Analysis of bone impairment by 3D DXA hip measures in patients with primary hyperparathyroidism: a pilot study

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Short title: Bone impairment by 3D DXA in primary hyperparathyroidism

Word count: 3491

Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

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Abstract:

Context: primary hyperparathyroidism (PHPT) has been related to bone loss. Dual-energy X-ray absorptiometry (DXA) cannot distinguish between trabecular and cortical bone compartments but the recently developed 3D-DXA software might overcome this issue.

Objective: to examine the differences in DXA-derived areal bone mineral density (aBMD) and 3D-DXA parameters at the hip site between patients with PHPT and a healthy control group.

Design: cross-sectional pilot study

Setting: hospital

Patients: 80 adults (59.5 ± 9.1 yrs), 40 with PHPT and 40 healthy age- and sex-matched healthy controls.

Measures: aBMD (g/cm^2) of the femoral neck, trochanter, shaft and total hip was assessed using DXA. Cortical surface (sBMD, mg/cm^2), cortical volumetric BMD (vBMD, mg/cm^3), trabecular vBMD (mg/cm^3), integral vBMD (mg/cm^3) and cortical thickness (mm) was assessed using 3D-DXA software.

Results: mean-adjusted values showed lower aBMD (7.5% to 12.2%, effect size: 0.51-1.01) in the PHPT group compared to the control group (all $p<0.05$). 3D-DXA revealed bone impairment (3.7% to 8.5%, effect size: 0.47-0.65) in patients with PHPT, mainly in cortical parameters (all $p<0.05$). However, differences in trabecular vBMD were not statistically significant ($p=0.055$). The 3D mapping showed lower cortical sBMD, cortical vBMD and cortical thickness at the trochanter and diaphysis in the PHPT group ($p<0.05$) compared to the control group. In both groups, the presence of osteopenia or osteoporosis is related to lower cortical bone.

Conclusions: aBMD and cortical 3D parameters are impaired in patients with PHPT versus healthy controls. The vBMD of the trabecular compartment seems to be affected though to a lower extent.

Keywords: parathyroid-related disorders, DXA, Bone QCT, Osteoporosis, 3D-DXA

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and parathyroid hormone (PTH) levels that are elevated or inappropriately normal (1, 2). In 80% of the cases, a single gland disorder causes the excessive secretion of PTH while in the remaining; a multiple gland disorder is the cause (1). In the United States, the prevalence of PHPT is higher in women (23 cases per 10,000 women) than in men (8.5 cases per 10,000 men) (3) and the condition has frequently been related to bone fragility.

Patients with PHPT present high rates of bone remodelling and a slow decline in bone mass. Findings from a 15-year observational study showed that the areal bone mineral density (aBMD) of the femoral neck and radius decreased while that of the lumbar spine was preserved (4). In a study with 52 patients with PHPT (5), the most important reductions in aBMD were found at the radius, a site of predominantly cortical bone whereas normal aBMD was found at the lumbar spine, a site of predominantly trabecular bone. With regards to femoral neck aBMD (mix of cortical and trabecular bone), 23% of the patients with PHPT had values that were lower than those of 80% of their age- and sex-matched healthy peers (5). Percutaneous bone biopsies confirmed the impairment of cortical bone with apparent preservation of trabecular bone in PHPT (5), which was backed up in other studies (6, 7). However, with the arrival of new and more precise technologies the way these findings were looked at changed. Studies using peripheral quantitative computed tomography (pQCT) showed a catabolic effect of PTH on both trabecular and cortical bone compartments (8, 9). Interestingly, a study using high-resolution pQCT (HRpQCT) suggested that mechanical loading helped to counteract the detrimental effects of PTH on trabecular bone of the tibia (not in the radius), but it did not ward off the loss of cortical bone in PHPT (10).

Epidemiology studies suggest that PHPT is associated to an increased overall risk of fracture (10, 11). Dual energy X-ray Absorptiometry (DXA) is considered the gold standard method for assessing aBMD by non-invasive means in a clinical setting and has been used worldwide in numerous population groups of different ages (12). It is also a valid method to diagnose osteoporosis and to predict the risk of fracture in adults (13), with special relevance to those of the femur due to the high prevalence of fractures at this site (14). As a limitation, DXA cannot distinguish between trabecular and cortical bone compartments DXA due to its limited resolving power (10). Advanced techniques, such as pQCT or HRpQCT enable *in vivo* assessment of trabecular and cortical bone microarchitecture but they are very expensive and only available in few laboratories worldwide. Therefore, combining DXA-derived aBMD data with 3D QCT-like parameters of cortical and trabecular bone would be an alternative in clinical settings. In this study, we not only used aBMD of hip sites but also the recently developed 3-dimensional (3D)-DXA software algorithm to quantify the cortical thickness and the volumetric bone mineral density (vBMD) of the cortical and trabecular bone compartments, among other parameters. This method models the femoral neck and the bone density distribution, and assesses the trabecular macrostructure and the cortex in 3D using an anteroposterior DXA projection (15). The accuracy of the 3D-DXA models and measurements has been evaluated using a database with 157 subjects and comparing the 3D-DXA analyses with QCT measurements (15). The 3D-DXA parameters have shown very strong correlations compared to QCT outcomes and are therefore, a feasible alternative when pQCT is not available (16).

