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Lack of periosteal apposition in the head and neck of femur after menopause in Chinese women with high risk for hip fractures — A cross-sectional study with QCT

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ABSTRACT

In elderly subjects and in particular in those with osteoporosis the evidence on age related volume changes of the hip is still very limited. Even less is known about bone changes of the femoral head. The aim of this study is to explore associations of bone size of the femoral head and neck with age in postmenopausal women with very high risk of hip fracture and to investigate associations of femoral head and neck bone mineral density. MIAF (medical image analysis framework)-Femur was used for the analysis of CT datasets from 319 females with acute hip fractures age 50 to 98. Integral BMD and volume of the head and neck were assessed. The femoral head was divided into four quadrants to address differential vBMD and volume responses of its superior, inferior, posterior and anterior parts. Areal BMD (aBMD) of femoral neck was also obtained. In this population of postmenopausal women we did not observe age-related changes in bone volume of the femoral head or neck between ages 50 and 98 years. Integral vBMD in the head in the 90–98 year group was 48.0 mg/cm^3 lower than that in 50–59 year group, which accounts for nearly 30% decrease in vBMD with 40 years increase. Age-related vBMD changes in the head quadrants were similar to that in total. With age, the trend line correlation coefficients for vBMD in quadrants were relatively small, but significant ($p < 0.001$) for all. The femoral head integral vBMD correlates well with neck vBMD and FN aBMD. FN aBMD explained 45% of head integral vBMD variance ($p < 0.0001$). Elderly women had relative preservation of femoral head and neck bone volume from 50 yrs. over four decades but markedly lower integral vBMD of proximal femur. The findings of our study call in question about the concept of bone expansion with aging even in elderly age.

1. Introduction

Hip fractures increase exponentially with age, causing severe disability and high mortality [1]. Decrease in bone mineral density (BMD) is the major cause but changes in bone geometry such as cortical thinning have also been identified as risk factors for hip fractures. In addition, several studies demonstrated expansion of the femoral neck and trochanter caused by periosteal apposition with increasing age [2–8]. Periosteal apposition can at least partly compensate for a decrease of bone strength caused by a decrease in BMD and cortical thickness. Thus increasing periosteal apposition with increasing age would be an important mechanism to slow the decrease of fracture resistance [9]. Several studies reported age related increases of bone size at different skeletal sites [10–15] but results were not always significant [16] and the amount of periosteal apposition varied with skeletal site, age and sex [14,16–18]. In women, periosteal apposition ceases after menopause [19].

In elderly subjects and in particular in those with osteoporosis the evidence on age related volume changes of the hip is still very limited. Interestingly, even less is known about bone changes of the femoral

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head. Several in vitro studies explored the microarchitecture and bone density of the femoral head by using microCT or HR-pQCT [20–22], but in vivo only a 3D based QCT analysis can provide such information. MIAF-Femur (MIAF: medical image analysis framework, University of Erlangen) is based on 3-dimensional segmentation of the whole proximal femur, which allows for assessments of the femoral head in vivo. In the European Femur Fracture Study (EFFECT) the integral femoral head BMD discriminated acute hip fractures [23]. Poor femoral head bone quality may also be an important cause of failure of head screw implants. Therefore, data on femoral head bone loss and size changes with age are important.

The aims of this cross-sectional study were to: 1. explore associations of bone size of the femoral head and neck with age in postmenopausal women with very high risk of hip fracture; 2. investigate associations of femoral head and neck bone mineral density. Both aims were addressed using CT scans of elderly Chinese women with acute hip fracture. As CT scans were taken within 48 h after fracture, for the purpose of this study we assumed that these subjects had a very high hip fracture risk.

2. Materials and methods

2.1. Participants

468 Chinese female participants with acute hip fracture were recruited between January 2012 and May 2016 from the Chinese Second Hip Fracture Evaluation (CSHFE), Clinical Trials.gov Identifier: NCT03461237. CSHFE is a longitudinal study to evaluate the risk of a second hip fracture in patients with previous hip fracture and to evaluate the ability of QCT to predict a second hip fracture. In this study we only used the baseline data of CSHFE. Each participant had hip QCT within 48 h after the low-energy hip fracture (limited to falls when walking or standing). Informed consent was obtained from each patient. The exclusion criteria included: previous hip fracture(s); diseases leading to long-term limitation of activity such as paralysis, a poorly healed lower extremity fracture, hip dysplasia, avascular necrosis of the femoral head; painful diseases within the past 3 months such as acute pancreatitis, lumbar fracture; metabolic bone disease (other than senile osteoporosis or postmenopausal osteoporosis); inflammatory arthritis, such as rheumatoid arthritis; indications of bone tumor or tumor-like lesion(s) of the proximal femur, such as bone metastases, chondrosarcoma, or bone island; malignant tumors with the potential to metastasize to bone; treatments that could affect the metabolism of bone tissue; and medications known to affect bone metabolism (e.g., glucocorticoids). Of the 468 patients, 319 were available for QCT analysis. Institutional Review Board (IRB) approval was obtained from the ethics committee of Beijing Jishuitan Hospital.

