Using QCT to evaluate bone mineral and abdominal adipose changes in patients with primary hyperparathyroidism and comparing it to DXA for bone status assessment: a retrospective case-control study

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Background: Patients with primary hyperparathyroidism (PHPT) show changes in bone metabolism and adipose tissue, but the results are inconsistent. Quantitative computed tomography (QCT) was reported useful for detecting bone mineral and adipose tissue change, but information on the role of QCT in PHPT is limited. We aimed to explore the changes of lumbar bone mineral density (BMD) and abdominal adipose tissue in patients with PHPT using QCT based on existed CT images, and to assess the consistency between QCT and dual-energy X-ray absorptiometry (DXA) in assessing bone status.

Methods: This retrospective case-control study was conducted on 48 PHPT patients, with healthy controls (HCs) matched by their age (±3 years) and gender, and the case-to-control ratio was approximately 1:3. Volumetric bone mineral density (vBMD), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and total adipose tissue (TAT) were measured by QCT in both PHPT and control groups and compared with the independent samples T-test. In the PHPT group, areal bone mineral density (aBMD) was measured by DXA. Pearson correlation analysis was used to investigate the association between QCT-derived vBMD and DXA-derived aBMD. Weighted kappa consistency analysis was used to clarify the agreement between QCT and DXA.

Results: Compared with HCs, the PHPT group had significantly lower vBMD (114.30±41.71 *vs.* 136.92±42.23 mg/cm^3; P=0.002) and higher TAT (261.98±74.65 *vs.* 236.69±69.00 cm^2; P=0.033); however, differences in SAT (120.81±40.19 *vs.* 109.94±36.83 cm^2; P=0.085) and VAT (141.17±48.11 *vs.* 126.75±50.50 cm^2; P=0.085) were not statistically significant. There was a strong correlation between QCT-derived vBMD and

DXA-derived aBMD (all r>0.68; P<0.001), and a moderate consistency [kappa(w) =0.48; 95% CI: 0.29 to 0.68; P<0.001] was presented when defining bone status according to the respective diagnostic criteria.

Conclusions: Our study may provide useful information regarding bone status and abdominal adipose tissue change in patients with PHPT without requiring additional scan and may further extend the clinical application value of QCT.

Keywords: Primary hyperparathyroidism (PHPT); quantitative computed tomography (QCT); bone mineral density (BMD); visceral adipose tissue (VAT); subcutaneous adipose tissue (SAT)

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Introduction

Primary hyperparathyroidism (PHPT) is a kind of endocrine disease characterized by hypercalcemia and inappropriately elevated parathyroid hormone (PTH) (1). In PHPT, continuous exposure to high levels of PTH causes bone remodeling, in which bone resorption prevails (1). Even in mild PHPT, catabolic skeletal actions of PTH are evidenced by reduced bone mineral density (BMD) and deterioration of bone microarchitecture (2); severe cases can manifest with fragility fractures (3,4). Therefore, radiological examination of bone density is a key component in the management of PHPT (5).

To date, dual-energy X-ray absorptiometry (DXA) has been the main tool for measuring BMD, the results of which are considered the gold standard for diagnosing osteoporosis (6). The typical DXA pattern in PHPT shows that preferential involvement at the skeletal site comprises primarily cortical bone, whereas trabecular bone appears to be relatively well preserved (7). These findings, however, are inconsistent with epidemiological studies that have revealed increased fracture risk at both vertebral (a skeletal site with a large component of trabecular bone) and non-vertebral sites in patients with PHPT (8). Moreover, high-resolution peripheral quantitative computed tomography (HR-pQCT) analyses have demonstrated that both cortical and trabecular bone are adversely affected by PHPT (9). Nevertheless, it is difficult to identify trabecular bone abnormalities in standard DXA technology due to its technological limitations, and HR-pQCT is not widely available in clinical practice. Therefore, research is needed to estimate the capability and feasibility of other methods in assessing trabecular bone health.

