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Effect of concomitant vitamin D deficiency or insufficiency on lumbar spine volumetric bone mineral density and trabecular bone score in primary hyperparathyroidism

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Abstract

Summary—Lower vitamin D and higher parathyroid hormone (PTH) levels are associated with higher volumetric BMD and bone strength at the lumbar spine as measured by central quantitative computed tomography in primary hyperparathyroidism (PHPT), but there are no differences in bone microarchitecture as measured by trabecular bone score (TBS).

Introduction—The purpose of this study was to evaluate the association between 25-hydroxyvitamin D (25OHD) and volumetric bone mineral density (vBMD) and the TBS at the lumbar spine (LS) in PHPT.

Methods—This is a cross-sectional analysis of PHPT patients with and without low 25OHD. We measured vBMD with quantitative computed tomography (cQCT) and TBS by dual-energy X-ray absorptiometry (DXA) at the LS in 52 and 88 participants, respectively.

Results—In the cQCT cohort, those with lower vitamin D (<20 vs. 20–29 vs. 30 ng/ml) tended to be younger ($p = 0.05$), were less likely to use vitamin D supplementation ($p < 0.01$), and had better renal function ($p = 0.03$). Those with 25OHD <20 ng/ml had 80 and 126 % higher serum PTH levels respectively vs. those with 25OHD 20–29 ng/ml ($p = 0.002$) and 25OHD 30 ng/ml ($p < 0.0001$). Covariate-adjusted integral and trabecular vBMD were higher in those with 25OHD 20–29 vs. those with 25OHD 30 ng/ml, but those with 25OHD <20 did not differ. Because there were few participants with 25OHD deficiency, we also compared those with vitamin D <30 vs.

30 ng/ml. Covariate-adjusted integral and trabecular vBMD were 23 and 30 % higher respectively (both $p < 0.05$) in those with vitamin D <30 vs. 30 ng/ml. TBS was in the partially degraded range but did not differ by vitamin D status.

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Compliance with ethical standards

Conflicts of interest Didier Hans is a co-owner of the patent for TBS and has corresponding ownership shares in Medimaps. Marcella D. Walker, Isra Saeed, James Lee, Chengchen Zhang, Thomas Lang, and Shonni Silverberg declare that they have no conflicts of interest.

Conclusion—In mild PHPT, lower 25OHD is associated with higher PTH, but vitamin D deficiency and insufficiency using current clinical thresholds did not adversely affect lumbar spine skeletal health in PHPT. Further work is needed to determine if higher vBMD in those with lower vitamin D is due to an anabolic effect of PTH.

Keywords

Central quantitative computed tomography; Primary hyperparathyroidism; Trabecular bone score; Vitamin D deficiency; Volumetric bone density

Introduction

The skeleton remains an important target organ in primary hyperparathyroidism (PHPT). While *osteitis fibrosa cystica* is rarely seen in the USA today, subclinical skeletal disease in asymptomatic PHPT is common. Dual-energy X-ray absorptiometry (DXA) demonstrates preferential loss of bone mineral density (BMD) at cortical sites such as the distal third of the forearm in PHPT while cancellous sites such as the lumbar spine are relatively spared [1]. This pattern is thought to reflect the catabolic vs. anabolic effects of parathyroid hormone (PTH) upon different skeletal compartments [2].

While data are limited, some studies suggest that coexisting vitamin D deficiency exacerbates skeletal disease in PHPT [3–10]. We recently reported that concomitant vitamin D deficiency (25-hydroxyvitamin D (25OHD) <20 ng/ml) in PHPT is associated with higher serum PTH levels [11]. The higher PTH, however, had nominal effects on skeletal health. By DXA, we found only modestly lower areal BMD at the predominantly cortical one-third radius site in women with PHPT and vitamin D insufficiency (25–hydroxyvitamin D 20–29 ng/ml) [11]. In contrast, we found no differences in areal BMD by vitamin D status at the more cancellous lumbar spine or hip sites using DXA.