2.2. QCT Scans

For patients with suspected or X-ray-proven hip fractures, the emergency service of the radiology department of this hospital included a routine hip CT imaging protocol using a 16-row detector CT scanner (Toshiba, Tokyo, Japan). The CT scanner was equipped with a Mindways QCT calibration phantom (Mindways Software Inc., Austin, TX, USA), which enabled the acquisition of hip CT scans according to QCT procedures. Both hips were scanned in the supine position from the top of the acetabulum to 3 cm below the lesser trochanter. The scan parameters were as follows: 120 kVp, 125 mAs, 1-mm thickness, 50-cm field of view (SFOV), and 512 × 512 matrix in spiral reconstruction and standard reconstruction (FC03).

2.3. CTXA measurements

CT images were analyzed using the CTXA hip function version 4.2.3 of Mindways QCT Pro software (Mindways Software Inc., Austin, TX, USA). After image segmentation and manipulation of proximal femur rotation, a two-dimensional projection image was generated from the three-dimensional CT dataset. Details of the procedure were described in a previous study [24]. CTXA was used to obtain the areal BMD (aBMD) of the contralateral normal femoral neck, which is equal to neck aBMD obtained from DXA [25].

2.4. MIAF measurements

CT images of the contralateral side were also analyzed by MIAF-Femur (Version 7.1.0MRH) with dedicated algorithms implemented. Standard VOIs obtained by MIAF-Femur are head, neck, trochanter, intertrochanter, and proximal shaft calculated relative to an anatomic coordinate system (ACS) with its origin centered at the smallest cross section of the neck. The borders between VOIs were determined automatically based on anatomical landmarks and the ACS. Each VOI was separated into integral (Intg), cortical (Cort), and trabecular (Trab) compartments for which vBMD and BMC and volume were determined. For femoral head, however, only integral vBMD, BMC and volume were measured. Furthermore, the femoral head can be divided into four quadrants to address differential vBMD and volume responses of its superior, inferior, posterior and anterior parts. Neck volume, neck vBMD and neck minimum cross-sectional area (Min-CSA) were measured with MIAF-Femur (Fig. 1). The details of proximal femur segmentation and analysis by MIAF Femur have been described previously [24,26]. Precision and accuracy results of MIAF-Femur have been published earlier [24,27].

2.5. Statistics

Continuous variables were described as mean ± standard deviation (SD). Linear regressions were used to compare bone and volume variables between head and neck. A generalized linear model (GLM) with adjustment for height and weight was used to compare changes in the femur head variables and other parameters between 50 and 90 years. Statistical analysis was performed using IBM SPSS Statistics for Windows version 20.0 (IBM SPSS Inc., Chicago, IL) and GraphPad Prism software for Windows version 6.0 (GraphPad Software, San Diego, Calif). Differences were considered significant at $p < 0.05$.

3. Results

3.1. Participants characteristics

319 participants with a mean age of 75.5 ± 9.6 years, a mean height of 158.2 ± 5.5 cm, and a mean weight of 58.4 ± 10.5 kg were eligible for further MIAF analysis and included in the study (Fig. S1). There were 191 femoral neck fractures and 128 trochanteric/intertrochanteric fractures. Among the 128 trochanteric/inter-trochanteric fractures three were combined with subtrochanteric fractures. 77 women had sustained other fractures before, 10 cases with lumbar vertebral fractures (only one had percutaneous vertebro plasty (PVP) treatment and others had conservative therapy), one case with multiple traumatic fractures caused in a traffic accident, one case with sacrum fracture and 64 cases with appendicular fractures. Only 13 women ever had received osteoporosis treatment while 31 cases had received calcium supplements and 15 cases calcium combined with Vit D supplements. Among the 5 age-groups stratified by age decades, the 70–79 years group had the largest number of participants. Also BMI of this decade was higher than in the other decades (Table 1). Table 1 shows characteristics of the 5 age-groups including unadjusted aBMD and vBMD results.

3.2. Volume

In this population of postmenopausal women we did not observe

Table 1
Characteristics of participants.

