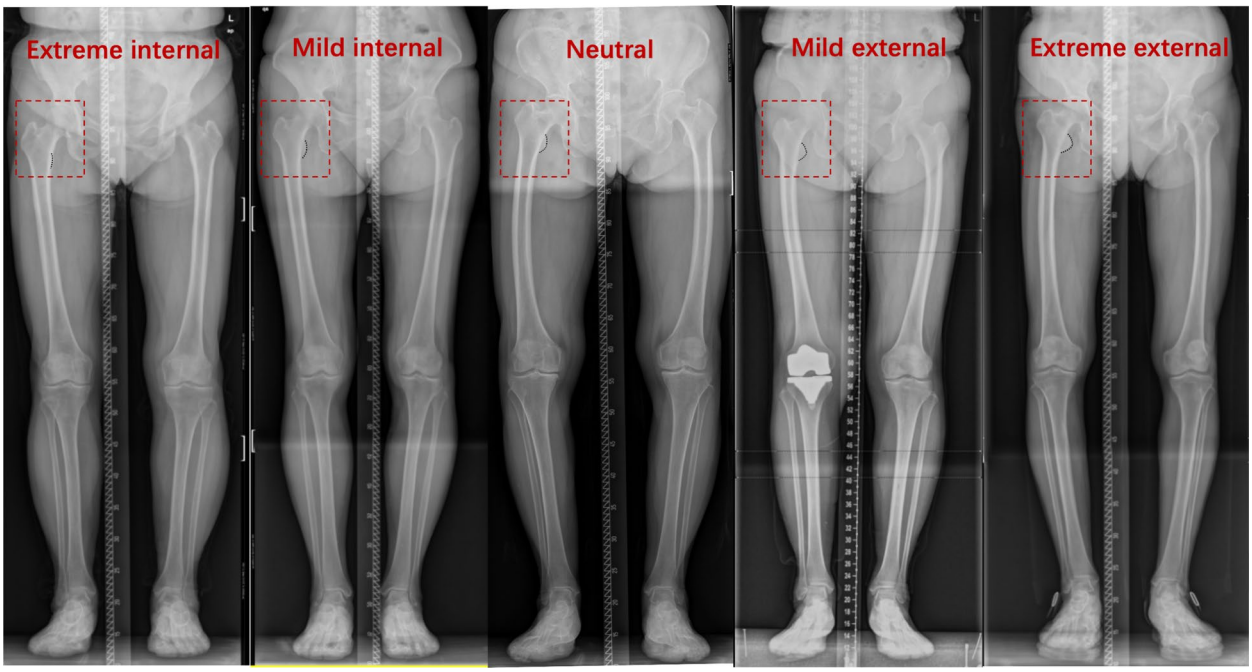

Fig. 3 Flowchart of the study

Table 1 Baseline characteristics

Characteristics	BP ($n=140$)	Control ($n=140$)	*P*	
Gender (women), (%)	97.1	97.1		1.000
Age (years), mean ± SD	70.8 ± 8.7	69.6 ± 5.8		0.817
Weight (kg), mean ± SD	61.8 ± 7.5	60.17 ± 7.3		0.0576
Height (cm), mean ± SD	161.6 ± 7.8	160.1 ± 6.5		0.0943
Body mass index (kg/m^2), mean ± SD	23.7 ± 2.8	23.23 ± 2.6		0.3673
BP therapy time (years), mean ± SD	8.1 ± 2.4	0		< 0.0001
Types of bisphosphonates				
Alendronate Sodium (%)	85	/		/
Zoledronic acid (%)	15	/		/
Osteoporotic status on DXA				1
Normal BMD (%)	12.9	12.9		/
Osteopenia (%)	35.7	35.7		/
Osteoporosis (%)	51.4	51.4		/
Rotation of femur				0.2819
Neutral position (%)	63.6	54.3		
Internal rotation (%)	13.5	17.9		
External rotation (%)	22.9	27.8		

Osteoporosis defined as at least one T-score ≤ – 2.5 SD and osteopenia as at least one T-score between -1 and -2.5 SD with none ≤ – 2.5 SD at the lumbar spine, total hip, or femoral neck

BP bisphosphonate, *BMD* bone mineral density, *DXA* dual energy X-ray absorptiometry, *SD* standard deviation

Although BP treatments reduce fracture risk, their long-term use has been associated with atypical femoral fracture (AFF), a rare potential side effect. AFFs are rare insufficiency fractures of the subtrochanteric or diaphyseal region of the femur, which occur in a number of metabolic bone disorders but are mainly recognized as a