Data regarding the effects of vitamin D deficiency in PHPT upon different skeletal compartments (cancellous vs. cortical) are limited and somewhat conflicting. Histomorphometric data from percutaneous iliac crest bone biopsies in our prior natural history study of PHPT demonstrated reduced cortical width in PHPT patients with vitamin D deficiency (<20 ng/ml) compared to those with higher levels (≥ 20 ng/ml) [12]. In contrast, trabecular indices including BV/TV, trabecular number, and separation were more favorable in those with vitamin D <20 vs. those with vitamin D ≥ 20 ng/ml. While this finding is consistent with an “anabolic” effect of the higher PTH levels in those with simultaneous vitamin D deficiency, it contrasts with our more recent data using high-resolution peripheral quantitative computed tomography (HRpQCT) [13]. In our HRpQCT study (in which mean serum 25OHD levels were higher and PTH levels were lower compared with those in the histomorphometric study by Stein et al. [12]), neither vitamin D deficiency nor insufficiency had a significant effect on either cortical or trabecular volumetric bone mineral density (vBMD) and microarchitecture or bone strength at the radius or tibia [13].

While our HRpQCT study provides insight regarding how vitamin D deficiency and insufficiency affect peripheral skeletal sites, data on trabecular vBMD and on microarchitecture at the clinically important cancellous lumbar spine are lacking. We

hypothesized that vitamin D deficiency and subsequent heightened PTH levels in PHPT might be associated with more favorable vBMD and trabecular bone score (TBS) values at the lumbar spine using cQCT and DXA, respectively. For purposes of this analysis we assessed the relevance of commonly employed clinical vitamin D thresholds which are recognized by the Endocrine Society Clinical Practice guidelines and other bone and mineral organizations (insufficiency: defined as 25OHD 20–29 ng/ml and deficiency: <20 ng/ml) [14] to skeletal health in PHPT.

Methods

This is a cross-sectional study assessing vBMD by quantitative computed tomography (cQCT) and TBS by DXA. All patients gave written, informed consent. This study was approved by the Institutional Review Board of Columbia University Medical Center (CUMC).

Subjects

Participants were recruited from the Metabolic Bone Diseases Unit as well as the Endocrine Surgery and General Endocrinology Clinics at CUMC. Participants represent a subset of participants in our previous reports on the effects of vitamin D deficiency and insufficiency in PHPT [11, 13]. DXA images and thus TBS data were available for 88 participants while 52 participants agreed to undergo cQCT. Forty-five participants had both cQCT and TBS values available. Participants with TBS did not differ from those without TBS in age ($p = 0.51$), sex ($p = 0.69$), race/ethnicity ($p = 0.69$), mean serum calcium ($p = 0.75$), PTH ($p = 0.30$), or vitamin D levels ($p = 0.17$). Likewise, participants who underwent cQCT did not differ from those who refused. Recruitment methods and enrollment criteria have been described [11, 13]. Briefly, participants had PHPT, diagnosed by both hypercalcemia (calcium >10.2 mg/dl) and an elevated or inappropriately normal PTH level on more than one occasion prior to enrollment. None had thiazide-induced hyperparathyroidism or familial hypocalciuric hypercalcemia (FHH; excluded on the basis of family history and 24-h urine calcium). Exclusion criteria included bisphosphonate use within 2 years; current use of cinacalcet or denosumab; current or previous use of prednisone 7.5 mg >6 months; current or past use of carbamazepine, phenytoin, or phenobarbital >3 months; malignancy within 5 years other than non-melanomatous skin cancer; granulomatous diseases, HIV, and serum creatinine level ≥ 1.5 mg/dl; liver disease; gastrointestinal diseases known to affect calcium metabolism such as Crohn's disease, celiac disease, or gastric bypass; and pregnancy.

Clinical and biochemical evaluation

Demographic data, medical history, and medication use were obtained from participants. Calcium and vitamin D intake and sun exposure were assessed by validated questionnaire [15, 16]. Fasting samples for serum calcium, phosphate, albumin, and creatinine were measured by an automated chemistry analyzer. PTH was measured by radioimmunoassay (RIA) for intact PTH, which detects PTH (1–84) and PTH (7–84) (Scantibodies, Laboratory, Santee, CA, USA). Serum 25OHD and 1,25-dihydroxyvitamin D were measured by liquid chromatography/tandem mass spectrometry (Quest Diagnostics, Teterboro, NJ, USA, and

Chantilly, VA, USA, respectively). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [17].

