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Analysis of the current status and characteristics of osteoporosis in adult hemophilia patients based on high-resolution peripheral quantitative computed tomography: a case control study

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Abstract

Background Current research on osteoporosis (OP) in hemophilia is insufficient. The suitability of high-resolution peripheral quantitative computed tomography (HR-pQCT) for evaluating osteoporosis in hemophilia remains unclear.

Aim To investigate the current status of osteoporosis and the applicability of HR-pQCT in adult hemophilia patients.

Methods Thirty three hemophilia patients aged 23–49 years were recruited. X-ray examinations were performed on the bleeding joints. Dual energy X-ray absorptiometry (DXA) and HR-pQCT were used to assess bone mineral density (BMD). The HR-pQCT values of the distal tibia and radius were compared between hemophilia patients and healthy controls(HCs).

Results All bleeding joints showed local osteoporosis on X-ray. Only 33.3% of patients had a hip BMD lower than the expected value according to DXA. The Tb.vBMD(98.5 ± 44.2 mg/cm^3), Tt.Ar(612.5 ± 163.5mm^2),Tb.Ar(487.0 ± 175.6mm^2), Ct.Ar(117.0 ± 25.7mm^2), Tb.BV/TV(0.2 ± 0.1), Tb.N(0.9 ± 0.3 1/mm), Ct.Pm(96.3 ± 13.8 mm) of the distal tibia and Tt.Ar(248.4 ± 53.1mm^2),Tb.Ar(186.0 ± 55.1mm^2), Ct.Ar(66.1 ± 14.4 mm^2), Ct.Pm(68.1 ± 7.1 mm) of the distal radius in the hemophilia group was significantly lower than the HCs(tibia Tb.vBMD:186.4 ± 44.3mg/cm^3, Tt.Ar:906.8 ± 135.0mm^2,Tb.Ar:743.7 ± 137.6mm^2, Ct.Ar:169.3 ± 21.9mm^2,Tb.BV/TV:0.3 ± 0.1, Tb.N:1.5 ± 0.2 1/mm,Ct.Pm:117.8 ± 8.2 mm; radius Tt.Ar:285.7 ± 35.6 mm^2, Tb.Ar:83.8 ± 7.9mm^2, Ct.Ar:0.3 ± 0.1mm^2, Ct.Pm:80.2 ± 4.3 mm) with statistically significant differences ($p < 0.05$). Correlation analysis showed a positive correlation ($r = 0.768$, $p = 0.016$) between femoral neck BMD with DXA and total volumetric BMD(Tt.vBMD) at the distal tibia.

Conclusion The bone health status of adult hemophilia patients in China is worrying. The occurrence of OP may be accompanied by varying degrees of bone loss, bone destruction, and structural abnormalities observed in both trabecular and cortical bones of the upper and lower limbs. The condition of the trabecular bones in the lower limbs is particularly severe. The correlation between BMD measurements obtained from HR-pQCT and DXA is strong.

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Keywords Hemophilia, Osteoporosis, Bone Mineral Density, High-resolution Peripheral Quantitative Computed Tomography, Adult Hemophilia Patients

Introduction

Hemophilia is a rare X-linked recessive hereditary bleeding disorder [1], characterized by recurrent joint bleeds, which may be complicated by hemophilic synovitis and arthritis [2]. Osteoporosis (OP) is a common comorbidity in patients with hemophilia(PWH). A study has shown that 27% of PWH have OP and 43% have osteopenia [3]. The risk of osteoporotic fractures in patients with hemophilia is 4.37 times higher than in the general population of the same sex and age group [4]. However, the underlying mechanism of hemophilic osteoporosis remains unclear, and there is a lack of consensus regarding its screening, prevention, and treatment [5]. Reports on the occurrence of osteoporosis in Chinese PWH are very limited. Dual-energy X-ray absorptiometry (DXA) is currently the gold standard for bone mineral density (BMD) testing [6], but it has certain limitations in the diagnosis of OP in patients with hemophilia. High-resolution peripheral quantitative computed tomography (HR-pQCT) is a newly developed method for BMD, bone microstructure and bone strength. It has been used for older men, postmenopausal women and fracture prediction [7–9] and has been explored as a tool for detecting OP in PWH in two studies [10, 11]. However, the HR-pQCT examination results of both studies were not compared with the DXA examination results. The value of this study is to compensate for this deficiency and provide a clinical basis for the early diagnosis and screening of osteoporosis in PWH by using HR-pQCT to assess the bone health status in adult PWH in China, analyze the incidence and clinical characteristics of OP.

