Vitamin D Treatment in Primary Hyperparathyroidism: A Randomized Placebo Controlled Trial

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Context: Low 25-hydroxyvitamin D levels are common in patients with primary hyperparathyroidism (PHPT) and associated with higher PTH levels and hungry bone syndrome after parathyroidectomy (PTX). However, concerns have been raised about the safety of vitamin D supplementation in PHPT.

Objective: We aimed to assess safety and effects on calcium homeostasis and bone metabolism of supplementation with high doses of vitamin D in PHPT patients.

Design, Setting: This was an investigator-initiated double-blind, randomized, placebo-controlled, parallel-group trial from a single center.

Patients: Forty-six PHPT patients were recruited, with a mean age of 58 (range 29–77) years, and 35 (76%) were women.

Interventions: Intervention included daily supplementation with 70 μg (2800 IU) cholecalciferol or identical placebo for 52 weeks. Treatment was administered 26 weeks before PTX and continued for 26 weeks after PTX.

Main Outcome Measures: PTH, calcium homeostasis, and bone metabolism were evaluated.

Results: Preoperatively, 25-hydroxyvitamin D increased from 50 to 94 nmol/L in the treatment group and decreased from 57 to 52 nmol/L in the placebo group ($P < .001$). Compared with placebo, vitamin D decreased PTH significantly by 17% before PTX ($P = .01$), increased lumbar spine bone mineral density by 2.5% ($P = .01$), and decreased C-terminal β-CrossLaps by 22% ($P < .005$). The trabecular bone score did not change in response to treatment, but improved after PTX. Postoperatively, PTH remained lower in the cholecalciferol group compared with the placebo group ($P = .04$). Plasma creatinine and plasma and urinary calcium did not differ between groups.

Conclusions: Daily supplementation with a high vitamin D dose safely improves vitamin D status and decreases PTH in PHPT patients. The vitamin D treatment is accompanied by reduced bone resorption and improved bone mineral density before operation. **(*J Clin Endocrinol Metab* 99: 1072–1080, 2014)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received November 1, 2013. Accepted December 30, 2013.
First Published Online January 13, 2014

Abbreviations: BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; CI, confidence interval; CTx, C-terminal β-CrossLaps; CV, coefficient of variation; DBP, vitamin D binding protein; DXA, dual x-ray absorptiometry; 24h-UCa, 24-hour urinary calcium; 25OHD, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; PHPT, primary hyperparathyroidism; PINP, N-terminal propeptide; PTX, parathyroidectomy; TBS, trabecular bone score.

Vitamin D is essential for calcium homeostasis, bone metabolism, and musculoskeletal health (1, 2). The plasma level of 25-hydroxyvitamin D (25OHD) reflects vitamin D status, and treatment of vitamin D insufficiency is a frequent topic of discussion. The definition of vitamin D insufficiency varies, although many researchers regard 25OHD <75 to 80 nmol/L as insufficient (3–8).

In primary hyperparathyroidism (PHPT), vitamin D insufficiency is more common than in the general population (4, 9, 10). Low 25OHD levels are associated with more aggravated disease with higher bone turnover, reduced bone mineral density (BMD), postoperative hypocalcemia, and elevated PTH levels (11–14). The underlying mechanism for the coexistence of PHPT and vitamin D insufficiency is not fully understood. However, PTH stimulates the renal 1α-hydroxylase, causing a conversion of 25OHD to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The subsequent increase in $1,25(OH)_2D$ both has a negative feedback on PTH production and secretion and stimulates further inactivation of 25OHD by 24-hydroxylases (15). Although the pathogenesis of low vitamin D levels in PHPT needs further study (16), 25OHD levels seem to normalize after parathyroidectomy (PTX) (17).

In uncontrolled studies, discrepant results of vitamin D supplementation to patients with PHPT have been reported. In a study by Tucci et al (18), vitamin D repletion did not lead to any adverse events, whereas other investigators reported increased plasma and urine calcium levels (19, 20). Moreover, uncontrolled studies suggested beneficial effects of vitamin D supplementation in PHPT in terms of decreased PTH levels (19) and increased BMD (21). After PTX, a recent randomized controlled trial and previous uncontrolled studies indicated beneficial effects of postoperative vitamin D supplementation on PTH normalization (22–24), whereas BMD was not affected by vitamin D treatment. However, no data are available from randomized trials on vitamin D supplementation to patients with PHPT before PTX.