Dual-energy X-ray absorptiometry

Areal bone density was measured at the lumbar spine, L1–L4 (LS) (Hologic Inc., Waltham, MA, USA). In vivo precision, determined according to the standard method at this facility, is 1.28 % at the lumbar spine [18].

Quantitative computed tomography

Helical CT images (GE LightSpeed 64 VCT Scanner; GE Medical Systems, Milwaukee, WI, USA) were acquired at the L1 and L2 vertebrae as previously described [19–21] at CUMC. De-identified images were processed to extract measures of integral and trabecular volumetric BMD and bone size using analysis techniques described previously at UCSF [19–21]. Cortical density cannot be measured with this methodology and software. The processing task included calibration of the CT images from the native scanner Hounsfield Units to equivalent concentration (in g/cm³) of calcium hydroxyapatite. The following BMD and geometric measures were determined according to previously published methods by a blinded reader [19–21]: L1–L2 vertebral cross-sectional area (CSA) as well as L1–L2 average mid-vertebra integral and trabecular volumetric BMD. Vertebral strength was estimated as [(cross-sectional area) × (mid-centrum integral vBMD)²]. Precision values for QCT measures are 1.76–2.93 % for lumbar spine density measures and 1.4–2.4 % for cross-sectional area.

Trabecular bone score

Site-matched spine TBS parameters were extracted from the DXA images using TBS iNsight software (v1.9, Medimaps Group, Geneva, Switzerland). TBS measurements were performed by an investigator blinded to vitamin D status in the Bone Disease Unit at the University of Lausanne, Lausanne, Switzerland, using de-identified spine DXA files from scans obtained at CUMC. TBS was evaluated by determining the variogram of the trabecular bone projected image, calculated as the sum of the squared gray-level differences between pixels at a specific distance and angle. As previously described, TBS was then calculated as the slope of the log-log transform of this variogram [22]. The mean value of the individual measurements for L1 to L4 represents the lumbar spine TBS (unitless). The precision of TBS ranges from 1.12 to 1.9 %, as previously reported [23, 24]. The following postmenopausal female norms were utilized for TBS: TBS = 1.31, normal; TBS 1.23–1.31, partially degraded; and TBS = 1.23, degraded [25]. In addition to the standard region of interest, we also assessed TBS limiting the region of interest (ROI) to L1–L2 to match that of cQCT. The TBS has been shown to be significantly associated with direct measurements of bone microarchitecture and mechanical behavior [22, 26, 27] and predictive of fragility fractures in postmenopausal women with primary and secondary [25, 28, 29] osteoporosis.

Statistical analysis

Between-group differences in demographic and skeletal indices were evaluated with analysis of variance (ANOVA), Student's *t* test, chi-square, or Fisher's exact test as appropriate.

Values are expressed as least squares means $\pm$ SD or percentages. Relationships between 25OHD, PTH, calcium, and skeletal indices were assessed with Spearman correlation. Analysis of covariance (ANCOVA) models were used to assess between-group differences adjusting for covariates and to assess for the interaction between vitamin D and PTH upon vBMD and vertebral strength (VSTR). Analyses were adjusted for age and weight regardless of between-group differences due to their known effects on BMD and microarchitecture and tendency to correlate with TBS (age $r = -0.38$, $p < 0.001$; weight $r = -0.31$, $p < 0.01$) as well as trabecular (weight $r = -0.26$, $p = 0.06$) and integral ($r = -0.24$, $p = 0.09$) vBMD. Statistical analysis was performed using SAS, Version 9.4 (Cary, NC, USA). A two-tailed p value < 0.05 was considered significant.

Results

cQCT cohort

Among the 52 participants with cQCT data, 86.5 % were female and mean age was 62.1 ± 10.1 years. Participants had mild PHPT (mean calcium 10.6 ± 0.6 mg/dl, PTH 75 ± 32 pg/dl, 25OHD 30.9 ± 11.4 ng/ml). Vitamin D ranged from 9 to 54 ng/ml. In this group, 19.2 % had vitamin D deficiency (mean 25OHD 14.1 ± 2.3 ng/ml) while 28.8 % had levels in the insufficient range (25OHD 26.0 ± 2.0 ng/ml) and 51.9 % were vitamin D replete (25OHD 39.8 ± 6.9 ng/ml). Only one participant had 25OHD < 10 ng/ml. None of the linear correlations between cQCT parameters and PTH, 25OHD, calcium, or TBS were significant.