Post-processing software can be used to quantitatively assess BMD using routine abdominal and thoracic computed tomography (CT). Numerous studies have been conducted on quantitative computed tomography (QCT) for lumbar spine bone density and revealed that QCT has several advantages over DXA, including the ability to truly measure trabecular bone density without the influence of osteophyte and abdominal aortic calcification that may falsely elevate DXA results (10-12). In a big data cohort study in China, researchers verified that QCT is more sensitive for detecting osteoporosis than DXA in males (13). Although QCT enables the measurement of cortical and cancellous bone density independently, few studies have focused on using QCT to assess BMD in PHPT patients or on the consistency between QCT and DXA to assess bone health (14,15).

Body weight and body mass index (BMI) have been shown to be affected by PTH and our previous study reported that fat distribution, especially that of abdomen adipose tissue, was associated with PTH (16). Other research has reported that increased body weight and fat mass are associated with higher serum parathyroid hormone levels and a higher prevalence of PHPT in females (17). The mechanism by which body weight is related to the prevalence of PHPT hasn't been directly investigated, and few previous studies have provided enough insight for a more refined explanation. QCT can help to assess fat tissue and distinguish SAT from VAT, and therefore determine potential fat distribution abnormality between patients and controls.

The PHPT patients would undergo routine chest and abdominal CT exams to exclude multiple endocrine adenomas or other conditions that affect bone and lipid metabolism when they were admitted. Therefore, we would like to use these CT images to quantify BMD or abdominal adipose tissue distribution without requiring additional examinations, radiation exposure, and time. We

aimed to innovatively used QCT to assess the condition of trabecular bone indicated by volumetric BMD (vBMD) and the abdominal adipose tissue distribution, and to assess the consistency of QCT and DXA in the assessment of bone health in PHPT patients, attempting to expand the clinical application of QCT in PHPT patients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1827/rc).

Methods

Study population

This study was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (No. 2017-201). The requirement for written informed consent was waived for the nature of retrospective study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We conducted this retrospective case-control study by including PHPT patients from the Department of Endocrine and Metabolic Diseases of Ruijin Hospital from December 2019 to July 2020. Patients with PHPT were included after meeting the criteria of having raised serum calcium levels in the face of inappropriately high serum PTH level. The exclusion criteria were are as follows: (I) diseases which may cause secondary hyperparathyroidism including: stage 3–5 chronic kidney disease, Vitamin D deficiency, hypercalciuria, calcium deficiency, or malabsorption; (II) multiple endocrine neoplasm; (III) taking medications that influence bone and lipid metabolism; (IV) patients who did not undergo abdominal CT and whole-body DXA examination.

Healthy individuals were enrolled from our health examination department from June 2020 to August 2020. Those who underwent chest/abdominal CT on the same CT scanner as the PHPT group were considered eligible. Diseases known to affect bone metabolism, using of glucocorticoids, bisphosphonates, or other medications that influence bone and lipid metabolism were considered exclusion criteria. The case and control groups were matched in terms of age (±3 years) and gender and the case-to-control ratio was approximately 1:3.

Clinical and anthropometric information

All demographic characteristic information were recorded, including participant age and gender. Weight (kg) and height (cm) were measured and recorded in both PHPT and HC groups, respectively. The BMI was calculated as weight (kg)/height (m^2). Abdominal circumference (AC) was the girth through the center of umbilical cord, measured with the participants wearing light clothing in units of cm. Serum PTH, albumin (Alb), and calcium (Ca) levels were obtained from the clinical laboratory information system. The albumin-corrected serum calcium (Alb-corrected Ca) (mmol/L) was calculated using the following formula: [40-serum albumin concentration (g/L)] × 0.02 + measured total serum calcium (mmol/L).

BMD and fat distribution measurement

For all participants, CT images including the lumber spine (L1–L2) were acquired using the same CT scanner (iCT256; Phillips Medical Systems, Eindhoven, Netherlands) at 120 kVp, 1-mm slice reconstruction thickness. Then, those images were transferred to the QCT workstation (Mindways QCT Pro Version 6.1, Mindways Software, Inc., Austin, TX, USA) for analysis. As proposed by the American College of Radiology (ACR) QCT Guideline, vBMD was measured at L1 and L2 vertebrae and the mean value (mg/cm^3) of the two vertebrae was taken. The DXA examinations were performed in PHPT patients as soon as they were admitted to hospital, and areal bone mineral density (aBMD) values (g/cm^2) at the lumbar spine (L1–L3, L1–L4, and L2–L4), femoral neck (FN), total femur, and whole body were provided from a dual-energy X-ray absorptiometer (Lunar Prodigy; GE Medical Systems, Madison, WI, USA). The values of L1–L3, L1–L4, and L2–L4 were used in this study. The T-scores at lumbar spine of L1–L3, L1–L4, L2–L4, and FN were recorded and used to assess bone health status.