Age group	N	Age	Height(cm)	Weight(kg)	BMI	Head vBMD(mg/cm^3)	Neck vBMD(mg/cm^3)	FN aBMD (g/cm^2)
50–59	24	56 ± 2.8	160.7 ± 5.1	59.1 ± 10	22.9 ± 3.6	152.8 ± 25	228.8 ± 32.5	0.54 ± 0.07
60–69	58	64.8 ± 2.9	159.9 ± 5	59.7 ± 9.2	23.3 ± 3.1	138.3 ± 29.4	215.9 ± 37.7	0.52 ± 0.09
70–79	115	75.2 ± 2.6	158.4 ± 5.4	60.8 ± 10.1	24.1 ± 4.4	128.8 ± 28.1	205.3 ± 39.5	0.50 ± 0.09
80–89	106	83.5 ± 2.6	156.9 ± 5.3	55.3 ± 10.3	22.6 ± 4.1	115.4 ± 20.1	187.2 ± 36.2	0.44 ± 0.09
90–98	16	92.3 ± 2.3	154.3 ± 6.4	51 ± 11.1	21.3 ± 3.7	101 ± 31.7	158.1 ± 29.3	0.39 ± 0.05

BMI body mass index; *vBMD* volume bone mineral density; *FN aBMD* femoral neck areal BMD.

Table 2
Integral BMD, BMC and volume in the head and neck after adjustments for height and weight for the youngest and oldest group of the study cohort.

Variables	50–59 years	90–98 years	Dif.(%) *	p value
HeadvBMD(mg/cm^3)				
Quadrant SA	157.4 ± 36.6	113.5 ± 40.3	40.5(26%)	< 0.001
Quadrant IA	160 ± 25.9	99.1 ± 29.6	55.8(35%)	< 0.001
Quadrant IP	140.7 ± 22	88 ± 27.7	49.1(35%)	< 0.001
Quadrant SP	149.6 ± 25.1	105.3 ± 33.3	41.4(28%)	< 0.001
Head BMC(mg)				
Quadrant SA	1554.2 ± 466	968.9 ± 372.8	430.0(29%)	< 0.001
Quadrant IA	1638.1 ± 338.4	955.3 ± 275.4	527.0(33%)	< 0.001
Quadrant IP	1324.3 ± 328.3	870.5 ± 304.2	336.7(26%)	< 0.001
Quadrant SP	1383.8 ± 333.2	905.2 ± 346.6	344.3(26%)	< 0.001
Head volume(cm^3)				
Quadrant SA	9.8 ± 1.6	8.7 ± 2.0	0.2(2%)	0.739
Quadrant IA	10.3 ± 1.3	9.8 ± 1.8	−0.4(4%)	0.468
Quadrant IP	9.4 ± 1.9	9.9 ± 1.5	−1.2(13%)	0.025
Quadrant SP	9.2 ± 1.6	8.6 ± 1.6	−0.2(2%)	0.711
Other variables				
Head vBMD(mg/cm^3)	152.8 ± 25	101 ± 31.7	48.0(32%)	< 0.001
Head BMC(mg)	5900.5 ± 1114.5	3699.8 ± 1136.5	1637.9(29%)	< 0.001
Head Volume(cm^3)	38.7 ± 4.3	36.9 ± 4.9	−1.6(4%)	0.324
Neck vBMD(mg/cm^3)	228.8 ± 32.5	158.1 ± 29.3	69.5(30%)	< 0.001
Neck BMC(mg)	3849.4 ± 889	3163.7 ± 930.8	1198.8(32%)	< 0.001
Neck Volume(cm^3)	16.7 ± 2.6	14.6 ± 1.9	0.6(4%)	0.52
Neck Min-CSA(cm^2)	6.7 ± 0.8	6 ± 0.6	0.2(3%)	0.43
HV/NV	2.3 ± 0.3	2.6 ± 0.5	−0.2(9%)	0.1
FN aBMD(g/cm^2)	0.54 ± 0.07	0.39 ± 0.05	0.14(26%)	< 0.001

Dif. Difference; *SA* Supero-anterior; *IA* Infero-anterior; *IP* Infero-posterior; *SP* Supero-posterior; *CSA* Cross-sectional area; *BMC* Bone mineral content; *HV* Head volume; *NV* Neck volume.
* Adjusted for height and weight.