In addition to the linear associations between vitamin D and cQCT, we were also interested in cQCT differences by vitamin D status, using common clinical cut points (< 20 vs. $20-29$ vs. 30 ng/ml). Between-group differences in demographic factors are shown in Table 1. Those with lower vitamin D tended to be younger ($p = 0.05$). They were also less likely to be using vitamin D supplementation ($p < 0.01$). There were no significant between-group differences in sex, race/ethnicity, height, weight, BMI, meeting surgical guidelines, or tobacco use. Lumbar spine T-score by DXA was normal (-1.0 ± 1.7) and did not differ by vitamin D status (Table 2).

Those with vitamin D deficiency had a mean PTH value above the reference range that was 80 and 126 % higher compared to those with vitamin D insufficiency ($p = 0.002$) and those who were replete respectively ($p < 0.0001$; Table 2). Mean PTH level was also above the reference range in those with vitamin D levels $20-29$ ng/ml, but did not differ from those with 25OHD 30 ng/ml ($p = 0.48$). Mean PTH was normal in those who were vitamin D replete. There was a non-significant trend toward higher calcium levels in those with lower vitamin D. Phosphate was lower in those with lower vitamin D ($p = 0.003$), but 1,25-dihydroxyvitamin D levels did not differ between groups. Estimated GFR tended to be higher in those with vitamin D deficiency and insufficiency vs. those who were vitamin D replete (Table 2).

As shown in Table 3, neither vertebral size, nor trabecular or integral vBMD, nor bone strength differed by vitamin D status before adjusting for covariates. After adjusting for age, weight, and eGFR, mid-vertebral (L1-L2) trabecular ($p = 0.03$) and integral vBMD ($p = 0.03$) as well as vertebral strength ($p = 0.04$) were higher in those with 25OHD $20-29$ vs.

those with 25OHD ≥ 30 ng/ml (Fig. 1a). There were no differences between those with 25OHD <20 ng/ml vs. the other groups or differences in vertebral size ($p = 0.92$) after adjusting for age, weight, and eGFR. Additionally adjusting for sex did not alter results. In order to assess the possibility that mild elevations in PTH (<100 pg/ml) above the normal range (as in the 25OHD 20–29 ng/ml) might be anabolic while higher levels (≥ 100 pg/ml) could be catabolic (as in the <20 ng/ml group), we assessed the interaction between 25OHD and PTH category upon vBMD and VSTR. None of the interaction terms were significant in adjusted or unadjusted models.

In the subset of women only ($n = 45$), there were no significant differences in age, height, weight, BMI, race/ethnicity, smoking, or meeting criteria for parathyroidectomy by vitamin D status. Those with higher vitamin D had higher rates of vitamin D supplementation (12.5 vs. 75 vs. 84 %, $p = 0.001$). Between-group differences in biochemistries were similar to the overall cQCT cohort. Before adjustment for covariates, there were no differences in trabecular or integral vBMD, vertebral size, or strength (Table 3). As shown in Fig. 1b, after adjusting for age, weight, and eGFR, trabecular ($p = 0.04$) and integral vBMD ($p = 0.04$) and bone strength ($p = 0.04$) were 26–63 % higher in those with 25OHD 20–29 vs. ≥ 30 ng/ml but those with 25OHD <20 did not differ from either group in any parameter. Likewise, vertebral size did not differ ($p = 0.91$).

Because there were few participants with vitamin D deficiency, we also compared those with vitamin D <30 vs. ≥ 30 ng/ml (including men and women). Between-group differences in demographic factors and laboratories were similar to the overall cQCT cohort. Mean PTH level (103 ± 60 vs. 62 ± 27 pg/ml, $p = 0.003$) was higher in those with 25OHD <30 vs. ≥ 30 ng/ml, while calcium levels did not differ (10.8 ± 0.7 vs. 10.5 ± 0.5 mg/dl, $p = 0.07$). There were no differences in cQCT parameters before adjustment for covariates (data not shown). As shown in Fig. 2, after adjusting for age, weight, and renal function, trabecular ($p = 0.02$) and integral ($p = 0.01$) vBMD as well as bone strength ($p = 0.03$) were 23–45 % higher in those with vitamin D <30 vs. ≥ 30 ng/ml. There were no differences in vertebral size (9.14 ± 11.7 vs. 9.13 ± 1.68 cm², $p = 0.98$). Additionally adjusting for sex did not change results.