Measurement of abdominal adipose tissue was conducted in both groups using the Supplementary Tissue Measurements application of the Mindways QCT-PRO v6.0 spine module software, as described previously (18). According to the QCT-PRO operator's manual, the mid-slice of the L2 vertebra was be selected and measured, and the TAT and VAT measurements were obtained. The SAT at the same level was obtained by subtracting VAT from TAT. Both measurements were in units of cm^2.

Definition of osteopenia and osteoporosis

According to the International Society for Clinical Densitometry (ISCD) and ACR (19), the diagnosis of osteoporosis using QCT can be as follows: osteoporosis,

Table 1 General characteristics of the PHPT and HC groups

Variables	PHPT (n=48)	Control (n=143)	P value
Age (year)	53.77±11.04	52.38±11.40	0.461
Gender (female)	38 (79.2)	111 (77.6)	0.823
Weight (kg)	61.73±9.95	60.98±9.58	0.642
BMI (kg/m^2)	23.51±2.72	22.59±2.41	0.029
AC (cm)	83.72±9.14	81.84±7.86	0.187
TAT (cm^2)	261.98±74.65	236.69±69.00	0.033
SAT (cm^2)	120.81±40.19	109.94±36.83	0.085
VAT (cm^2)	141.17±48.11	126.75±50.50	0.085
vBMD (mg/cm^3)	114.30±41.71	136.92±42.23	0.002
Alb-corrected Ca (mmol/L)	2.70±0.21	2.25±0.10	<0.001
PTH (pg/mL)	159.35 (117.60, 284.53)	47.20 (37.80, 56.00)	<0.001

PHPT, primary hyperparathyroidism; HC, healthy control; BMI, body mass index; AC, abdominal circumference; TAT, total adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; vBMD, volumetric bone mineral density; Alb-corrected Ca, the albumin-corrected serum calcium; PTH, parathyroid hormone.

BMD <80 mg/cm^3; osteopenia, BMD 80–120 mg/cm^3; and normal, BMD >120 mg/cm^3. When it comes to DXA, the most widely used method is T-score proposed by the World Health Organization (WHO) (20). Osteoporosis is defined as BMD measurements in women that have fallen by more than 2.5 standard deviations (SD) below the young adult average value (T-score ≤–2.5). Normal and osteopenia were defined as BMD within 1 SD of the young adult mean value (T-score ≥–1.0) and BMD more than1 SD below the young adult mean, but less than 2.5 SD below this value (–2.5< T-score <–1.0), respectively.

Statistical analysis

All statistical analyses were performed with the software SPSS 26.0 (IBM Corp., Armonk, NY, USA) and the significance level was set at two-sided P<0.05. Continuous variables were tested for normality with the Kolmogorov-Smirnov test and represented by mean ± SD (normally distributed) or medians with 25th and 75th percentiles (abnormally distributed). Independent samples *T*-test (normally distribution) and Mann-Whitney U test (abnormally distribution) were used for comparisons, as appropriate. Categorical variables were expressed as frequency (percentage) and were compared using the chi-squared test. Associations with BMD and clinical parameters were investigated using Spearman correlation analysis and Multiple linear regressions. Pearson correlation analysis was used to investigate the association between QCT-derived vBMD and DXA-derived aBMD. Weighted kappa consistency analysis was used to clarify the agreement between QCT and DXA. A weighted kappa value of 0.00–0.20 indicated slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; 0.81 to less than 1.00, almost perfect agreement; and 1.00, perfect agreement.

Results

Clinical and biochemical features in PHPT and HCs

A total of 50 PHPT patients and 150 age- and gender-matched healthy individuals were enrolled after meeting the inclusion and exclusion criteria. There were 2 patients and 7 healthy individuals extra excluded because of poor image quality. Finally, 191 participants were included in this study, including 48 PHPT patients, and 143 HCs. The mean age of the study population was 52.73 years (SD 11.30); 78.01% were female. The recruited groups were very homogenous and there were no differences between them in age and gender (all P>0.05). The PHPT group displayed markedly higher PTH and Alb-corrected Ca compared to the HC group. Specific descriptive characteristics of the participants in the 2 groups are summarized in *Table 1*.