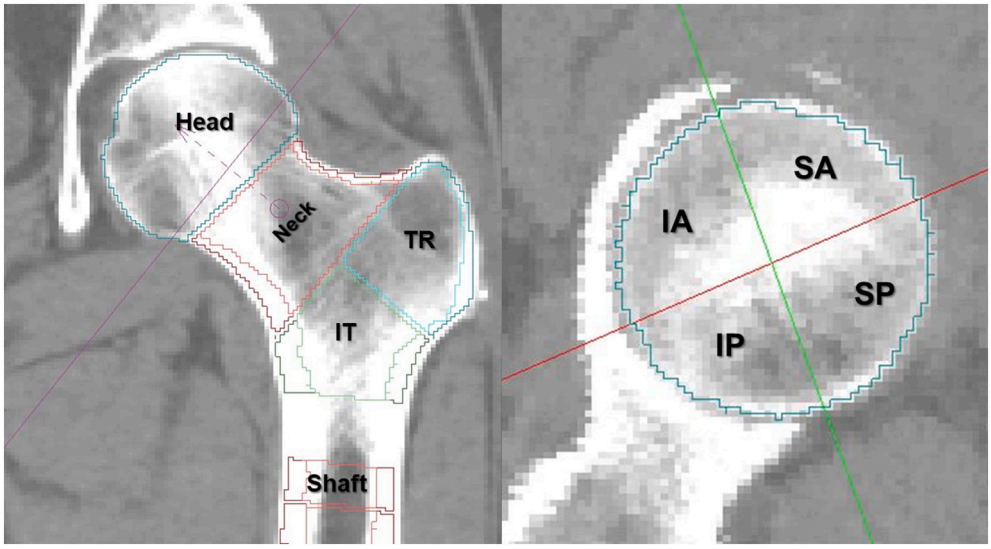

Fig. 1. Volumes of interest (VOIs) analyzed in the proximal femur by MIAF Femur(left). Axial view along with the neck axis showing anatomic quadrants of femoral head. TR Trochanter; IT Intertrochanter; *SA* Supero-anterior; *IA* Infero-anterior; *IP* Infero-posterior; *SP* Supero-posterior.

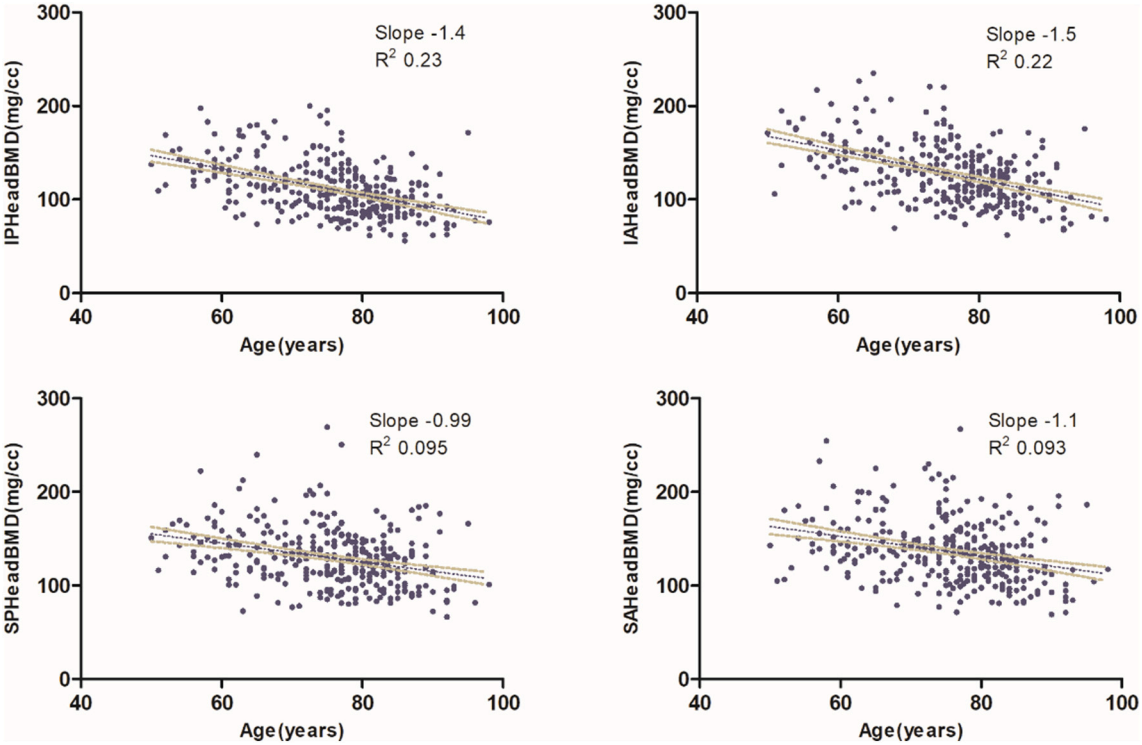

Fig. 2. Ager elated BMD decrease per quadrant of the femoral head. Slopes are given as BMD in mg/cm^3 change per year. All slopes were significant ($p < 0.001$).