TBS cohort

The characteristics of the 88 participants with TBS were similar to that of the cQCT cohort: predominantly female (81 %; mean age 62 ± 13 years) and with mild PHPT (mean calcium 10.7 ± 0.6 mg/dl, PTH 86 ± 51 pg/dl, 25OHD 29 ± 10 ng/ml). Vitamin D levels ranged from 6 to 54 ng/ml. Vitamin D deficiency was present in 19.3 % (mean 25OHD 14 ± 3 ng/ml), while 37.5 % had levels in the insufficient range (25OHD 25 ± 3 ng/ml) and 43.2 % were vitamin D replete (25OHD 38 ± 7 ng/ml). Seven participants had 25OHD <10 ng/ml. As shown in Table 4, between-group differences in demographics and biochemistries were similar to the cQCT cohort (Table 4).

Mean lumbar spine DXA T-score was normal (-1.0 ± 1.7 SD), while mean TBS was in the partially degraded range (1.302 ± 0.124). Neither PTH ($r = -0.14$, $p = 0.21$), nor 25OHD ($r = -0.12$, $p = 0.27$), nor serum calcium ($r = -0.08$, $p = 0.46$) levels correlated with TBS. TBS did not differ by vitamin D status (<20 vs. 20–29 vs. ≥ 30 ng/ml) before (1.306 ± 0.134 vs.

1.331 $\pm$ 0.105 vs. 1.274 $\pm$ 0.132, $p = 0.15$) or after adjusting for age, weight, and GFR ($p = 0.24$). There were no differences additionally adjusting for sex ($p = 0.40$).

Subgroup analyses of TBS data were not revealing. In the subset of women only ($n=71$), TBS results were similar to the larger cohort: TBS was in the partially degraded range (mean 1.293 $\pm$ 0.121) and did not correlate with vitamin D ($r=-0.04$, $p=0.73$). TBS did not differ by vitamin D status (<20 vs. 20–29 vs. 30) before (1.300 $\pm$ 0.129 vs. 1.303 $\pm$ 0.105 vs. 1.283 $\pm$ 0.132, $p = 0.81$) or after adjusting for age and weight ($p=0.63$). Similarly, comparing those with vitamin D <30 vs. 30 ng/ml (including men and women), between-group differences in demographic factors and laboratories were similar to the analysis comparing those <20 vs. 20–29 vs. 30. A trend toward higher TBS in those with 25OHD <30 vs. 30 ng/ml (1.323 $\pm$ 0.115 vs. 1.274 $\pm$ 0.132, $p=0.07$) was attenuated after adjusting for age, weight, and eGFR or additionally sex ($p=0.10$ for both). Limiting the ROI of TBS to L1–L2, there were no significant differences in TBS by vitamin D status in the whole group or any subgroup using either threshold (data not shown).

Discussion

In this study, we assessed the association between low serum 25OHD levels, vBMD, bone strength, and TBS at the lumbar spine in patients with PHPT. To our knowledge, this is the first study to utilize cQCT to assess the effects of vitamin D status upon the skeleton in PHPT. We hypothesized that those with lower vitamin D levels and heightened PTH elevations might have more favorable trabecular vBMD and TBS due to an anabolic effect of PTH. These hypotheses were not uniformly confirmed. After adjusting for between-group differences in demographic factors, we found that those with 25OHD levels in the insufficient range (20–29 or <30 ng/ml) had higher integral and trabecular vBMD as well as higher vertebral strength compared to those with vitamin D 30 ng/ml; however, we found no statistical differences between those with the lowest vitamin D (<20 ng/ml) compared to those with vitamin D insufficiency and sufficiency and no between-group statistical differences in TBS.