Using a randomized double-blind design, we aimed to assess safety and effects on calcium homeostasis and bone metabolism of treatment with a daily oral dose of 70 μg (2800 IU) cholecalciferol or placebo to patients with PHPT for 6 months (26 weeks) before PTX and for 6 months after surgical cure.

Subjects and Methods

Participants

We recruited patients from the outpatient clinic at Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Denmark. We included patients above 18 years of age with established hyperparathyroid hypercalcemia on at least 2 occasions and vitamin D insufficiency. We chose 25OHD <80 nmol/L as the definition of vitamin D insufficiency in accordance with guidelines and recommendations (5, 7). Hypercalcemia was defined as ionized plasma calcium levels above the upper limit of reference range (>1.32 mmol/L). A state of hyperparathyroidism was defined as PTH levels in the upper third of the reference interval or above (>5.0 pmol/L). To be included, patients were also required to be eligible for PTX either because they fulfilled the criteria for surgery as defined by the Third International Workshop on Asymptomatic PHPT (25), or because they requested PTX despite not fulfilling the criteria. At baseline, information was collected on medical history, socioeconomic factors, and dietary habits including intake of various fish, fruit, milk, and milk products as well as use of vitamin supplements.

We excluded patients with plasma Ca^{2+} >1.60 mmol/L (mean of 2 measurements), creatinine >120 μmol/L, pregnancy, current or former alcohol abuse, malignant disease within the last 5 years, malabsorption, sarcoidosis, active pancreatitis, allergy to the study drug or compounds of the drug, or intake of α-calcidol, cinacalcet, or narcotics. We included patients from June 2008 to May 2012. The study was performed in accordance with the Declaration of Helsinki II and guidelines on Good Clinical Practice. The Good Clinical Practice Unit at Aarhus University Hospital monitored the study. The study was approved by the Ethical Committee of Central Denmark Region (M20080011) and the Danish Data Protection Agency. The study was registered at ClinicalTrials.gov (NCT00674154).

Study design

The study was an investigator-initiated, double-blind, randomized, placebo-controlled, parallel-group trial comparing treatment with a daily oral supplement of 70 μg (2800 IU) cholecalciferol (vitamin D3) or placebo for 1 year. The cumulative dose of 490 000 IU during the 25 preoperative weeks is comparable with the dose used in other studies (19, 21). Participants had PTX performed after 6 months of study (at week 26) ie, treatment was administered for 6 months before PTX and for 6 months after PTX. Cholecalciferol and identical placebo tablets were purchased commercially from Natur-Drogeriet and delivered to the pharmacy at Aarhus University Hospital. Randomization was performed by the Hospital Pharmacy using a computer-generated randomization code. A restricted block randomization procedure with serial entry in permuted blocks was used. Eight individuals were included in each block; 4 subjects were randomly allocated to placebo, whereas the other 4 subjects received vitamin D. As investigators, we were unaware of the number of subjects in each block and permutations within blocks during the trial.

Efficacy measures

The primary endpoint was changes in preoperative plasma PTH levels. Secondary endpoints included safety markers and measures of calcium homeostasis and bone metabolism. We assessed the safety of vitamin D treatment in terms of adverse events, increases in plasma creatinine and calcium levels, as well as increases in urinary calcium levels. Any measure of Ca^{2+} above 1.70 mmol/L resulted in exclusion. We assessed changes in bone metabolism by biochemical markers of bone turnover, BMD, and trabecular bone score (TBS) as measured by dual x-ray absorptiometry (DXA). We measured compliance as intake of tablets per day during the course of the study.