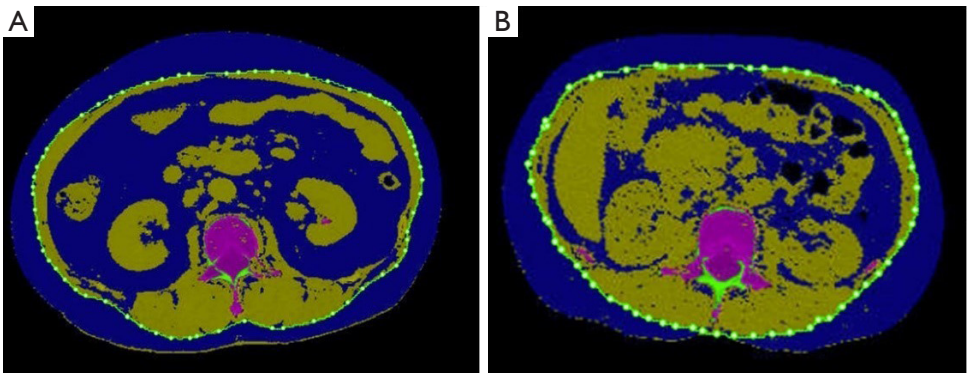

Figure 1 Abdominal adipose tissue distribution in patients and controls. The blue color represents the fat tissue, and the green dashed line depicts the abdominal wall. The fat inside this wall is VAT, while the fat outside the wall is SAT. TAT = VAT + SAT. (A) A 64-year-old female patient, whose VAT, SAT, and TAT were 240.5 cm^2, 149.7 cm^2, and 390.2 cm^2 respectively. (B) A 64-year-old HC group female whose VAT, SAT, TAT was 90.8 cm^2, 117.7 cm^2, 208.5 cm^2 respectively. VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total fat area; HC, healthy control.

The differences of QCT-derived vBMD and the abdominal fat distribution between PHPT and HC groups

As shown in *Table 1*, vBMD in the PHPT group was obviously lower than that in the HC group (114.30±41.71 *vs.* 136.92±42.23 mg/cm^3; P=0.002). It demonstrated that lumber's trabecular bone was impaired. Meanwhile, compared with controls, the PHPT group had significantly higher TAT (261.98±74.65 *vs.* 236.69±69.00 cm^2; P=0.033) and a suggestive significant trend of higher SAT (120.81±40.19 *vs.* 109.94±36.83 cm^2; P=0.085) and VAT (141.17±48.11 *vs.* 126.75±50.50 cm^2; P=0.085). *Figure 1* shows 2 representative images of the abdominal adipose tissue distribution in the patients and controls.

The relationship between vBMD and PTH level, age, TAT, SAT, VAT

Nonparametric Spearman rank correlation coefficient analysis showed that the vBMD was significantly and negatively correlated with PTH level in all participants (r=–0.254; P<0.001), but not those in the PHPT group (r=–0.182; P=0.215) or in the HC group (r=–0.153; P=0.068). Nevertheless, our data indicated that PTH level was significantly and negatively associated with aBMD of lumbar spine of L1–L3, L1–L4, L2–L4, and femoral neck in the PHPT group, as indicated in *Figure 2*.

Taking the 2 groups together, nonparametric Spearman rank correlation coefficient analysis showed that the vBMD was significantly and negatively correlated with TAT (r=–0.339; P<0.001), SAT (r=–0.284; P<0.001), VAT (r=–0.308; P<0.001). After adjustment for age and PTH level, multiple linear regression analysis showed that vBMD was negatively correlated with VAT (β=–0.115; P=0.025). When analyzing the 2 groups separately, nonparametric Spearman rank correlation coefficient analysis showed that lumbar vBMD was significantly and negatively correlated with all abdominal fat distribution parameters (TAT, SAT, VAT) in the HC group, and with VAT and TAT in the PHPT group, as indicated in *Table 2*. After adjustment for age and PTH level, multiple linear regression analysis showed that TAT (β=–0.183; P=0.002) was the significant correlation factor to vBMD in HC group, however, age was the only significant correlation factor to vBMD in PHPT group (β=–0.729; P<0.001).