Table 2 Geometric parameter of femur in patients

Geometric parameter	BP ($n=140$)	Control ($n=140$)	*P*
FLB (°), mean ± SD	5.9 ± 4.3	3.7 ± 1.7	< 0.001
HKSA (°), mean ± SD	6.6 ± 2.6	5.1 ± 1.5	< 0.001
FNSA (°), mean ± SD	128.1 ± 3.4	129.3 ± 2.5	0.0028

FLB femoral lateral bowing, *HKSA* hip–knee–shaft angle, *FNSA* femoral neck shaft angle;

long-term complication in BP users. The long-term use of BPs is typically defined as more than 5 years. A recent study has shown that although overall AFF occurrence was 1.74 fractures per 10,000 person-years for women over 50 years of age, the incidence rate increased from 0.07/10,000 person-years for BP treatment duration less than 3 months to 13.10/10,000 person-years with 8 or more years of BP use. The AFF incidence reduced rapidly with BP discontinuation [21]. However, the molecular and biomechanical mechanism is still not clear.

Studies show that lateral bowing angle had an impact on the location of the AFF. Patients with higher lateral bowing angle experienced diaphyseal AFF, whereas patients with lower lateral bowing angles experienced subtrochanteric AFF (diaphyseal vs. subtrochanteric mean: $>7°$ vs. $\leq 7°$; 7.8° vs. 1.6°; −4.3° vs. −0.9°, respectively) [3, 22]. Several studies also found that AFF patients have smaller femoral neck shaft angle compared to both non-fracture (mean: 129.5° vs. 133.8°; 126.4° vs. 130.3°,