age-related changes in bone volume of the femoral head or neck between ages 50 and 98 years (Table 2, Fig. 3). At 95 years, the unadjusted head and neck volume were lower than at 55 years, however, after adjustment for body size, age-related differences were no longer detected. Interestingly, volume of the IP quadrant of the head significantly decreased with age, although the combined volume of all 4 quadrants did not. The difference in IP volume between age 55 and age 95 was 1.2 cm^3 ($p = 0.025$). The adjusted min-CSA of femoral neck also did not change significantly between age 55 (6.56 cm^2) and 95 (6.35 cm^2) (See Fig.3).

3.3. BMD and BMC

Age and weight adjusted comparisons of integral BMD, BMC and volume of the head and neck between the youngest and oldest group of the study cohort are shown in Table 2. Integral head vBMD in the 90–98 year group was 48.0 mg/cm^3 about 30% of integral head vBMD in the 50–59 year group after adjustments for height and weight. Age-related vBMD changes in the individual quadrants of the head were similar. Age related decreases of vBMD varied from 1.0–1.5 mg/cm^3 per year (Fig. 2) and were significant for each quadrant but coefficients of correlation were quite low (Quadrant IA $R^2 = 0.23$, Quadrant IP $R^2 = 0.22$, Quadrant SA $R^2 = 0.095$, and Quadrant SP $R^2 = 0.094$, respectively). Differences among quadrants were statistically significant. BMD of the inferior quadrants of the femoral head was more strongly associated with age compared to BMD of the superior quadrants. Similar to BMD, BMC differences between age 55 and age 95 were of largest in the Quadrant IA. Similar to the integral head vBMD, neck vBMD in the 90–98 year group was 158.1 mg/cm^3 or about 30% of neck vBMD in the 50–59 year group after adjustment for height and weight. The age-related neck BMC difference between the two age groups was 32% after adjustment.

3.3.1. Comparisons of femoral head and neck bone

Integral vBMD of the head was lower than neck vBMD (Fig. 4, Table 2). However, age-related decreases of integral vBMD were similar in the femoral head and neck (Fig. 4). Fig. 4 also shows age-related changes in FN aBMD and head vBMD, with different corresponding trends between the two variables. The femoral head integral vBMD correlates well with neck vBMD and FN aBMD. FN aBMD explained 45% of head integral vBMD variance ($p < 0.0001$), and neck vBMD performed better in explaining the head integral vBMD variance (59%, $p < 0.0001$).

4. Discussion

This QCT study did not find periosteal apposition of the head or neck in women after menopause. This observation is consistent with Nicks' study in which almost all volume changes were non-significant in postmenopausal women [2]. Our study results also confirm findings of previous hip fracture discrimination studies that strength-related parameters like bone volume and cross-sectional area did not significantly improve hip fracture discrimination [28,29]. Thus, our data provides new insight into this important aspect of aging and suggests that in postmenopausal women increasing hip fracture risk with aging is caused by lower BMD and thinner cortex (from the bone perspective) and that there is no significant compensation by increase in bone size. This is the first study to report on global and sub regions of the femoral head in vivo in a large cohort. Most previous studies have analyzed bone density or microstructure in sub regions of the femoral head using clinical CT, HR-pQCT, microCT, and MRI [20–22,26,30–32].

We also found that BMD of the inferior region of the head was more associated with age than superior regions. Further, we observed that neck vBMD and FN aBMD correlated well with femoral head vBMD, which indicates that neck vBMD can be used as a substitute for head vBMD.

The periosteum covers the external bone surface to regulate the outer bone shape. As shown previously, in coordination with the inner cortical endosteum the periosteum also regulates cortical thickness and bone size [33]. The importance of periosteal apposition in establishing structural strength during growth and maintaining it during aging has been recognized [9]. Further, the reduction with age of osteoblast [34]