The correlation and consistency between QCT and DXA in assessing bone status

Pearson correlation coefficient showed that there was a strong correlation between QCT-derived vBMD and DXA-derived aBMD (*Figure 3*). Patients with PHPT were divided into 3 categories including normal, osteopenia, and osteoporosis according to the bone status by QCT and DXA measurements. The results showed that the 2 methods concurred on 29 participants' bone status and diverged on 19, as indicated in *Table 3*. In general, the weighted kappa coefficient of the diagnosis results of the 2 modalities was 0.48 (95% CI: 0.29 to 0.68; P<0.001), showing a moderate consistency.

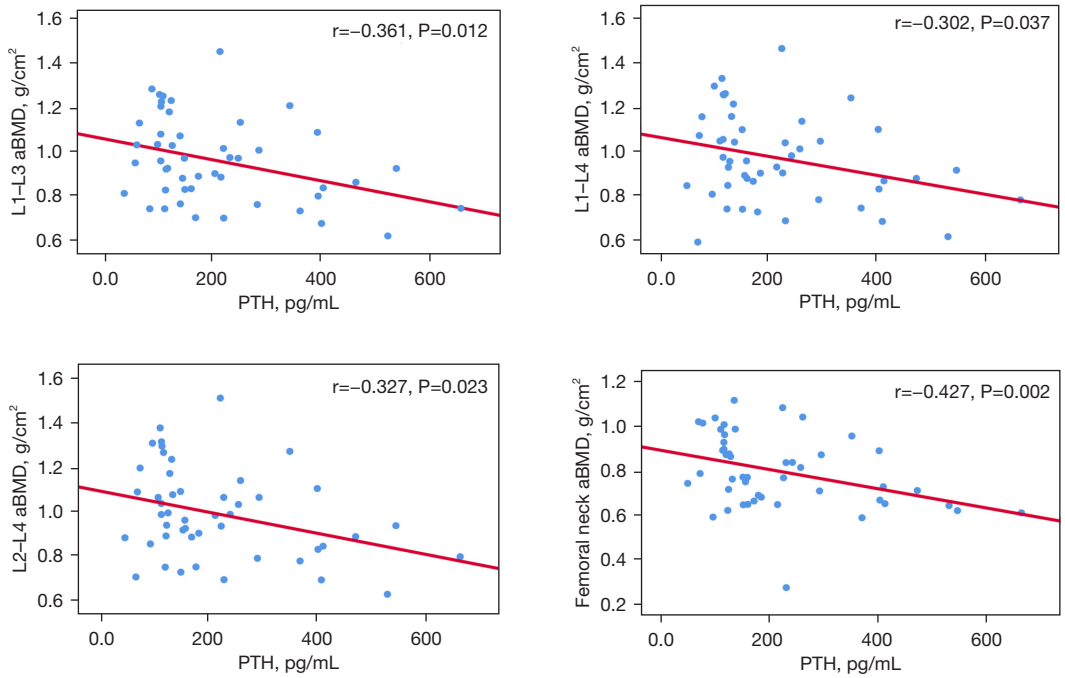

Figure 2 Correlation between PTH and aBMD. aBMD, areal bone mineral density; PTH, parathyroid hormone.

Table 2 Nonparametric Spearman rank correlation coefficient analysis between abdominal fat content and vBMD in PHPT and HC groups

Parameter	PHPT, r (P)			HC, r (P)		
	TAT	VAT	SAT	TAT	VAT	SAT
vBMD	−0.296 (0.041)	−0.324 (0.025)	−0.168 (0.255)	−0.332 (<0.001)	−0.293 (<0.001)	−0.305 (<0.001)
SAT	0.818 (<0.001)	0.457 (0.001)	–	0.675 (<0.001)	0.259 (0.002)	–
VAT	0.852 (<0.001)	–	–	0.864 (<0.001)	–	–

vBMD, volumetric bone mineral density; PHPT, primary hyperparathyroidism; HC, healthy control; TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