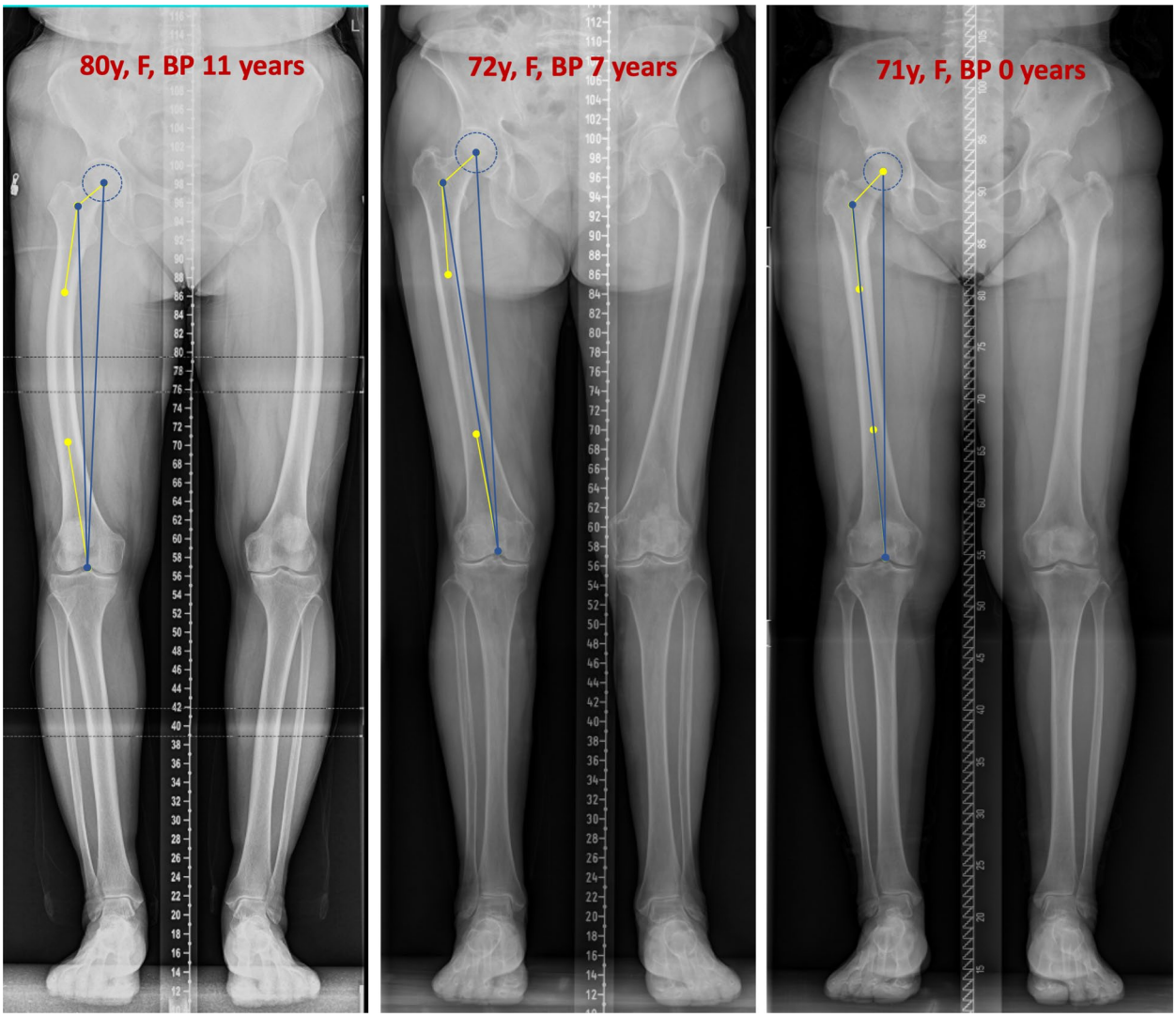

Fig. 4 Representative lower limbs X-ray of BP users and control patients. Left: an 80-year-old woman who took alendronate sodium tablets for 11 years to prevent fragility fracture. Middle: a 72-year-old woman who took alendronate sodium tablets for 7 years to prevent fragility fracture; right: a 71-year-old woman receive lower limbs X-ray in outpatient due to joint pain

Table 3 Geometric parameter in patients with neutral position (NE) of femur

Geometric parameter	BP–NE ($n=89$)	Control–NE ($n=76$)	*P*
FLB (°), mean ± SD	6.0 ± 4.2	3.2 ± 1.7	< 0.001
HKSA (°), mean ± SD	6.5 ± 2.5	5.0 ± 1.5	< 0.001
FNSA (°), mean ± SD	128.2 ± 3.3	129.1 ± 2.8	0.0511

NE neutral position, *FLB* femoral lateral bowing, *HKSA* hip–knee–shaft angle, *FNSA* femoral neck shaft angle

respectively) [23, 24]. The increasing lateral bowing in mid-shaft leads to elevated levels of stress at the lateral femoral cortex [25]. However, whether the long-term BP treatment contributes to the deformation is not clear according to previous studies. To address these issues, we designed this trial and found long-term use of bisphosphonates is associated with femur deformation. According to this study, the mean femur lateral bowing and hip–knee–shaft angle differs by ~ 2.2° and ~ 1.5°, respectively, between the BP group and control group. The mechanical mechanisms through which femoral geometry may impact AFF were only investigated in a limited number of computational studies. A finite element study based on computed tomography images from AFF and non-fracture patients demonstrated elevated levels of stress at the lateral femoral cortex with increasing lateral bowing in mid-shaft AFF patients (mean lateral bowing angle: 7.2° vs. 1.3°; 6° vs. 1.4°, respectively). Elevated stress levels were also reported in sub-trochanteric AFF patients with smaller neck–shaft angle compared to that of nonfracture controls (mean: 125.8° vs. 131.8°) [12]. However, the quantitative relationship between the FLB and the mechanical load still requires further study as far as we know.

The physiological metabolism of the human skeleton includes two different approaches: bone modeling and bone remodeling; both involve bone formation and bone resorption, but they are very different. Bone modeling includes osteoblasts in formation drifts and osteoclasts in resorption drifts, where osteoblasts and osteoclasts are independent of each other but intrinsically coordinated, contributing to changes in bone morphology and structure ultimately. Bone remodeling is a process in which osteoblasts and osteoclasts are closely coupled, resulting in a dynamic balance or imbalance between bone formation and bone resorption, mostly in the form of normal maintenance or gradual reduction of bone mineral mass [26]. Previous literature has suggested that the osteogenic and osteoclastic activities that cause bone modeling usually cease (or end) when the bone matures, but recent studies have shown that bone modeling can occur throughout life and is not only active during infancy and early childhood [8]. In the context of osteoporosis, some bone medications can have a significant effect on the process of bone modeling, suggesting a significance of bone modeling in increasing bone mass [10]. The impact of bisphosphonates on bone modeling—a distinct process from remodeling—warrants closer examination. Long-term bisphosphonate use has raised concerns about over suppression of bone turnover, which may impair the bone's ability to adapt to stress and repair microcracks, increasing susceptibility to fractures. By reducing resorption-induced microdamage, BPs may diminish the stimulus for modeling-driven repair, potentially leading to cumulative damage/deformation over time. Studies have shown that BP-treated cancellous bone from fracture patients had more microfractures than both untreated typical fractures and nonfracture controls (both human femoral head cancellous bone) [27, 28]. Several other studies in large animal models investigated the influence of BPs on microdamage accumulation. Prolonged BP treatment (both canine rib cortical bone) [29, 30] and high dose of BP treatment was shown to increase microfracture density [31]. Reduced remodeling due to BP treatment may impact microfracture repair, therefore, increasing microfracture density. However, there is no conclusive evidence