In this pilot study, we aimed to examine between-group differences in DXA-derived aBMD and 3D-DXA parameters at the hip site between patients with PHPT and a healthy control group. Additionally, we aimed to examine within-group differences in 3D-DXA parameters according to the World Health Organization criteria for osteoporosis and osteopenia. We

hypothesized that patients with PHPT would present poorer bone health than controls and that both cortical and to a lower extent trabecular vBMD, would be affected.

Material and methods

Study design and participants

The current cross-sectional pilot study includes data from 80 adults (59.5 ± 9.1 years old, 58 females) from Granada (Spain). Data were obtained between 2016 and 2017 at the Endocrinology Unit of the University Hospital San Cecilio of Granada. Forty patients (n=40) with PHPT, having hypercalcemia (mean and standard deviation: 10.7±0.5 mg/dL) and elevated PTH levels (mean and standard deviation: 114.9±40.8 mg/dL), were included. None of them had osteitis fibrosa cystica. Early menopause, familial hypocalciuric hypercalcemia and the use of glucocorticoids, bisphosphonates or other antiresorptive treatment in the two years before inclusion were considered exclusion criteria.

An age- and sex-matched healthy control group (n=40) was also recruited. None of the participants presented, at the moment of recruitment, diseases known to affect bone metabolism. Early menopause, a history of previous fragility fracture and the use of glucocorticoids, bisphosphonates or other antiresorptive treatment in the two years before inclusion were considered exclusion criteria.

The study was conducted according to the Declaration of Helsinki and the approval of the Ethics Committee of the Provincial Biomedical Research of Granada. Informed consent was obtained from all participants.

Outcome measures

Areal bone mineral density

A left hip scan using a Hologic QDR 4500 densitometer (Hologic Series Discovery QDR, Bedford, MA, USA) was used to measure aBMD at the femoral neck, trochanter, shaft and total

hip. Of note, the shaft location was defined along a line 2cm distal to the user located midpoint of the lesser trochanter, measured along the shaft axis (17). In addition, we used the World Health Organization criteria for osteoporosis and osteopenia (18). All DXA scans and analyses were performed by the same experienced operator following recommendations from the International Society of Clinical Densitometry (19). The DXA equipment was calibrated on a daily basis using a spine phantom. The coefficients of variation within our laboratory were 1.8% and 1.5% for the femoral neck and total hip, respectively. Moreover, the coefficients of variation in a previous study with men and women over the age of 60 years were 2.13% and 3.14% for the shaft and trochanter, respectively (20).

3D-DXA modeling

The 3D-Shaper software (version 2.2, Galgo Medical, Barcelona, Spain) was used to assess the trabecular macrostructure, the cortex and femoral shape from DXA scans of the PHPT and control groups. Detailed information of the modelling method used in the software has been published elsewhere (15). Briefly, this method is based on a statistical shape and density model of the proximal femur generated from a database of QCT scans of Caucasian women and men (15). The 3D model is registered onto the DXA scan in order to obtain a 3D QCT-like participant-specific model of the proximal femur shape and BMD distribution. The cortical thickness and density is computed by fitting a mathematical function to the density profile computed along the normal vector at each node of the proximal femur surface mesh (21). The cortical thickness (mm) and the vBMD (mg/cm^3) of the trabecular, cortical, and integral bone compartments of the total femur was computed (22). In addition, the cortical surface BMD (sBMD, mg/cm^2) at each vertex of the femoral surface mesh is computed as the product between cortical thickness (cm) and the cortical vBMD (mg/cm^3) along its thickness (16). Cortical sBMD, cortical vBMD and cortical thickness measure the cortical compartment, while

trabecular vBMD measures the density of the trabecular compartment. Integral vBMD measures the integral compartment, being the union of the trabecular and cortical compartments. All measurements are performed at the total femur region of interest. The correlations between QCT and 3D-DXA for integral vBMD, trabecular vBMD, cortical vBMD and cortical thickness were 0.95, 0.86, 0.93 and 0.91, respectively (15). The coefficients of variation for cortical thickness, trabecular vBMD, cortical vBMD and cortical sBMD were 1.5%, 4.5%, 1.7% and 1.5% (16).