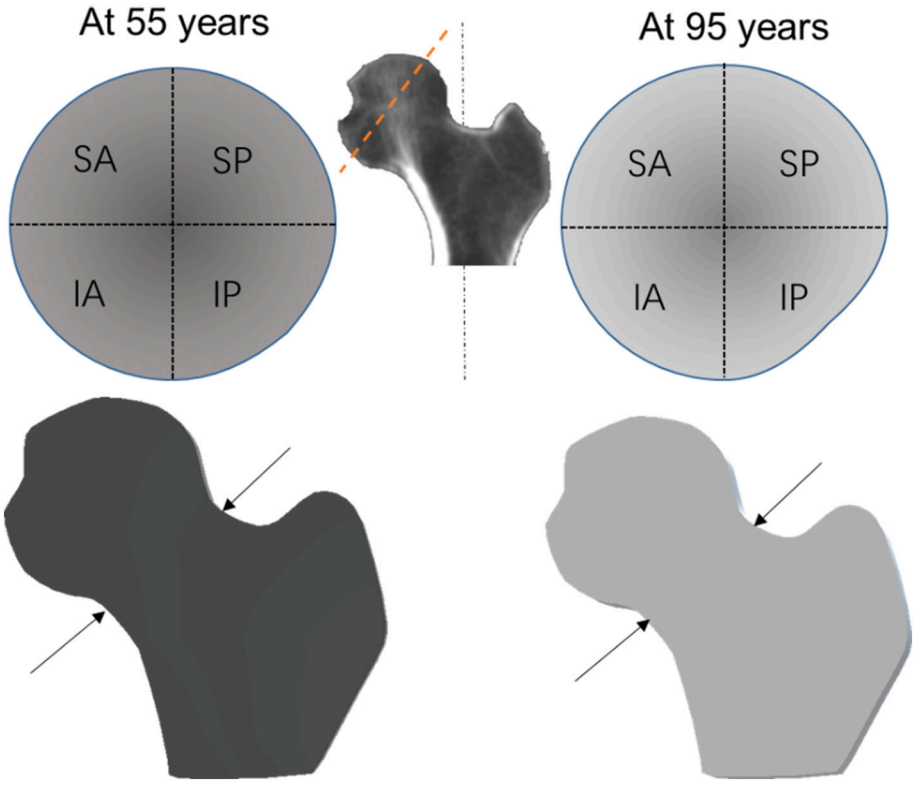

Fig. 3. The pictograms show, after adjustment of body size, no age-related differences in the integral size of femoral head and neck min-CSA between women at 55 years and 95 years. The difference in Quadrant IP of head volume was detected between age 55 and age 95.

and periosteal fibroblast numbers and of vessel density throughout the periosteum [33], may help explain why periosteal bone formation declines with age.

For women, endocortical bone loss accelerates during the menopause but interestingly periosteal apposition ceases around the same time [15,19,35]. Widening of bone, specifically of the femoral neck, is