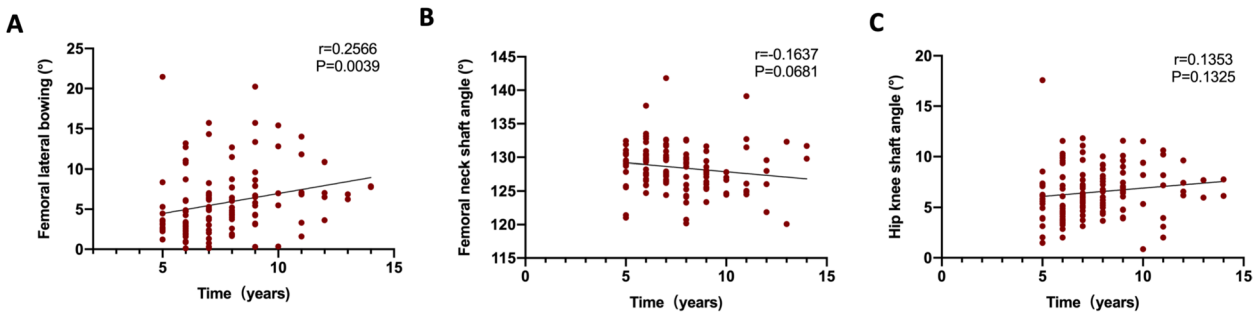

Fig. 5 Association between the geometric parameters of femur and the duration of BP therapy. Relationships between the time of BP therapy and femoral lateral bowing (**A**) and femoral neck shaft angle (**B**) and hip–knee–shaft angle (**C**)

on whether occurrence of AFF is related to a potential increase in microcrack density with BP treatment. As hypothesized previously in the literature, progression of a single microcrack may be sufficient for AFF without the existence of many microcracks in the bone tissue [32]. Despite bone bowing deformation occurs due to bone metabolism, it's hard to ignore the biomechanical mechanisms. Clinical evidence suggests that coronal/sagittal spinal malalignment (e.g., scoliosis or kyphosis), vertebral compression fractures or joint pain can significantly alter lower limb biomechanical loading by redistributing trunk weight-bearing patterns [33]. Such conditions often lead to compensatory gait adjustments (e.g., trunk tilting or reduced stride length), potentially increasing asymmetric stress on the femoral lateral cortex.

We recognize the limitations of this study including the retrospective design and selection bias in our population, and sample size. The use of a case control methodology was used to negate this. Future prospective studies might be helpful to confirm our findings. Second, although the rotation of femur is not significantly different between two groups by our semi-quantitative method, we still cannot deny possible bias without strict calibration. Further research based on CT database might be more accurate. Third, while we rigorously matched participants for age, sex, and BMD status—factors most strongly associated with bone metabolism in prior literature [34], comorbidities (e.g., diabetes, rheumatoid arthritis), and nutritional supplementation (vitamin D/calcium) could influence outcomes. For instance, reduced physical activity may independently induce bone loss through catabolic metabolism [35]. Comorbid conditions like diabetes could also alter bone microarchitecture [36]. Regional variations in vitamin D supplementation practices at our tertiary center may limit generalizability to populations with different nutritional profiles [37].

Finally, this study does not investigate the clinical significance of the morphological change of femur in the study group. It is still not clear the morphological change of femur is directly related to increasing risk of atypical femoral fractures. The modeling status of BP users still needs to be evaluated with biopsy and histological examination at a microscopic level, while this study has shown that there is a change in femoral geometry at the macro level. Though further research is needed, this study suggest that morphological changes in the femur could be effective predictors of AFFs.

In conclusion, patients who took bisphosphonates for more than 5 years had increased femoral lateral bowing, increased hip–knee–shaft angle and a smaller femoral neck shaft angle than non-treatment patients. This study suggests that BPs may influence bone modeling in adults and thereby altering the mechanical environment by increasing stress at the lateral femoral cortex which may be a factor in development of AFF.

Author contributions

JXZ designed the study. JXZ analyzed the data and wrote the manuscript. LFJ participated in the study design, data analysis, editing and review of the manuscript. RM, GWL, LFJ contributed to editing and review of the manuscript. CCS, DHL, JPB were responsible for collecting, sorting and statistical data. LFJ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Funding

This study was funded by The National Natural Science Foundation of China (81871793).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board at the Second Affiliated Hospital of Zhejiang University School of Medicine. The requirement for informed consent was waived because of the retrospective nature of the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

All the authors consented for publication.

Competing interests

The authors declare no competing interests.

Received: 20 March 2025 Accepted: 4 June 2025
Published online: 01 July 2025

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