Our cQCT findings could point to a potential anabolic effect of higher PTH in those with lower vitamin D at the spine, though not all our findings are consistent with this possibility; first, we would have anticipated a “dose response” relationship with the highest trabecular vBMD in those with the lowest vitamin D and highest PTH (i.e., those with 25OHD deficiency), which was not the case. However, we cannot completely rule out this possibility with the current study. Absolute adjusted vBMD and VSTR values in the <20 ng/ml group were higher than those with 25OHD 30 ng/ml, but with the small number of participants with 25OHD <20 ng/ml, we had limited power to detect an effect in this group. For this reason, we conducted continuous analyses and also grouped patients using a 25OHD threshold of 30 ng/ml. We also assessed an alternative possibility—that mildly elevated PTH levels in the 25OHD 20–29 group might be anabolic but higher levels in the <20 ng/ml group could be catabolic. However, we did not find evidence for this effect.

Secondly, PTH was significantly higher in those with deficiency vs. insufficiency and higher in those with deficiency vs. sufficiency, but not significantly different in those with

insufficiency vs. sufficiency, where we observed differences in vBMD. It is possible, however, that there is a threshold effect of PTH to induce vBMD changes, and it is notable that PTH levels were frankly elevated compared to the reference range in those with vitamin D deficiency and insufficiency but normal in those who were sufficient.

In our prior work on the effect of vitamin D deficiency in PHPT, higher-order imaging was used at peripheral sites only. There is reason to pursue site-specific data in PHPT, where fracture rates are increased at some (wrist) but not all (hip) sites. Although the data are not uniform, most studies suggest an increased risk of vertebral fractures in PHPT [30–33]. Using vertebral fracture assessment by DXA, Vignali et al. found a marked increase in morphometric vertebral fractures in the 150 PHPT women than in 300 matched healthy controls (25 vs. 4.0 %) [33]. More recently, Lundstam et al. reported that incident vertebral fracture rates tended to be higher in PHPT patients randomized to observation vs. PTX [34]. Both studies point to the value of obtaining higher-order imaging data specifically at the spine in PHPT, where aBMD by DXA often tends to be preserved.

The higher trabecular vBMD at the lumbar spine in the current study in those with 25OHD <30 ng/ml is generally consistent with prior histomorphometric data in PHPT indicating more favorable trabecular indices (BV/TV, trabecular number and separation) at the iliac crest in those with 25OHD <20 vs. 20 ng/ml [12]. In contrast, we did not find higher trabecular vBMD or microarchitecture at the radius or tibia by HRpQCT in a cohort which included the subset of patients described in this study. The disparate results could be due to differences in technology and their sensitivities. Alternatively, taken together, these data could support differences in the site-specific effects of PTH (radius and tibia vs. lumbar spine and iliac crest).

Similar to prior studies, we found TBS to be in the partially degraded range in these patients with mild PHPT [35]. The absence of between-group differences in TBS (a surrogate for trabecular microarchitecture) according to vitamin D status is somewhat unexpected in light of higher trabecular vBMD in those with 25OHD <30 ng/ml. Potential explanations for this include an effect of vitamin D upon mineralization but not microarchitecture or lower sensitivity of TBS. While our study does not enable us to distinguish between these possibilities, the data are consistent with a prior study that demonstrated no change in TBS with vitamin D treatment in PHPT [36].

The data from this study and our recent work using DXA and HRpQCT suggest that neither vitamin D deficiency nor insufficiency using the currently utilized thresholds (<20 and 20–29 ng/ml) has detrimental effects on trabecular bone at the LS, radius, or tibia in PHPT [11, 13]. Even in the general population without PHPT, there are limited data using newer imaging modalities (such as cQCT and TBS) on the effect of vitamin D deficiency and insufficiency on skeletal health. In a subset of the MrOS study, 25OHD level was positively associated with integral vBMD and cortical volume at the hip as measured with cQCT in elderly men [37]. Standard clinical thresholds for vitamin D deficiency and insufficiency, however, were not utilized in this study and the effect of 25OHD level was small. The spine was not assessed. The limited available data suggest no association between vitamin D level and TBS in the general population [38, 39].

Our study has several limitations. Most notably, few participants had very low 25OHD levels (<10 ng/ml), which may have impaired our ability to detect between-group differences. Our recent work suggests that vitamin D deficiency is now less common in PHPT than in the past, likely related to increasing use of vitamin D supplementation [40]. The findings of this study therefore cannot be generalized to populations with more widespread, severe, or prolonged vitamin D deficiency and may not be applicable to PHPT patients in other countries where vitamin D supplementation is uncommon. It is also possible that a single 25OHD level may not be reflective of chronic exposure, particularly when many participants were taking vitamin D supplements. Additionally, duration of vitamin D deficiency was unknown. Further, the 25OHD ≥ 30 ng/ml group was older than the other groups. However, given that BMD was lower in this group only after adjusting for this difference, age is unlikely to account for this finding. It is unfortunate that the limitations of cQCT did not allow us to measure cortical parameters at the spine.