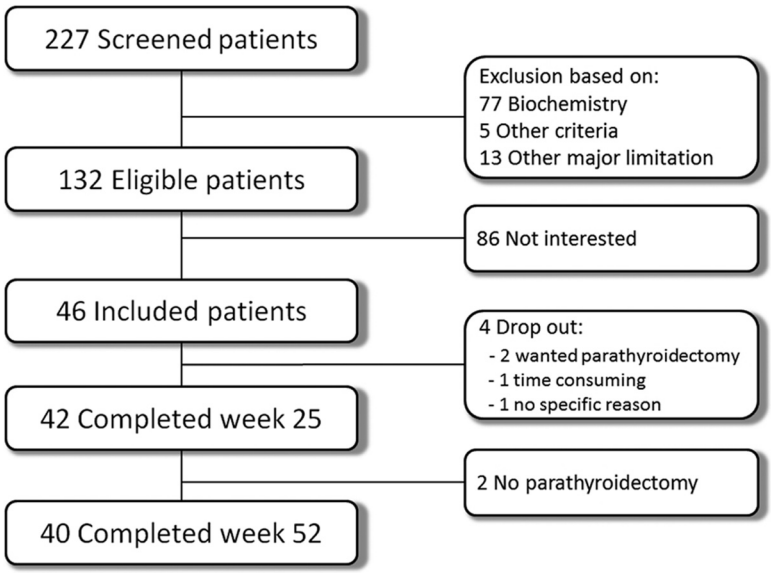

Figure 1. Detailed depiction of patient inclusion for study participation.

Clinical visits and measurements

Clinical visits were performed at weeks 0 (baseline), 2, 6, 12, 18, 25 (preoperative), 30, 42, and 52 (end of study). At all 9 visits, we collected blood samples and a 24-hour urine sample. At all clinical visits, patients were consulted by the primary investigator (L.Ro.). Information regarding any events or changes in medicine intake was noted in the case report files.

Biochemistry

We used standard laboratory methods for measurements of total alkaline phosphatase and plasma and urinary levels of calcium, creatinine, albumin, and phosphate. They were all analyzed immediately. To reduce analytical variation, we analyzed PTH, vitamin D metabolites, vitamin D binding protein (DBP), and biochemical markers of bone turnover obtained at all time points for each patient in a single batch. Blood samples were kept frozen at −80°C until the time of analysis. We measured plasma intact PTH using a second-generation electrochemoluminescent immunoassay on an automated instrument (Cobas 6000; Roche Diagnostics). The available assay had a coefficient of variation (CV) of 3.3% and 2.7% at PTH levels of 3.7 and 26.6 pmol/L, respectively. We analyzed plasma 25OHD by isotope dilution liquid chromatography-tandem mass spectrometry according to a method described previously (26). Calibrators are traceable to NIST SRM 972 (Chromsystems). The CV values for $25OHD_3$ were 6.4% and 9.1% at levels of 66.5 and 21.1 nmol/L and for $25OHD_2$, the CV values were 8.8% and 9.4% at levels of 41.2 and 25.3 nmol/L, respectively. For $1,25(OH)_2D$ analyses, we used an RIA (γ-B 1,25-Dihydroxy Vitamin D; Immunodiagnostic Systems Ltd) with a 16 to 220 pmol/L measuring range and a CV of 6.8% to 14.0%. We analyzed C-terminal β-CrossLaps (CTx), procollagen I, N-terminal propeptide (PINP), and osteocalcin by ELISA (Cobas 6000; Roche Diagnostics, GmbH). All bone markers had assay CV values between 1.0% and 3.0%. For bone-specific alkaline phosphatase (BSAP), we used an immunoassay (METRA BAP EIA kit; Quidel Corporation) with the use of a Spectra II ELISA Reader (PerkinElmer Life and Analytical Sciences Inc). The CV values for BSAP were 4.2% at 15 U/L and 6.7% at 65 U/L. For DBP, we used an immunoassay (R&D Systems) with CV values of 6.8% and 7.3% at 273 and 365 μg/mL, respectively. For measures of 25OHD, albumin, DBP, and $1,25(OH)_2D$, we calculated the free 25OHD and $1,25(OH)_2D$ using previously described methods (27).

Dual x-ray absorptiometry

We measured BMD at the distal forearm, lumbar spine (L1–L4), and hip using the Hologic Discovery DXA scanner. The CV values were 1.5% for the lumbar spine, 2.1% for total hip, and 1.9% for the forearm (28). All patients were scanned at weeks 0, 25, and 52 (±4 weeks). We used the iNsight software to measure TBS at the lumbar spine (L1–L4). The TBS was calculated from gray-level variations of the anterior-posterior DXA image of the lumbar spine (29) and the score for each vertebra was collected for an L1–L4 score.