Materials and methods

Study design and study population

This was a case control study designed to investigate the current status of OP with DXA and HR-pQCT in moderate (with FVIII: C 1–5 IU/dL) to severe (with FVIII: C < 1 IU/dL) patients with type A hemophilia [12] at Peking Union Medical College Hospital.

Thirty-three adult male PWH were included in this study.The following were excluded from participation in the data collection: (1) motor dysfunction caused by trauma or other diseases; (2) joint abnormalities caused by other congenital hereditary disease or developmental abnormalities; (3) severe diseases of vital organs such as hearts, lungs and kidneys; (4) joint or muscle bleeding in the past two weeks.

The healthy controls (HCs) consisted of thirty-three healthy adult males aged 31.8 ± 7.6 years. Inclusion Criteria: (1) in good health; (2) 18–50 years old. Exclusion Criteria: (1) motor dysfunction caused by trauma or other diseases; (2) joint abnormalities caused by other congenital hereditary disease or developmental abnormalities.

We received PWH from all over China to collect basic clinical information including the modalities and dosage of alternative treatments, duration and the timing of initiation of prophylaxis. X-ray of the hemorrhagic joints and HR-pQCT of the distal upper and lower extremities were performed respectively, and BMD of the hip and lumbar spine was measured using DXA.

The study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital, Beijing, China(NO.I-25PJ0326) and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each patient.

DXA

The DXA technique was used to collect the areal BMD of the lumbar spine and proximal femur (Prodigy Advance; GE Lunar Corporation, Madison, WI, USA), while anterior and lateral X-ray examinations of affected joints with a history of bleeding was performed at the Radiology Department of Peking Union Medical College Hospital. According to the World Health Organization (WHO) classification system [6], the Z-score is recommended for patients under 50 years of age and the scores are compared with expected BMD levels of an age-matched healthy population. A Z-score of −2 standard deviations or below is considered "lower than expected for age", Z-score between −2 and −1 standard deviations are "low normal", and Z-scores above −1 standard deviation are considered normal [13].

HR-pQCT

In this study, HR-pQCT scans (Xtreme CTII, Scanco Medical AG, Brüttisellen, Switzerland) in distal tibia and radius were performed on the left limb with a high history of bleeding. Each image was composed of 168 slices with an isotropic resolution of 61 μm. The scan region was positioned 9.0 mm and 22.0 mm proximal to the reference line for the distal radius and distal tibia, respectively. Image analysis was performed according to the manufacturers' standard in vivo acquisition protocols [14]. The following three types of parameters were calculated directly and reported automatically [15]. Volumetric BMD (vBMD) parameters included total volumetric BMD (Tt.vBMD), trabecular volumetric BMD (Tb.vBMD), and cortical volumetric BMD (Ct.vBMD), which were derived from their respective volumes and expressed in mg hydroxyapatite (mg/cm^3). The geometric structural parameters of bones included total area (Tt.Ar, mm^2), trabecular area (Tb.Ar, mm^2), and cortical area (Ct.Ar, mm^2). The bone microstructure parameters included trabecular bone volume/total volume (Tb.BV/TV), trabecular number (Tb.N, 1/mm), trabecular thickness (Tb.Th, mm), trabecular separation (Tb.Sp, mm), trabecular heterogeneity (Tb.1/N.SD, tmm), cortical thickness (Ct.Th, mm), Cortical perimeter (Ct.Pm, mm) and cortical porosity (Ct.Po, %). The HR-pQCT parameters in the left distal tibia and radius of 33 healthy males who were matched in age, height, and weight to the PWH were searched from the HR-pQCT database [14].

Statistical analysis

Statistical analysis was performed using the SPSS 25.0 statistical software package. An independent sample t test was used to compare the differences in HR-pQCT parameters between the PWH and the HCs. The Pearson correlation analysis was used to determine the correlation between the two types of BMD value. Difference was considered as statistically significant when $P < 0.05$.