Despite these limitations, the study has important strengths, including the comprehensive assessment of skeletal health in this cohort using newer techniques, such as cQCT and TBS as well as more traditional methods, and the use of liquid chromatography/tandem mass spectroscopy to measure vitamin D [11]. In addition, we assessed the utility of commonly employed clinical vitamin D thresholds to assess the effects of vitamin D upon the skeleton.

Taken together with our prior work in this area, these data on the lumbar spine highlight the importance of examining the influence of vitamin D broadly across the skeleton, as the effect of vitamin D may be site-specific. Inconsistencies in vBMD and PTH data across vitamin D levels do not permit us to make definitive conclusions regarding a potential anabolic effect of higher PTH in those with lower vitamin D. Though some results are suggestive in this regard, further work is needed. We conclude that despite the increased risk of vertebral fractures in PHPT, advanced imaging techniques do not suggest that vitamin D insufficiency or deficiency, using current clinical thresholds, has a further negative effect on skeletal health at the lumbar spine.

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Fig. 1. cQCT-measured volumetric vBMD and vertebral strength by vitamin D status in **a** the whole cohort and **b** women only. 25-Hydroxyvitamin D <20, 20–29, and ≥30 ng/ml are denoted by *black*, *charcoal*, and *light gray*, respectively (color figure online)

Fig. 2. cQCT-measured volumetric vBMD and vertebral strength by vitamin D status in the whole cohort. 25-Hydroxyvitamin D <30 and ≥30 ng/ml are denoted by *black* and *charcoal*, respectively (color figure online)

Table 1

cQCT cohort characteristics by vitamin D level

Variable	25OHD <20 ng/ml (<i>n</i> = 10)	25OHD 20–29 ng/ml (<i>n</i> = 15)	25OHD ≥ 30 ng/ml (<i>n</i> = 27)	<i>p</i> value
Age (years)	59.4 ± 12.4	58.0 ± 9.6	65.4 ± 8.6 ^a	0.05
Female (%)	80.0 %	80.0 %	92.6 %	0.41
White race (%)	88.9 %	86.7 %	100 %	0.17
Hispanic ethnicity (%)	20.0 %	20.0 %	18.5 %	0.99
Height (in.)	63.8 ± 5.7	63.8 ± 3.2	64.1 ± 2.8	0.96
Weight (pounds)	167.3 ± 53.7	162.7 ± 25.6	158.5 ± 38.2	0.82
BMI (kg/m ²)	28.3 ± 5.3	28.2 ± 4.5	27.1 ± 5.7	0.73
Vitamin D supplements (%)	20 %	73 %	86 %	<0.01
Meet 2008 PTX criteria	90.0 %	60.0 %	74.1 %	0.25
Current tobacco (%)	0 %	0 %	11.1 %	0.54

Values represent mean ± SD or percentages

^aVs. 20–29, *p* = 0.06

Table 2

cQCT cohort biochemistries and DXA by vitamin D status

	Normal range	25OHD <20 ng/ml (<i>n</i> = 10)	25OHD 20–29 ng/ml (<i>n</i> = 15)	25OHD ≥30 ng/ml (<i>n</i> = 27)	<i>p</i> value
25OHD (ng/ml)	30–100	14.1 ± 2.3	26.0 ± 2.0	39.8 ± 6.9	N/A
Calcium (mg/dl)	8.6–10.2	11.0 ± 0.7	10.6 ± 0.6	10.5 ± 0.5	0.06
PTH (pg/ml)	14–66	140 ± 74	78 ± 30 ^a	62 ± 27 ^a	<0.0001
1,25(OH) ₂ D (pg/ml)	18–72	71.6 ± 25.8	76.2 ± 17.3	63.9 ± 22.7	0.26
Phosphate (mg/dl)	2.7–4.5	2.7 ± 0.4	3.0 ± 0.4	3.3 ± 0.4 ^a	0.003
GFR (ml/min/1.73 m ²)	60	88 ± 14 ^b	86 ± 19 ^b	73 ± 17	0.03
LS areal BMD T-score	–1.0	1.0 ± 1.8	–1.3 ± 1.3	0.8 ± 1.8	0.71