Statistical analysis

Before study initiation, we performed a power calculation based on an expectation of a 20% drop in plasma PTH in the treatment group compared with the placebo group. We assumed a mean PTH level of 12 pmol/L (SD of 3 pmol/L) in the study population. To detect the assumed between-group difference in plasma PTH levels with 90% statistical power at a level of significance of 5%, we had to include 50 patients in the trial. We analyzed all data with the intention-to-treat approach only after excluding the 4 dropouts from the statistical analyses. We assessed differences between groups using the Student's *t* test or Wilcoxon rank-sum test as appropriate. For serial changes, we used ANOVA for repeated measurements. Correlations between variables were tested by bivariate correlation analyses (*r*) and by multiple regression analyses. We present all data as mean values with 95% confidence interval (CI) or median with 25th and 75th percentiles. We considered values of $P < .05$ as statistically significant. We used STATA version 10.0 for all statistical analyses.

Results

Figure 1 details the recruitment and inclusion of participants. Of 227 screened PHPT patients, 132 were eligible for participation. After oral information, 86 patients refused to participate. The remaining 46 patients provided informed consent and were randomized. There were 4 dropouts within the first week of the study. Two patients regretted agreeing to PTX and dropped out after completing the preoperative examinations. The remaining 40 patients (20 on placebo and 20 on vitamin D) completed the entire study. Table 1 shows baseline characteristics of included patients. Patients had a mean age of 59 (range 30–77) years, and 35 (76%) were women. At baseline, there was no difference between groups regarding Ca^{2+}, daily

Table 1. Baseline Characteristics of Included Patients With PHPT[a]

	Reference Range	All	Vitamin D	Placebo	*P* Value
n (%)		46 (100)	23 (50)	23 (50)	
Females, n (%)		35 (76)	16 (70)	19 (83)	.22
Characteristics, mean (range)					
Age, y		59 (30–77)	60 (30–77)	58 (31–73)	.51
Height, cm		170 (155–204)	170 (157–189)	169 (155–204)	.41
Weight, kg		81 (55–121)	77 (55–114)	86 (56–121)	.11
Plasma, mean (95% CI)					
Calcium, mmol/L	1.18–1.32	1.41 (1.39–1.43)	1.40 (1.37–1.43)	1.41 (1.38–1.44)	.74
PTH, pmol/L	1.6–6.9	13.0 (11.1–15.0)	13.6 (11.3–15.9)	12.5 (9.2–15.7)	.55
25OHD, nmol/L	50–160	54.0 (47.9–60.0)	50.2 (40.6–59.8)	57.0 (49.3–65.5)	.23
Creatinine, mmol/L	45–90	69.1 (65.3–72.9)	67.4 (61.7–73.0)	70.7 (65.2–76.2)	.38
Phosphate, mmol/L	0.76–1.41	0.77 (0.72–0.82)	0.75 (0.68–0.82)	0.78 (0.71–0.85)	.49
Alkaline phosphatase, U/L	35–105	84.6 (77.1–92.1)	85.7 (75.6–95.8)	83.6 (71.8–95.5)	.79
Albumin, g/L	34–45	44.2 (43.2–45.2)	43.9 (42.4–45.4)	44.4 (42.9–45.9)	.60
Urine, mean (95% CI) (male/female)					
Calcium, mmol/d	2–9/2–7	9.4 (8.0–10.8)	9.7 (7.4–11.9)	9.2 (7.2–11.1)	.74
Creatinine, mmol/d	8–22/6–15	12.0 (10.6–13.3)	11.7 (9.5–13.8)	12.2 (10.3–14.1)	.67
Phosphate, mmol/d	11–63/8–44	32.0 (28.4–35.7)	30.8 (25.7–35.9)	33.2 (27.6–38.8)	.52

[a] Results are presented as mean values (range or 95% CI) or number (percentage), as appropriate. The *P* values indicate between-group differences.

calcium intake (placebo group, 765 g; vitamin D group, 850 g), creatinine, PTH, 25OHD, age, sex, bone markers, BMD, or 24-hour urinary calcium (24h-UCa). Nine patients (21%) were asymptomatic, 20 (48%) had osteoporosis, 11 (26%) had previous relevant fractures, 13 (31%) had hypercalcemic symptoms, and 12 (30%) had kidney stones or renal calcifications.