Results

Participant characteristics

A total of 33 men with hemophilia type A aged 31.1 ± 8.4 years (from 23 to 49 years old), including twenty-two severe patients and eleven moderate patients, and receiving FVIII prophylaxis (10–15 IU/kg/injection, 2–3 injections per week, for 1 month to 4 years),were included in this study. All patients had a history of left lower limb joint bleeds. Twenty-nine patients had a history of right lower limb joint bleeds. Twenty-eight patients had a history of left upper limb joint bleeds, and twenty-six patients had a history of right upper limb joint bleeds. The joint bleeding rate in the past year was 0–5 times.

The incidence of OP in adult PWH

According to the X-ray reports of the radiology department on the bleeding joints, all bleeding joints were exhibited by varying degrees of local OP, with an incidence rate of 100% (Fig. 1 for an example). Accordingto the *Z*-value with DXA, only 11/33 patients (33.3%) had hip BMD lower than the expected age, while there were no significant abnormalities in lumbar BMD.

Fig. 1 Example of anterior-position X-ray of bilateral ankle joints in a 36 year old patient

Differences in HR-pQCT parameters between PWH and HCs

Compared with HCs, the Tb.vBMD, Tt.Ar, Tb.Ar, Ct.Ar, Tb.BV/TV, Tb.N and Ct.Pm of the left distal tibia in PWH were significantly lower, with a statistically significant difference ($p < 0.05$); the Tt.vBMD, Ct.vBMD and Ct.Th were slightly lower than the HCs, the Tb.Sp and Tb1/N.SD were slightly higher than those of the HCs, with no statistically significant difference ($p > 0.05$) (Table 1), indicating that the BMD, geometric structure, and microstructure of the distal tibial trabecular bone in PWH were significantly abnormal. The geometric structure and microstructure of the cortical bone were also abnormal, with more prominent trabecular bone loss and structural damage of the lower limb bones.

Compared with HCs, the bone geometry parameters Tt.Ar, Tb.Ar and Ct.Ar and bone microstructure index Ct.Pm of the left distal radius in PWH significantly decreased, and the difference was statistically significant ($p < 0.05$); Tt.vBMD, Tb.vBMD, Ct.vBMD, Tb.BV/TV, Tb.N, and Ct.Th were slightly lower than in HCs, Tb.Sp and Tb.1/N.SD were slightly higher than in HCs, and the difference was not statistically significant ($p > 0.05$)

Table 1 Comparison of HR-pQCT parameters in the left distal tibia between PWH and HCs

Parameters	PWH (Mean ± SD) (*n* = 33)	HCs (Mean ± SD) (*n* = 33)	*P* value
Tt.vBMD (mg/cm^3)	268.6 ± 76.2	324.8 ± 56.6	0.095
Tb.vBMD (mg/cm^3)	98.5 ± 44.2	186.4 ± 44.3	0.001[a]
Ct.vBMD (mg/cm^3)	922.1 ± 56.7	933.0 ± 35.1	0.634
Tt.Ar (mm^2)	612.5 ± 163.5	906.8 ± 135.0	0.001[a]
Tb.Ar (mm^2)	487.0 ± 175.6	743.7 ± 137.6	0.003[a]
Ct.Ar (mm^2)	117.0 ± 25.7	169.3 ± 21.9	0.000[a]
Tb.BV/TV	0.2 ± 0.1	0.3 ± 0.1	0.000[a]
Tb.N (1/mm)	0.9 ± 0.3	1.5 ± 0.2	0.000[a]
Tb.Th (mm)	0.3 ± 0.1	0.3 ± 0.0	0.590
Tb.Sp (mm)	0.7 ± 0.2	0.6 ± 0.1	0.195
Tb.1/N.SD (tmm)	0.3 ± 0.1	0.3 ± 0.0	0.227
Ct.Th (mm)	1.5 ± 0.3	1.7 ± 0.3	0.147
Ct.Pm (mm)	96.3 ± 13.8	117.8 ± 8.2	0.001[a]
Ct.Po (%)	0.0 ± 0.0	0.0 ± 0.0	0.637