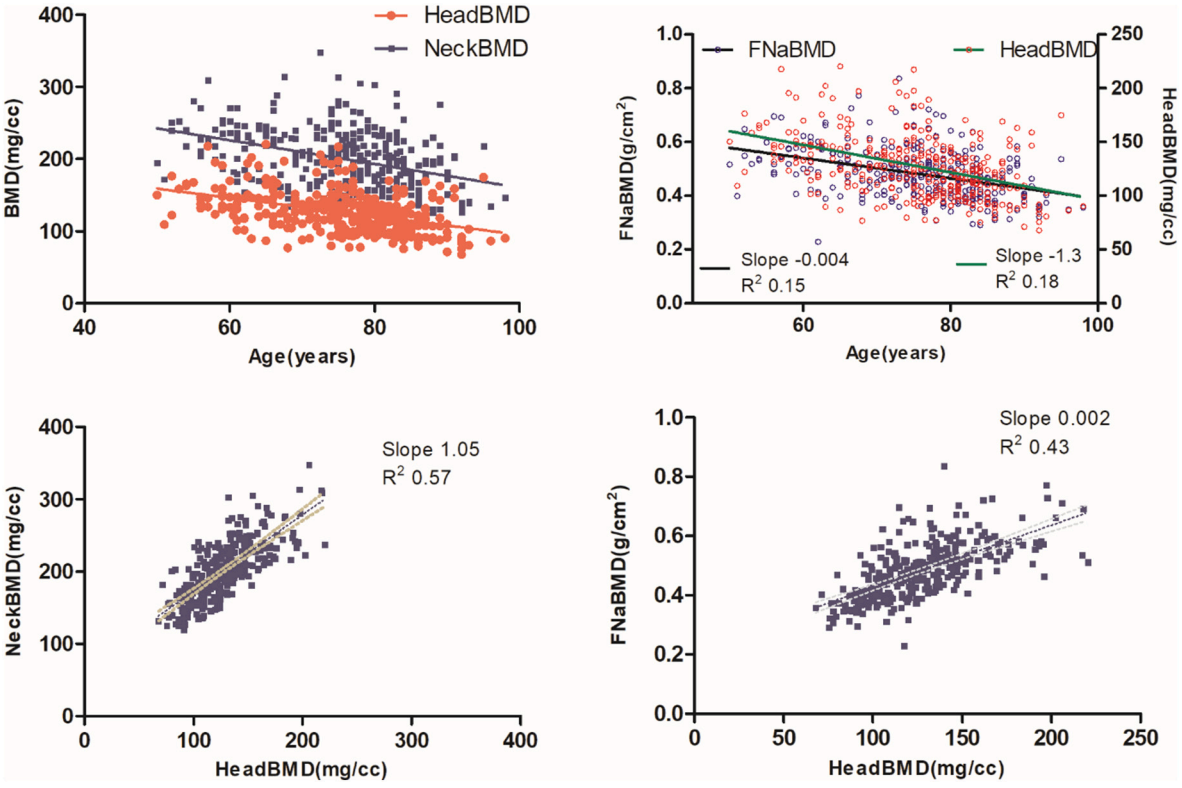

Fig. 4. Plots of the femoral head vBMD and femoral neck aBMD/vBMD with age.

driven by periosteal bone formation associated with compensatory endosteal resorption [36]. Obviously, the decrease of periosteal apposition in postmenopausal women has an impact on bone size change. Furthermore, the femoral neck has less cellular periosteum and more mineralized periosteum than for example femoral diaphyseal bone [37]. Further investigations on the expansion of the femoral neck with aging in postmenopausal women is warranted, in particular as their sex specific differences of periosteal apposition with age have been reported [14,16,17,38]. Unfortunately, periosteal apposition in men could not be addressed in this study.

The topic of periosteal apposition is complex. Periosteal activity is site specific and varies among different bones, but this has been addressed by a very limited number of studies. Riggs et al. reported that periosteal apposition increased bone size in women from 20 to 90 years by14% of the lumber spine and by 13% of the femoral neck. In men the age-related increase in cross-sectional area of the vertebrae was 2-fold higher than that of femoral neck [39]. In an animal study, clear differences in periosteal bone formation rates were observed among skeletal sites [40]. Such variations suggest that periosteal regulation may differ throughout the weight-bearing axial skeleton and also by sex. It has been speculated that induction of periosteal apposition may be a target of pharmaceutical intervention [33], however, existing evidence of such a mechanism in vivo is weak. In particular it has never been in studies using 3D QCT.

Most previous in vivo studies related to periosteal apposition of the femur were based on DXA assessments and used 2D bone cross-sectional area or width as an indicator of periosteal apposition [33]. The limited spatial resolution of DXA is recognized [41] and may account for the high variability among studies investigating periosteal apposition in humans. In contrast QCT studies of femoral neck periosteal apposition with age show a more consistent picture, provided their results are interpreted appropriately. Over the full age range from 20 to about 90 years or in younger women before menopause there is periosteal apposition as shown in Caucasian women [3,6,42]. However, in elderly women, essentially after menopause there is no periosteal apposition as shown in study reported here and the study from Nicks [2]. Nicks' study actually showed a volume increase of head and neck over the full age range of 20–90 years but when only data after menopause were analyzed it did not show any geometry related compensation of the age-related increase of fracture risk due to decreasing vBMD.

One would expect that femoral neck expansion continued across old age to at least partly compensate the decline of bone strength caused by the decrease of bone mass and cortical thickness, however, the above mentioned CT studies [2,8] apparently do not support this assumption. Our study observation and two other studies with similar results suggest that at least at the femur, much of the age associated increase in bone size may occur in younger women, but bone size expansion might stop during older age. Apparently hip fracture etiology in our cohort differed with age. Neck aBMD of about 0.5 of the 50–70 age range of our cohort (Table 1) corresponds to a T-score of about −2.2 when using Chinese DXA aBMD reference values(43), while normal Chinese subjects at age 50–59 have a neck T-score between −0.7 and − 1.9 [43]. Thus hip fracture risk of the younger population of our cohort was increased compared to age matched normals potentially due to higher occurrence of secondary osteoporosis but unfortunately data were not available. However, despite different etiologies head size did not change with age thus apparently it was not affected by hip fracture etiology.

Age related bone size changes seem to be similar in a normal unfractured population (Nicks et al. study) and a population with high risk of acute hip fracture (our study). The difference in BMD between the two studies may be partly attributed to race but also partly to the difference between cohorts with and without hip fracture. The well matched results indicate same mechanism of bone changes with age in Caucasian and Asian populations.