Anthropometric measures

Weight (kg) and stature (cm) were measured with an electronic scale (SECA 861 and 760, Hamburg, Germany) and a stadiometer (SECA 225 and 220, Hamburg, Germany), respectively. The body mass index (BMI) was calculated as: weight (kg)/stature (m^2).

Serum measurements

Venous blood samples were obtained by venipuncture after an overnight fast. Serum parathormone (PTH, pg/mL) was measured using two-site immunoassay for PTH (Roche Diagnostics SL, Barcelona, Spain). Calcium (mg/dL, adjusted for serum albumin) was measured using standard automated laboratory techniques. Normal levels for calcium range between 8.8 and 10.2 mg/dL and for PTH between 12-88 pg/mL.

Statistical analysis

Data were analyzed using SPSS IBM statistics (version 20 for Windows, Chicago, IL) and the significance level was set at $p<0.05$. The distribution of variables was checked and verified using Kolmogorov-Smirnov test, skewness and kurtosis values, visual check of histograms, Q-Q and box plots.

Descriptive analyses comparing the PHPT and control groups were performed by independent samples *T*-test (for continuous variables) or chi-square test (for categorical variables).

Analysis of covariance (ANCOVA) was used to examine differences in the outcome variables (aBMD and 3D-DXA parameters) between the PHPT and control groups. Sex, age and BMI were used as covariates. The effect size (ES, Cohen's *d*) is also provided and the interpretation is: 0.2 small, 0.5 medium and 0.8 large (23). Percentages of difference between groups for the significant variables in the ANCOVA analysis were used to quantify the magnitude of the differences. 3D spatial distribution of differences between PHPT and control groups in the cortical bone (cortical sBMD, cortical vBMD and cortical thickess) were computed.

Finally, the discrimination of bone status (normal, osteopenia, osteoporosis) by 3D-DXA measurements in patients with PHPT and controls was performed using ANCOVA and including sex, age and BMI as covariates.

Results

Table 1 shows descriptive characteristics of the participants in the PHPT and control groups. The proportion of males (27.5%) and females (72.5%) was the same in both groups and the higher number of females reflects the higher prevalence of PHPT. The recruited groups were very homogenous and there were no differences between them in age, height, weight and BMI (all $p>0.05$). Crude aBMD and 3D-DXA parameters of the cortical sBMD, integral vBMD and cortical thickness were significantly lower in the PHPT group compared to the control group (all $p<0.05$).

Table 2 presents mean-adjusted (by age, sex and BMI) differences in aBMD and 3D-DXA parameters between groups. aBMD was significantly lower in the PHPT group compared to the

control group at all sites: femoral neck ($p=0.023$, ES=0.51), trochanter ($p=0.001$, ES=0.75), shaft ($p<0.001$, ES=0.91) and total hip ($p<0.001$, ES=1.01). More specifically, the aBMD was 7.5%, 10.2%, 11.7% and 12.2% lower in the PHPT group compared to the control group at the femoral neck, trochanter, shaft and total hip, respectively (Figure 1). 3D-DXA parameters showed poorer cortical sBMD ($p=0.005$, ES=0.65), cortical vBMD ($p=0.037$, ES=0.47), integral vBMD ($p=0.022$, ES=0.52) and cortical thickness ($p=0.011$, ES=0.63) in the PHPT group compared to the control group. However, the difference between groups in trabecular vBMD did not reach statistical significance ($p=0.055$). More specifically, the cortical sBMD, cortical vBMD, integral vBMD and cortical thickness of the PHPT was 4.3%, 8.4%, 3.7%, and 8.5% lower than the control group (Figure 1).

3D mapping showing the anatomical distribution of differences between groups in the cortical compartment indicates that the PHPT group had significantly lower cortical sBMD, cortical vBMD and cortical thickness at the trochanter and diaphysis ($p<0.05$), while differences at the femoral neck were not statistically significant (Figure 2).

Finally, patients with PHPT and diagnosed with osteoporosis or osteopenia had significantly lower cortical vBMD compared to those with normal bone values (Figure 3). For the rest of the 3D-DXA outcomes, lower values were also observed with increasing bone deterioration however; a statistical significance was not reached ($p>0.05$). With regards to the control group, those diagnosed with osteopenia had significantly lower cortical sBMD, cortical vBMD, integral vBMD and cortical thickness compared to those with normal bone density values (Figure 3). No controls were classified into the osteoporosis category.