Abbreviations: Tt.vBMD total volumetric BMD, *Tb.vBMD* trabecular volumetric BMD, *Ct.vBMD* cortical volumetric BMD, *Tt.Ar* total area, *Tb.Ar* trabecular area, *Ct. Ar* cortical area, *Tb.BV/TV* trabecular bone volume/total volume, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *Tb.1/N. SD* trabecular heterogeneity, *Ct.Th* cortical thickness, *Ct.Pm* Cortical perimeter, *Ct. Po* cortical porosity, *PWH* patients with hemophilia, *HCs* healthy controls, *x* ± *s* mean ± standard deviation

[a] Denotes a *P* value < .05, showing a significant difference between PWH and HCs

Table 2 Comparison of HR-pQCT parameters in the left distal radius between PWH and HCs

Parameters	PWH (Mean ± SD) (*n* = 33)	HCs (Mean ± SD) (*n* = 33)	*P* value
Tt.vBMD (mg/cm^3)	339.7 ± 48.6	362.3 ± 83.1	0.517
Tb.vBMD (mg/cm^3)	156.2 ± 55.9	177.3 ± 46.2	0.425
Ct.vBMD (mg/cm^3)	899.6 ± 33.2	920.3 ± 47.0	0.326
Tt.Ar (mm^2)	248.4 ± 53.1	365.2 ± 39.6	0.000[a]
Tb.Ar (mm^2)	186.0 ± 55.1	285.7 ± 35.6	0.001[a]
Ct.Ar (mm^2)	66.1 ± 14.4	83.8 ± 7.9	0.009[a]
Tb.BV/TV	0.2 ± 0.1	0.3 ± 0.1	0.472
Tb.N (1/mm)	1.3 ± 0.3	1.6 ± 0.2	0.154
Tb.Th (mm)	0.2 ± 0.0	0.2 ± 0.0	0.783
Tb.Sp (mm)	0.7 ± 0.2	0.6 ± 0.1	0.126
Tb.1/N.SD (tmm)	0.3 ± 0.1	0.2 ± 0.0	0.135
Ct.Th (mm)	1.2 ± 0.1	1.2 ± 0.3	0.787
Ct.Pm (mm)	68.1 ± 7.1	80.2 ± 4.3	0.001[a]
Ct.Po (%)	0.0 ± 0.0	0.0 ± 0.0	0.177

Abbreviations: Tt.vBMD total volumetric BMD, *Tb.vBMD* trabecular volumetric BMD, *Ct.vBMD* cortical volumetric BMD, *Tt.Ar* total area, *Tb.Ar* trabecular area, *Ct. Ar* cortical area, *Tb.BV/TV* trabecular bone volume/total volume, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *Tb.1/N. SD* trabecular heterogeneity, *Ct.Th* cortical thickness, *Ct.Pm* Cortical perimeter, *Ct. Po* cortical porosity, *PWH* patients with hemophilia, *HCs* healthy controls, *x* ± *s* mean ± standard deviation

[a] Denotes a *P* value < .05, showing a significant difference between PWH and HCs

(Table 2), indicating that the distal radius was mainly characterized by abnormal bone geometric structures of cortical and trabecular bones, accompanied by abnormal bone microstructure of cortical bones. However, bone loss and structural damage in the upper limb bones were milder than those of lower limb bones.

Correlation between DXA and HR-pQCT BMD detection results in the PWH

The correlation analysis between the two BMD detection methods (Table 3) showed a positive correlation ($r = 0.768$, $p = 0.016$, Fig. 2) between DXA femoral neck BMD and left distal tibia Tt.vBMD; the Wards triangle BMD was also positively correlated with the left distal tibia Tt.vBMD ($r = 0.733$, $p = 0.025$, Fig. 3), indicating good consistency between the BMD results of the HR-pQCT and the DXA methods.

Table 3 Correlation analysis of BMD detection values between DXA (Z score) and HR-pQCT in PWH

Correlative factor	Pearson coefficient *r*-value	*P* value
Femoral neck BMD (−1.1 ± 1.0)—Tt.vBMD (268.6 ± 76.2 mg/cm^3)	0.768	0.016[b]
Wards Triangle BMD (−1.5 ± 0.9)—Tt.vBMD (268.6 ± 76.2 mg/cm^3)	0.733	0.025[b]

Abbreviations: BMD bone mineral density, *Tt.vBMD* total volumetric BMD

[b] Denotes a *P* value < .05, showing a significant correlation between the DXA femoral neck BMD and the left distal tibia Tt.vBMD, the Wards triangle BMD and the left distal tibia Tt.vBMD