PTH and vitamin D

Plasma 25OHD increased as expected in the group of participants randomized to vitamin D supplements compared with placebo ($P < .001$). During the first 25 weeks, 25OHD increased from 50.2 to 94.2 nmol/L (88%) in response to vitamin D supplementation (Figure 2). Compared with the placebo group, PTH levels decreased by 17% ($P = .01$; absolute difference, 2.4 ± 1.2 pmol/L) in the vitamin D group during the first 25 weeks of treatment (Figure 2). Also postoperatively, PTH values were lower in the vitamin D group ($P = .039$). We did not clinically observe incidents of hungry bone syndrome, although a similar number of patients (5 vs 7) experienced PTH elevation (>6.9 pmol/L). Concomitantly, $1,25(OH)_2D$ levels increased during the preoperative vitamin D treatment from 98 to 127 pmol/L (30%, $P = .008$), whereas $1,25(OH)_2D$ was unchanged in the placebo group (Figure 2). The preoperative change in $1,25(OH)_2D$ correlated with changes in 25OHD ($r = 0.83$, $P < .001$). Levels of DBP were not affected by vitamin D treatment or PTX (Figure 2). Similar to total levels, the calculated free 25OHD and $1,25(OH)_2D$ increased significantly in response to vitamin D treatment (data not shown). Second, we divided the treatment group into 2 groups according to baseline 25OHD levels. The group with the lowest 25OHD levels (mean 34 nmol/L) increased 215% in 25OHD preoperatively compared with a 50% 25OHD increase in the group with higher 25OHD levels at baseline (mean 66 nmol/L, $P = .01$). The preoperative increase in $1,25(OH)_2D$ levels was also higher in case of low baseline 25OHD levels (72% vs 11%, $P < .01$).

Creatinine, calcium, and phosphate

Despite the significant changes in plasma PTH, 25OHD, and $1,25(OH)_2D$, we did not find any differences between groups at any time point in plasma Ca^{2+} before or after PTX (Figure 3). In all patients, Ca^{2+} dropped significantly after PTX and no persistence or recurrence of PHPT was seen. The 24h-UCa was also unaffected by treatment allocation (Figure 3). In multiple regression analyses, 24h-UCa did not vary as a function of daily calcium intake, 25OHD, or $1,25(OH)_2D$ levels. The only significant predictors of 24h-UCa were plasma calcium and PTH levels. The 24h-UCa decreased significantly in both groups after PTX from 9.4 to 4.9 mmol/d, but changes did not differ between groups. Patients with kidney stones did not have increased 24h-UCa at baseline compared with other included patients, and treatment did not affect 24h-UCa differently in these patients.

Creatinine did not change before ($P = .96$) or after ($P = .55$) surgery in the vitamin D group compared with placebo, and none of the included patients developed plasma creatinine levels above the upper reference range. However, there was a small mean increase from 69 to 72