Discussion

Our pilot study is the first combining hip DXA-derived and 3D-DXA outcomes of cortical and trabecular bone to examine differences between PHPT patients and healthy controls. The main findings of the present study show that: 1) the aBMD of the femoral neck, trochanter, shaft, and total hip was significantly lower in PHPT patients compared to the control group; 2) the 3D-DXA parameters involving cortical bone compartments (cortical sBMD, cortical vBMD, integral vBMD and cortical thickness) were significantly lower in PHPT patients than the control group while a trend for a lower trabecular vBMD was also observed in this group, which is consistent with our hypothesis. The ES of the differences observed between PHPT and healthy controls ranged from 0.51 to 1.01 (for aBMD parameters) and from and 0.47 to 0.65 (for 3D-DXA parameters), suggesting a medium to large effect sizes.

From a DXA point of view, in patients with PHPT trabecular bone is relatively preserved while cortical bone is largely affected. Therefore, lower aBMD is usually observed in PHPT patients compared to controls at the hip or radius (4-7), sites with a high proportion of cortical bone. Our findings on the catabolic effects of excess PTH on aBMD agree with those from the study of Rubin et al (4), in which declines in femoral neck aBMD were evident in patients with PHPT. Similarly, a study conducted in elderly men with PHPT observed lower aBMD at the total hip (~7%), femoral neck (7.7%) and trochanter (11.6%) compared to a control group without the disease (24). This approach is based on the catabolic action of PTH on cortical bone, acting on osteocytes, osteoblasts and osteoclasts and increasing bone remodelling in favour of bone resorption (25) to ultimately, result in bone loss (26).

Recent scientific evidence using more advanced techniques and devices have shown trabecular bone deterioration assessed by TBS (27-29), pQCT (8, 9) and HRpQCT (10, 30-32) in patients with PHPT. In this regard, we recently showed TBS to reflect degraded bone structure and diagnose bone fragility in patients with PHPT better than aBMD (33), a finding that is consistent with a study using HRpQCT (10). Therefore, the catabolic effects of PTH in both cortical and

trabecular bone seem now to be evident as shown in a HRpQCT study (10). In the present study, using 3D-DXA parameters (more affordable than QCT devices) we have observed deterioration of cortical bone and a non-significant deterioration of trabecular bone. Our data suggest reduced vBMD of mainly cortical and to a lower extent trabecular (though non-significant) compartments, thinner cortices and also reduced sBMD, a highly accurate indicator of cortical bone strength (34). Our 3D-DXA findings are consistent with those reported in studies using HRpQCT (10, 35) in PHPT patients. In addition, the non-significant (but borderline) deleterious effect of PHPT on trabecular vBMD in the present study can be partially explained by the compensatory effect of mechanical loading which is very likely to have a protective effect in the hip (36), and is known to preserve the loss of trabecular bone (10). In addition, the relatively small sample size might have contributed to this non-statistically significant finding.

Our 3D mapping shows that the greatest differences in cortical vBMD, cortical sBMD and cortical thickness between groups are in the trochanteric area rather than the femoral neck, which might suggest a greater risk of fractures in this site. Previous studies have found a higher but statistically non-significant risk of fracture at the proximal femur and femoral neck in patients with PHPT compared to those without the condition (37, 38), backing up our findings. In addition, Fischer et al. observed the presence of (secondary) hyperparathyroidism in 30.2% of the patients with femoral neck fracture and in 41.3% of those with trochanteric fracture. Interestingly, PTH was significantly higher in patients with trochanteric fracture than in those with the femoral neck fracture (39), supporting the role of PTH in site-specific fractures.

Finally, our data also suggest that patients with PHPT with osteopenia or osteoporosis had their femoral neck cortical bone more impaired than those with normal bone density. However, trabecular bone and cortical thickness did not differ according to the bone diagnosis. These findings support the fact that the presence of osteopenia or osteoporosis is due to the greater bone deterioration of the cortical bone compartment of the femoral neck. This agrees with the

studies of Bandeira et al. (40) in which cortical osteoporosis was found at the femoral neck in patients with PHPT and the recent study of Osima et al. (41) in which PTH was associated with increased femoral cortical subtrochanteric cortical porosity in postmenopausal women. However, we only had 5 patients (12.5%) with PHPT with normal bone density which may have (negatively) affected comparisons. With regards to the healthy control group, our data suggest that those with osteopenia had their cortical and trabecular bone more impaired than those with normal bone density. It is important to highlight that since we recruited a healthy control group, none control participants had osteoporosis. Therefore, sample sizes are more even for normal bone density (n=23) and osteopenia (n=17) enabling more solid comparisons.