Discussion

Osteoporosis is a serious complication of hemophilia. Katsarou conducted DXA examinations on 78 moderate to severe PWH aged 18–60 and found that the proportion of patients with decreased bone density in the femoral neck and lumbar spine was 86.1% and 65.3%, respectively. Among them, 30.5% of patients who underwent femoral neck BMD examination experienced bone loss and 55.6% had osteoporosis. Among patients undergoing lumbar BMD examination, 52% experienced bone loss and 13.3% had osteoporosis [16]. Wu et al. used the DXA to study and found that in 53 severe hemophilia A patients aged 20–69, the incidence of osteoporosis was 41.51% [17]. The BMD in femoral neck, Wards triangle, greater trochanter and hip joint of PWH were significantly lower than those of HCs, while there was no significant difference in lumbar BMD. This suggested that the BMD of severe hemophilia A patients was much

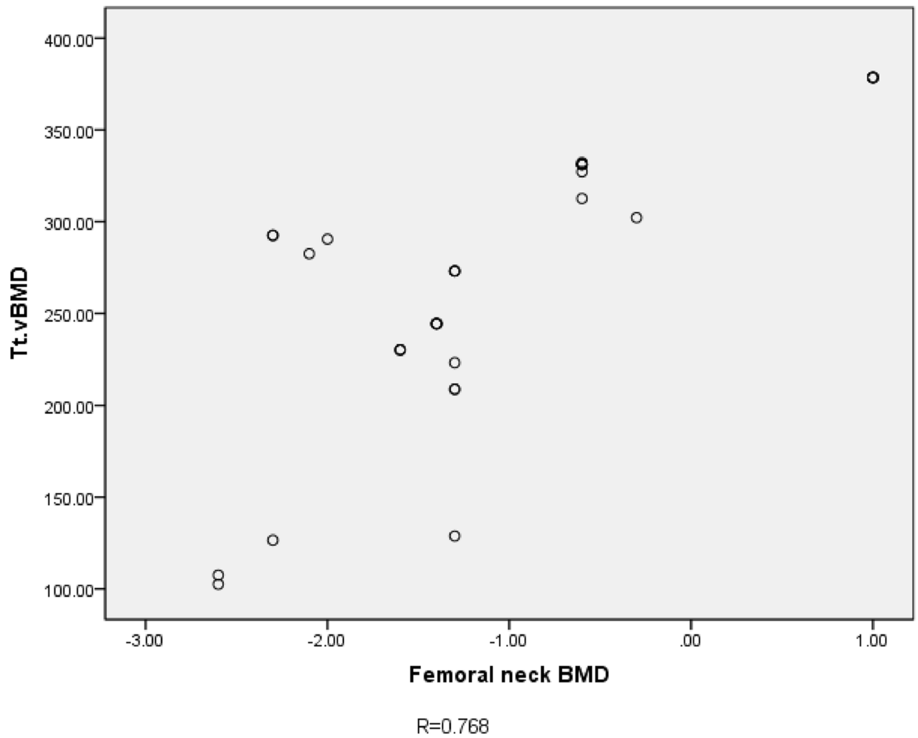

Fig. 2 Scatter plot of relationship between femoral neck BMD and Tt.vBMD

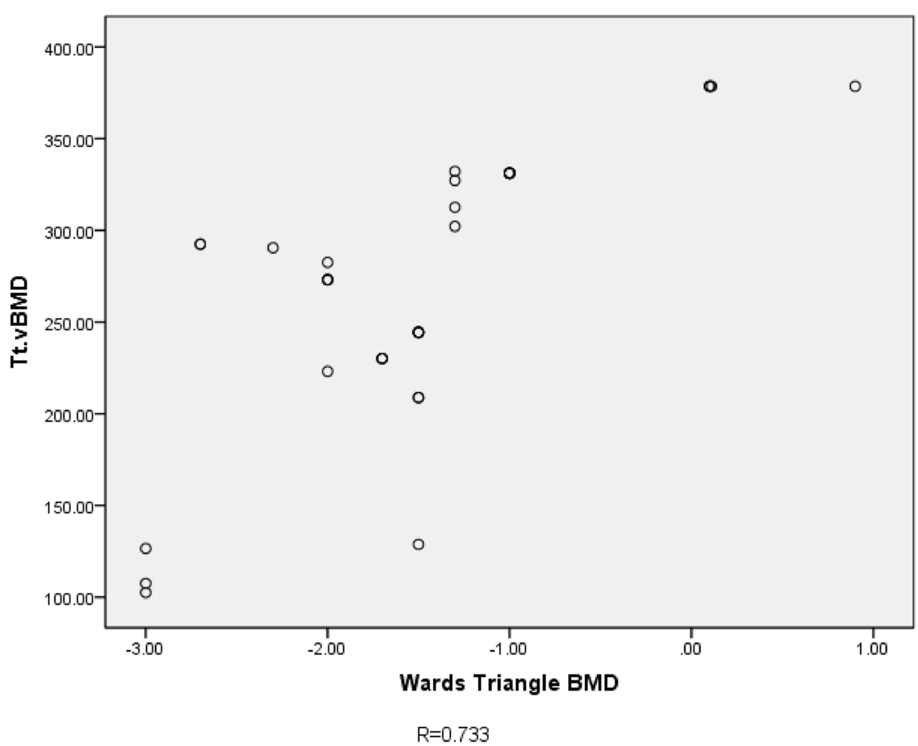

Fig. 3 Scatter plot of relationship between Wards Triangle BMD and Tt.vBMD

lower than that of the healthy population, and the difference was mainly manifested in the hip.Nair et al. studied 50 severe PWH aged 20–50 who received on-demand treatment and found that the risk of fractures in PWH was significantly increased, 21.4–24 times that of other patient populations of identical gender and age [18]. This study found that through X-ray examination, the incidence of local OP in moderate to severe PWH with an average age of 31 years old was as high as 100%. Using the HR-pQCT method to detect the vBMD of peripheral bone,we found that the Tb.vBMD in the left distal tibia of PWH was significantly lower than that of HCs ($p < 0.05$); Tt.vBMD and Ct.vBMD were slightly lower than HCs ($p > 0.05$); the Tt.vBMD, Tb.vBMD, and Ct.vBMD of the left distal radius were slightly lower than those of HCs ($p > 0.05$), indicating that peripheral bone loss was very common in peripheral joint affected by hemophilia. Trough DXA method, we found that 33.3% of adult PWH had hip BMD lower than the expected age, meeting the diagnostic criteria for OP, while there were no significant abnormalities in lumbar BMD, indicating that PWH was mainly characterized by a decrease in hip BMD, which was consistent with previous research results [16, 17].