Discussion

The common endocrine disorder, PHPT, is characterized by hypercalcemia and elevated PTH. The PTH is a main regulator in calcium homeostasis and metabolism by acting on several organ systems. In bone, PTH stimulates the release of calcium from bone and increases bone resorption, leading to osteopenia, or even osteoporosis. Elevated PTH in PHPT patients mainly exerts negative effects on cortical bone but with relative preservation of trabecular bone. Recent new insights have clearly demonstrated that both cortical and trabecular bone compartments are affected in PHPT using high-resolution peripheral quantitative CT (HR-pQCT) and three-dimensional (3D)-DXA (9,15). In the lumbar spine, trabecular compartment reduction is also observed (21,22), which could explain the increased fracture risk at vertebral sites observed in PHPT patients. It has been well-documented that PTH is negatively correlated with changes in aBMD acquired by DXA, but the relationship between PTH and vBMD detected by QCT has scarcely been reported in PHPT. In accordance with previous studies, our data demonstrated that PTH was significantly and negatively associated with aBMD and vBMD. Moreover, in our present study, lumbar spine trabecular BMD (vBMD) in PHPT was also observed significantly reduced compared to the HC group. Thus, our data supported that trabecular bone is reduced in the lumbar spine, which might be associated with elevated

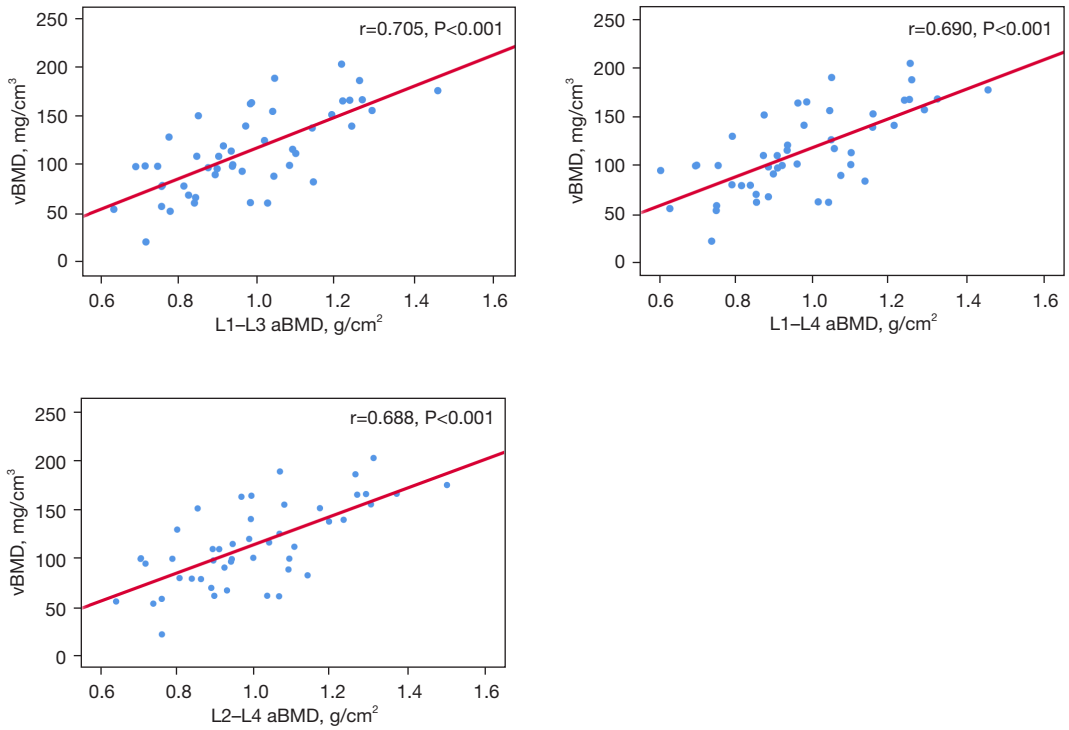

Figure 3 Correlation between DXA-derived aBMD and QCT-derived vBMD. vBMD, volumetric bone mineral density; aBMD, areal bone mineral density; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography.

Table 3 The crosstab of PHPT group' bone status

Bone status	DXA, n (%)	QCT, n (%)
Normal	15 (31.25)	19 (39.58)
Osteopenia	20 (41.67)	17 (35.42)
Osteoporosis	13 (27.08)	12 (25.00)

Kappa value (w) =0.48; P<0.001. PHPT, primary hyperparathyroidism; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography.