Our findings suggest that the combination of aBMD with 3D-DXA parameters may be useful for clinicians wishing to evaluate bone health in everyday practice at the hip site in patients with PHPT. Despite the guidelines for the management of asymptomatic primary hyperparathyroidism recommended lumbar spine, hip and forearm scans in patients with PHPT (42), there is evidence showing that the forearm is not routinely assessed and therefore, a substantial but unrecognized bone loss may be present (43). The 3D-DXA derived parameters may provide useful information on cortical bone and complement the forearm scan. This is important since other technique, such as HRpQCT is only available in a few places worldwide and unlikely to become widely used (44).

Strengths and limitations

Our study is the first to report 3D-DXA outcomes and compare cortical and trabecular bone and quantify the differences between PHPT patients and healthy controls using an approach based on 3D QCT-like participant-specific models of the proximal femur shape and BMD distribution. Despite the sample size is relatively small the recruitment of an age- and sex-matched control group ensured having two very homogenous groups. In our study the

proportion of males and females with PHPT in both groups was 27.5% and 72.5%, respectively. This was expected since the prevalence of the disease is almost triple in females (3).

As limitations, the cross-sectional design precludes any determination of causality in our findings. However, whilst the catabolic effect of PTH on bone mass has been described, the mechanisms by which a greater or lower bone mass could affect PTH concentrations are unknown. In addition, we only had 5 patients with PHPT with a normal densitometric diagnosis and this may have affected our results on the differences in 3D-DXA parameters according to DXA bone diagnosis. This might explain why significant differences were only found for the cortical vBMD but not for the rest of the parameters in the PHPT group while significant differences were observed in all parameters of the control group (n with normal bone = 23). Moreover, we recruited a healthy control group and none of them had osteoporosis. This has to be kept in mind when interpreting the between-group and within-group differences from this study. Finally, since information on lifestyle behaviours such as exercise, nutrition or tobacco smoking among others was not collected, we cannot rule out the possibility that these factors contributed to the existing differences described in this study. Future longitudinal studies, including osteoporotic controls and assessing fracture risk are warranted to test the potential of 3D-DXA in clinical settings.

Conclusions

The findings indicate that patients with PHPT have lower aBMD at the hip sites and reduced cortical 3D parameters compared to an age- and sex-matched healthy control group. In addition, the vBMD of the trabecular compartment seems to be affected though to a lower extent. Longitudinal studies including fracture assessment are needed to confirm the usefulness of 3D-DXA software for routine clinical practice with PHPT patients.

Acknowledgements

We thank all participants and Ludovic Humbert for his support with 3D-DXA software. This work was supported by Fondo de Investigación Sanitaria (Instituto de Salud Carlos III) (Grant PI18/01235) with co-financing from FEDER. In addition, LG-M is funded by "La Caixa" Foundation within the Junior Leader fellowship programme (ID 100010434).

Authors' roles: Study design: MM-T and AG-M. Data collection: BG-F. Data analysis: LG-M. Data interpretation: LG-M, BG-F, EU-G, DV and MM-T. Drafting manuscript: LG-M. Revising and approving manuscript content: LG-M, BG-F, EU-G, DV, AG-M and MM-T.

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Figure 1. Significant differences (%) in adjusted (by age, sex and body mass index) areal bone mineral density (aBMD, g/cm^2) and 3D-DXA parameters between patients with primary hyperparathyroidism (PHTP, n=40) and the healthy control group (n=40). * denotes a significant difference relative to the control group ($p<0.05$)

Figure 2. Distribution of the average differences ($p < 0.05$) in (A) cortical surface bone mineral density (cortical sBMD), (B) cortical volumetric bone mineral density (cortical vBMD) and (C) cortical thickness of the total femur region in the primary hyperparathyroidism (PHTP, n=40) group relative to the healthy control group (n=40). Regions with no significant differences are coloured in grey ($p>0.05$).

Figure 3. 3D-DXA parameters of patients with primary hyperparathyroidism (PHTP, n=40) and the healthy control group (n=40) according to the World Health Organization criteria for osteoporosis and osteopenia. White bars = normal bone density; grey bars = osteopenia and black bars = osteoporosis. Results (mean and standard error) are adjusted by age, sex and body mass index.

PHPT group: Normal bone density (n=5), osteopenia (n=15) and osteoporosis (n=20).

Healthy control group: Normal bone density (n=23), osteopenia (n=17) and osteoporosis (n=0).

* denotes within-group significant differences ($p<0.05$) versus normal bone density.