Although DXA is widely used in BMD detection, DXA only evaluates 2D areal bone mineral density and does not provide details of microarchitecture of cortical and cancellous bones. Besides, there might be false increases of BMD due to bone hyperplasia, spinal degeneration and aortic calcification in lumbar spine DXA. In addition, due to the influence of body and bone size, its use for evaluating BMD in children and adolescents is challenged, and it is difficult to display early bone loss or peripheral bone loss in adult PWH. A report using DXA method to study the BMD of PWH showed that the total hip and femoral neck BMD of severe adult PWH were significantly lower than those of HCs, but there was no significant difference in lumbar BMD compared to the HCs; 19.4% of PWH patients under 50 years old had BMD Z-values lower than expected age, while 60% of PWH patients over 50 years old had BMD T-values that meeted OP diagnostic criteria, and 20% showed decreased bone mass [19]. DXA is limited in evaluating hemophilic OP due to a lack of sensitivity and specificity. Christoforidis attempted to use quantitative ultrasound methods to evaluate the bone health status of children PWH, but found that only a small number of children and young adults PWH had bone health damage detected, and there was no correlation between quantitative ultrasound and DXA methods in displaying bone health damage in hemophilia [20]. HR-pQCT allows noninvasive assessment of bone microstructure and vBMD at peripheral sites at high resolution (82 μm isotropic voxel size) and with relatively low radiation exposures (3–5 μSv) [21]. Moreover, HR-pQCT can reflect bone health status from various aspects such as bone density, bone geometry, bone microstructure, and bone strength through three-dimensional evaluation of cortical and trabecular bones [22, 23]. Lee et al. evaluated the skeletal condition of 18 adult PWH using HR-pQCT and found that compared to HCs, PWH had decreased trabecular and cortical bone BMD and bone strength, abnormal bone microstructure, and a negative correlation between Gilbert joint score and BMD, suggesting a correlation between the severity of hemophilic arthritis and decreased BMD [11]. Xafaki et al. also used the HR-pQCT method to evaluate the bone characteristics of children with hemophilia and found that subjects with a history of target joints in the upper limbs had significantly lower bone density of the radial trabecular bone in the target area than in the non-target area, subjects with left upper limb target joints had significantly lower bone density of the left radial trabecular bone than those without target joints, the cortical bone mass and geometric parameters of the inhibitor group were lower than those of HCs, and the left and right differences and left dominance of the upper and lower limbs were significant, indicating long bone abnormalities in children with hemophilia, low trabecular bone density in the upper limbs and poor cortical bone mass in the lower limbs were confirmed [10]. In this study, the femoral neck BMD with DXA method showed a positive correlation with left distal tibia Tt.vBMD. The Wards triangle BMD was also positively correlated with the left distal tibia Tt.vBMD, indicating good consistency between the HR-pQCT and DXA BMD detection results. In addition, a multidimensional analysis of the bone health status of PWH was conducted using HR-pQCT. The results showed that in addition to a decrease in BMD, there were also significant abnormalities in bone geometry and microstructure in the distal tibial trabecular bone of PWH. The bone geometry and microstructure of cortical bone were also abnormal. In comparison, bone loss and structural damage in the lower limb trabecular bone were more prominent, which might be associated with more bleeding in the joints of the lower extremities and more severe hemophilic arthritis in PWH. On the other hand, the distal radius of the upper limb was mainly characterized by abnormal bone geometric structures of cortical and trabecular bones, accompanied by abnormal bone microstructure of cortical bones. However, bone loss and structural damage were milder than those of the lower limb bones. It indicated that there was varying degrees of bone loss and structural abnormalities in the trabecular and cortical bones of the peripheral bones of the upper and lower limbs in hemophilia. The mechanism of osteoporosis in hemophilia may be very complex, and peripheral mechanisms may play an important role.

The major limitation of the study is the small sample size. We look forward to recruiting more hemophilia patients and conducting further related research in the future. Additionally, due to the lack of HR-pQCT reference values for healthy children, we were unable to compare the differences in bone health between children with hemophilia and HCs.

Conclusion

This clinical study suggested that in Chinese adults PWH, the local OP in hemorrhagic joints was common, and the loss of trabecular bone and bone structure of the lower limbs were more significant, while the bone geometry of cortical bone and trabecular bone was mainly abnormal in the upper limbs. DXA method has low sensitivity for hemophilic OP. HR-pQCT is expected to be a useful complementary tool for hemophilia OP.

Abbreviations

OP	Osteoporosis
HR-pQCT	High-resolution peripheral quantitative computed tomography
DXA	Dual energy X-ray absorptiometry
BMD	Bone mineral density
HCs	Healthy controls
PWH	Patients with hemophilia
Tt.Vbmd	Total volumetric BMD
Tb.vBMD	Trabecular volumetric BMD
Ct.vBMD	Cortical volumetric BMD
Tt.Ar	Total area
Tb.Ar	Trabecular area
Ct.Ar	Cortical area
Tb.BV/TV	Trabecular bone volume/total volume
Tb.N	Trabecular number
Tb.Th	Trabecular thickness
Tb.Sp	Trabecular separation
Tb.1/N. SD	Trabecular heterogeneity
Ct.Th	Cortical thickness
Ct.Pm	Cortical perimeter
Ct.Po	Cortical porosity

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Clinical trial number

Not applicable.

Authors' contributions

Ying Liu conceived the project, Ying Liu, Mingnan Shi and Ying Ge performed the study and data collection, Li Zhang completed HR-pQCT scans and image analysis. Ying Liu and Lixia Chen analysed the data, Weibo Xia provided input on data analysis, as well as critical review and revision of the manuscript for import intellectual content. All authors approved the final manuscript for submission.

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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 Medical Ethics Committee of Peking Union Medical College Hospital, Beijing, China and was conducted in accordance with the Helsinki Declaration. A written informed consent was obtained from each patient.

Consent for publication

All authors have read and approved the final manuscript and consent to its publication.

Competing interests

The authors declare no competing interests.

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