Values represent mean ± SD or percentages LS lumbar spine, BMD bone mineral density

^a *p* < 0.01 vs. <20 ng/ml group^b *p* = 0.08 vs. ≥30 ng/ml

Table 3

Lumbar spine volumetric bone density, size, and strength by vitamin D status

Variable	25OHD <20 ng/ml	25OHD 20–29 ng/ml	25OHD ≥30 ng/ml	p value	p value adjusted for age, weight, and eGFR
Whole cohort					
N	10	15	27		
Vertebral cross-sectional area (cm ²)	9.21 ± 2.09	9.09 ± 1.43	9.02 ± 1.43	0.94	0.92
Trabecular vBMD (g/cm ³)	0.096 ± 0.03	0.121 ± 0.04	0.095 ± 0.04 ^a	0.09	0.03
Integral vBMD (g/cm ³)	0.126 ± 0.03	0.144 ± 0.04	0.122 ± 0.03 ^a	0.14	0.03
Vertebral strength (g ² /cm ⁴)	0.147 ± 0.05	0.204 ± 0.11	0.146 ± 0.08 ^a	0.11	0.04
Women only					
N	8	12	25		
Vertebral cross-sectional area (cm ²)	8.84 ± 1.64	9.30 ± 1.39	8.96 ± 1.34	0.73	0.91
Trabecular vBMD (g/cm ³)	0.102 ± 0.02	0.122 ± 0.04	0.092 ± 0.0 ^a	0.09	0.03
Integral vBMD (g/cm ³)	0.132 ± 0.02	0.144 ± 0.04	0.119 ± 0.03 ^a	0.12	0.03
Vertebral strength (g ² /cm ⁴)	0.156 ± 0.05	0.210 ± 0.12	0.137 ± 0.08 ^a	0.07	0.04

^a $p < 0.05$ vs. 25OHD 20–29 ng/ml after adjustment for age and weight

Table 4

TBS cohort demographic and biochemical characteristics by vitamin D level

Variable	25OHD <20 ng/ml (n = 17)	25OHD 20–29 ng/ml (n = 33)	25OHD ≥ 30 ng/ml (n = 38)	p value
Age (years)	57 ± 14	58 ± 13	67 ± 9 ^a	0.001
Female (%)	82.4 %	72.3 %	86.8 %	0.36
White race (%)	88.2 %	84.9 %	92.1 %	0.68
Hispanic ethnicity (%)	29.4 %	15.2 %	13.2 %	0.37
Height (in.)	65.1 ± 4.8	65.3 ± 3.8	64.0 ± 2.8	0.23
Weight (pounds)	181.4 ± 56.9	174.2 ± 36.8	156.5 ± 38.5	0.053
BMI (kg/m ²)	29.6 ± 6.3	28.7 ± 5.9	26.7 ± 6.0	0.16
Vitamin D supplements (%)	17.7 %	60.6 %	84.2 %	<0.0001
Meets surgical guidelines (%)	82.4 %	57.6 %	73.7 %	0.18
Current tobacco use (%)	5.9 %	1.1 %	4.6 %	0.63
25OHD (ng/ml)	14 ± 3	26 ± 2	38 ± 7	N/A
Calcium (mg/dl)	10.8 ± 0.8	10.7 ± 0.6	10.6 ± 0.6	0.45
PTH (pg/ml)	130 ± 64	81 ± 43 ^b	71 ± 39 ^b	0.0001
1,25(OH) ₂ D (pg/ml)	79 ± 29	72 ± 21	64 ± 22	0.08
Phosphate (mg/dl)	2.8 ± 0.4	3.0 ± 0.4	3.2 ± 0.4 ^b	0.003
GFR (ml/min/1.73 m ²)	77 ± 17	86 ± 21	92 ± 18 ^c	0.02

Values represent mean ± SD or percentages

^a $p < 0.05$ vs. <20 ng/ml and 20–29 ng/ml^b $p < 0.01$ vs. <20 ng/ml group^c $p < 0.05$ vs. <20 ng/ml