Information about low BMD of the femoral head may be helpful for clinical procedures. Investigating the age-related changes and sub-regional features of the femoral head in patients with hip fractures may contribute to a theoretical basis for surgical interventions. Intramedullary nails are widely used in the treatment of intertrochanteric fractures. The proximal femoral nail antirotation (PFNA) and the gamma nail (GN) are the main types. For the choice of the head screw in the intramedullary nail fixation, bone quality of the femoral head is critically important. The lag screw of the Gamma nail can exert a compression effect at the fracture site. It requires good bone quality of the femoral head to provide a sufficient gripping force. The spiral blade of PFNA can increase bone density during hammering it into the femoral head. It is more suitable for serious bone loss of the femoral head in the osteoporosis patients. Poor bone quality caused by osteoporosis is the main cause for failure of implant [44]. A previous study tried to use QCT to assess sub-regional vBMD of the femoral head, however, precision of the vBMD measurement of the femoral head was poor [45]. Another study established a more precise method in evaluating spatial vBMD of the intramedullary nail tract based on a complicated voxel-based morphometry(VBM) method, although it may not be applied to clinical use [46]. It is critical to know the femoral head bone density across different ages. Nicks showed that integral head density at age 90 was about 162 mg/cm^3, higher than 101 mg/cm^3 found in the Chinese women of this study. In the EFFECT study [23], head vBMD of acute hip fracture females with a mean age of 81.6 years was 182 mg/cm^3, which is higher than head vBMD of 115 mg/cm^3 at age 80–89 in this study. In this study, we also found differential age-related vBMD declines of the inferior and superior quadrants of the femoral head. This observation is consistent with the findings from a previous tensor-based morphometry (TBM) QCT study [47]. BMD of the inferior quadrants of the femoral head was more strongly associated with age compared to BMD of the superior quadrants, which is interestingly different to the finding of the relative preservation of the inferior cortices thickness and BMD of femoral neck with age [3]. However, due to very limited data, this observation must be further validated in further studies.

The femoral head and neck are a continuous bony unit. The femoral head directly participates in the weight-bearing transfer to the femoral neck. Therefore, the femoral neck and the trochanter are affected by stresses and strains in the femoral heads. Thus with respect to hip fracture risk, the traditional DXA based separation [41] in regions such as the femoral neck, trochanter and intertrochanter may not be fully adequate to capture the risk of hip fractures. Therefore, it is important to explore the association of head and neck bone density, and the relationship between regional deteriorations of the femoral head and the femoral neck fractures. In the EFFECT study, BMD of the femoral head was a powerful hip fracture discriminator [23]. In another QCT study based on a VBM-based atlas analysis, spatial vBMD loss of the head was also found to be associated with hip fractures [48].

Our study has several limitations. First, we performed a cross-sectional study which is a weaker study design than a longitudinal study, but there may be no study following up people over decades which makes a longitudinal design rather unrealistic. Second, this study population of acute low-energy hip fracture patients may limit the generalization of the results to a healthy elderly population. However, one main aim of this study was to provide data of global and sub-regional vBMD of the femoral head at different ages for subjects with a very high hip fracture risk. Third, all women were Chinese, limiting the interpretation of the results to other ethnicities because there have been studies showing structural differences of the proximal femur between Asian and other ethnicities [49,50].

5. Conclusions

This study showed that elderly women had relative preservation of femoral head and neck bone volume from 50 yrs. over four decades but markedly lower integral BMD of the proximal femur, which are consistent with the observations in white postmenopausal women. The findings of our study call in question about the concept of bone

expansion with aging even in elderly age.

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Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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CRediT authorship contribution statement

Yongbin Su:Methodology, Writing - original draft.**Ling Wang**:Conceptualization, Methodology, Writing - review & editing, Supervision.**Xiaoyan Liu**:Writing - original draft, Validation.**Minghui Yang**:Methodology, Writing - review & editing.**Chen Yi**:Investigation, Validation.**Yandong Liu**:Investigation, Validation, Writing - original draft.**Pengju Huang**:Investigation, Validation, Writing - original draft.**Zhe Guo**:Methodology, Writing - review & editing.**Aihong Yu**:Writing - review & editing.**Xiaoguang Cheng**:Conceptualization, Methodology, Writing - review & editing.**Xinbao Wu**:Conceptualization, Writing - review & editing.**Glen M. Blake**:Writing - review & editing.**Klaus Engelke**:Conceptualization, Methodology, Writing - review & editing.

Declaration of competing interest

Klaus Engelke is a part time employee of BioClinica, Inc. Other authors declare that they have no conflict of interest.

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