PTH concentration in PHPT patients. The QCT can directly assess the true vBMD, which is widely used for opportunistic screening of osteoporosis in China without additional cost, time, or radiation exposure to patients (13,23). Moreover, as a limitation, DXA cannot distinguish between trabecular and cortical bone compartments, due to its limited resolving power. Therefore, QCT has complementary value focused on trabecular bone compared with DXA focused on cortical bone alone in clinically evaluating bone condition in PHPT patients.

Another focus in our study was that lumbar QCT provides comparable results for detecting bone mineral loss compared to DXA as demonstrated by the strong correlation between DXA and QCT parameters. However, in the absence of clinical follow-up data such as the risk of incident vertebral fractures, we were unable to compare the superiority and inferiority of these 2 methods in assessing bone health. Interestingly, in a previous retrospective study, trabecular BMD assessed by opportunistic QCT showed a high association with the risk of incident vertebral fractures in a mixed population of mainly neurosurgical and oncologic patients. In contrast, the association of T-score measures by DXA was non-significant (24). Detailed results concentrating on these 2 methods need to be elucidated by further studies.

Regarding the fat distribution determined by QCT, our current study indicated that PHPT patients had significantly higher TAT and marginally higher VAT and SAT compared with HCs and this fat distribution abnormality was associated with bone metabolism. This leads us to ponder the following ideas: Firstly, the morbidity and mortality of patients with PHPT were significantly increased and cardiovascular-associated complications and death have received growing attention due to their

pivotal role in the progression of PHPT. As reported, hypertension, atherosclerosis, valve calcification, left ventricular hypertrophy, and impaired vascular endothelial function are considered associated with PHPT (2), but the potential biological and hormonal mechanisms involved are not explicit. It has been well-accepted that VAT seems to be associated with a variety of cardiovascular diseases (25-27). As expected, we found that the PHPT patients manifested significant abnormal fat distribution, as indicated by the increment of VAT and TAT. Thus, we propose that this fat metabolism disorder might be one of the main causes of cardiovascular diseases. Conversely, we found that TAT and VAT all were negatively correlated with BMD in both the PHPT group and HCs, but the causal relationship between fat metabolism and BMD remains to be studied. An earlier study (28) and the current study found that PTH level was correlated with VAT and BMD, moreover, it has been well-documented that both are the main target organs of PTH. Furthermore, after adjustment for age and PTH, the multiple linear regression analysis showed that neither TAT nor VAT were significantly correlated with BMD. Therefore, PTH may be the true intermediate factor causing the correlation between fat metabolism and BMD. However, researchers have also observed that body compositions contribute differently to BMD in different ages and genders (29,30). Further investigation is required on the causal relationship between fat tissue and BMD in PHPT patients.

There were several strengths to the present study. To our knowledge, we innovatively adopt QCT outcomes of trabecular BMD and abdominal adipose tissue to investigate differences between PHPT patients and HCs. As the trabecular bone was affected in PHPT patients and BMD was improved in trabecular bone after parathyroidectomy (31), QCT may be helpful in follow-up examinations. Moreover, parameters such as VAT and TAT acquired by QCT can provide more information which may be important in assessing disease condition. However, our study had several limitations. First, the number of patients was only 48, we could not conduct further study vBMD in different genders, of which the effects of estrogen deficiency in postmenopausal women may be more important than PTH (32). Second, no DXA data were collected in the HC group because DXA examination is not frequently used in this age bracket.

Conclusions

The present study provided the following new insights into the application of QCT in PHPT patients: The vBMD of the trabecular bone was significantly lower in the PHPT patients compared with the HCs. The change of abdominal adipose tissue distribution in PHPT patients can be identified by QCT. QCT have a moderate consistency with DXA assessing bone status. Our study further extended the application value of QCT without additional scan in patients with PHPT including assessment of bone conditions and adipose tissue.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1827/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1827/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1827/coif). All authors report that the study was supported by the Natural Science Foundation of Shanghai (No. 21ZR1439800) and "Yanhai-Ruijin Artificial Intelligence Aided Imaging Diagnostic Platform" Special Fund (No. 2018188). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (No.2017-201). The written informed consent for retrospective study is exempt.

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