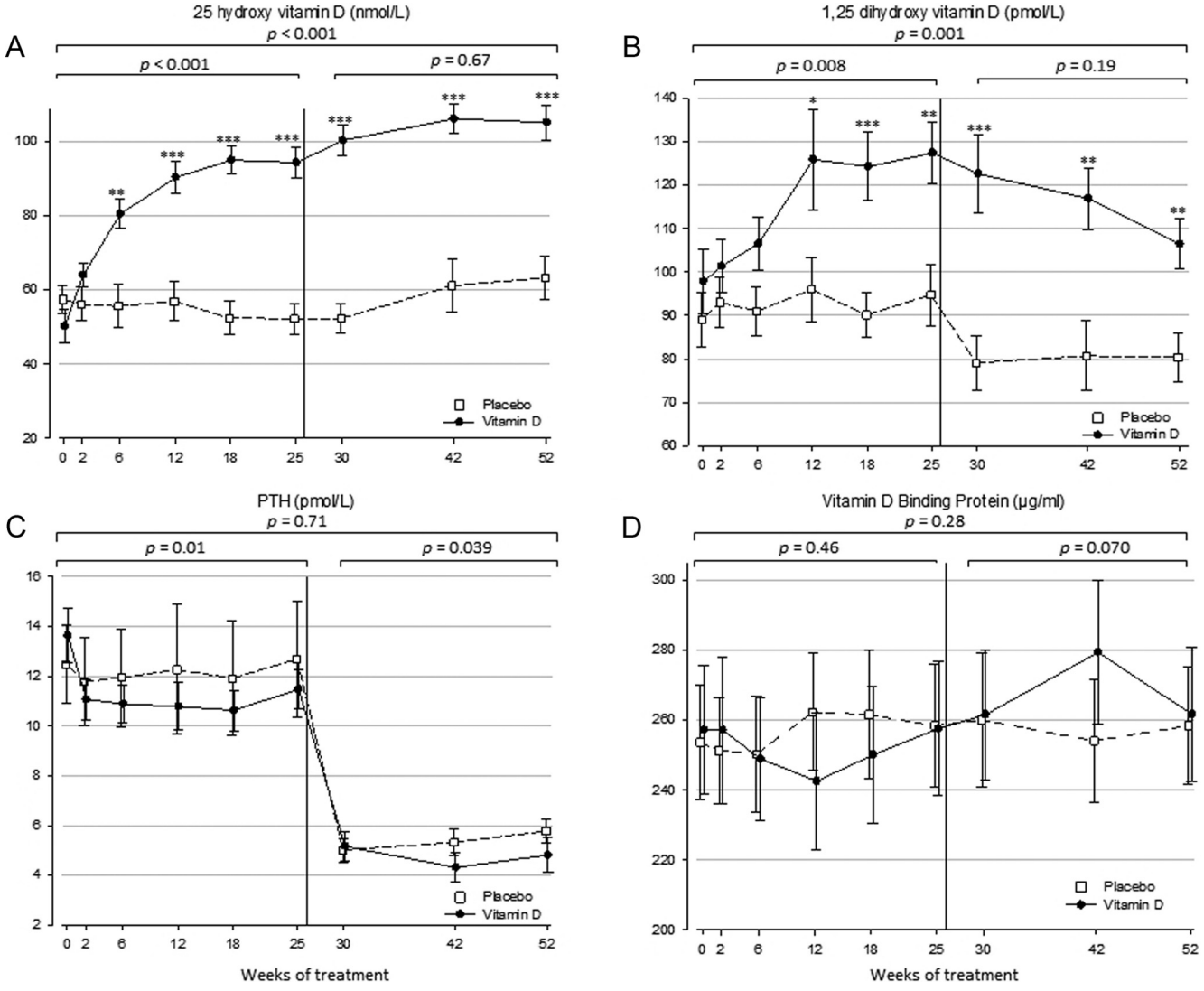

Figure 2. Variations in total plasma levels of 25OHD (A), 1,25$(OH)_2$D (B), PTH (C), and DBP (D) during the 52 weeks of treatment with vitamin D (black circles) or placebo (white squares). The vertical line at week 26 indicates the time of PTX. The *P* values indicate between-group differences by ANOVA for the preoperative period, the postoperative period, or the whole 52 weeks of the study. Asterisks indicate between-group differences by 2-sample *t* test: *, $P < .05$; **, $P < .01$; ***, $P < .001$.

µmol/L in all patients during the 52 weeks ($P = .005$). Plasma phosphate increased in both groups after PTX with no difference between groups. Over time, plasma phosphate did not change in either of the groups before ($P = .70$) or after ($P = .47$) PTX. The 24-hour urinary phosphate decreased significantly in both groups after PTX from 31.6 to 27.1 mmol/d, but the changes did not differ between groups, and no changes were seen before or after PTX.

Bone markers

Compared with placebo, treatment with vitamin D caused a 22% decrease in CTx ($P < .005$) preoperatively, whereas no significant change was seen in PINP (Figure 3), BSAP, or osteocalcin (data not shown). All 4 markers decreased significantly after PTX with no difference between groups. Total alkaline phosphatase did not change significantly before PTX ($P = .12$), but the postoperative values were higher in the placebo group 4 weeks after PTX ($P = .03$) although similar at week 52 ($P = .82$).

Parathyroidectomy

Operation for PHPT was performed at week 26 ± 4 weeks (always after measurements at week 25). All 40 patients were successfully cured by PTX. In 95% of the patients, an adenoma was removed, whereas 2 patients had hyperplasia in all glands. These 2 patients had a subtotal PTX with removal of 3½ glands. In one patient with multiple endocrine neoplasia 1 and hyperplasia in all 4 glands, PTX caused a permanent postoperative hypoparathyroidism. There were no other incidents of hypoparathyroidism or recurrent laryngeal nerve palsies. All patients were recommended a postoperative calcium intake of at least 1000 mg daily. In 30 of 40 patients, the diet did

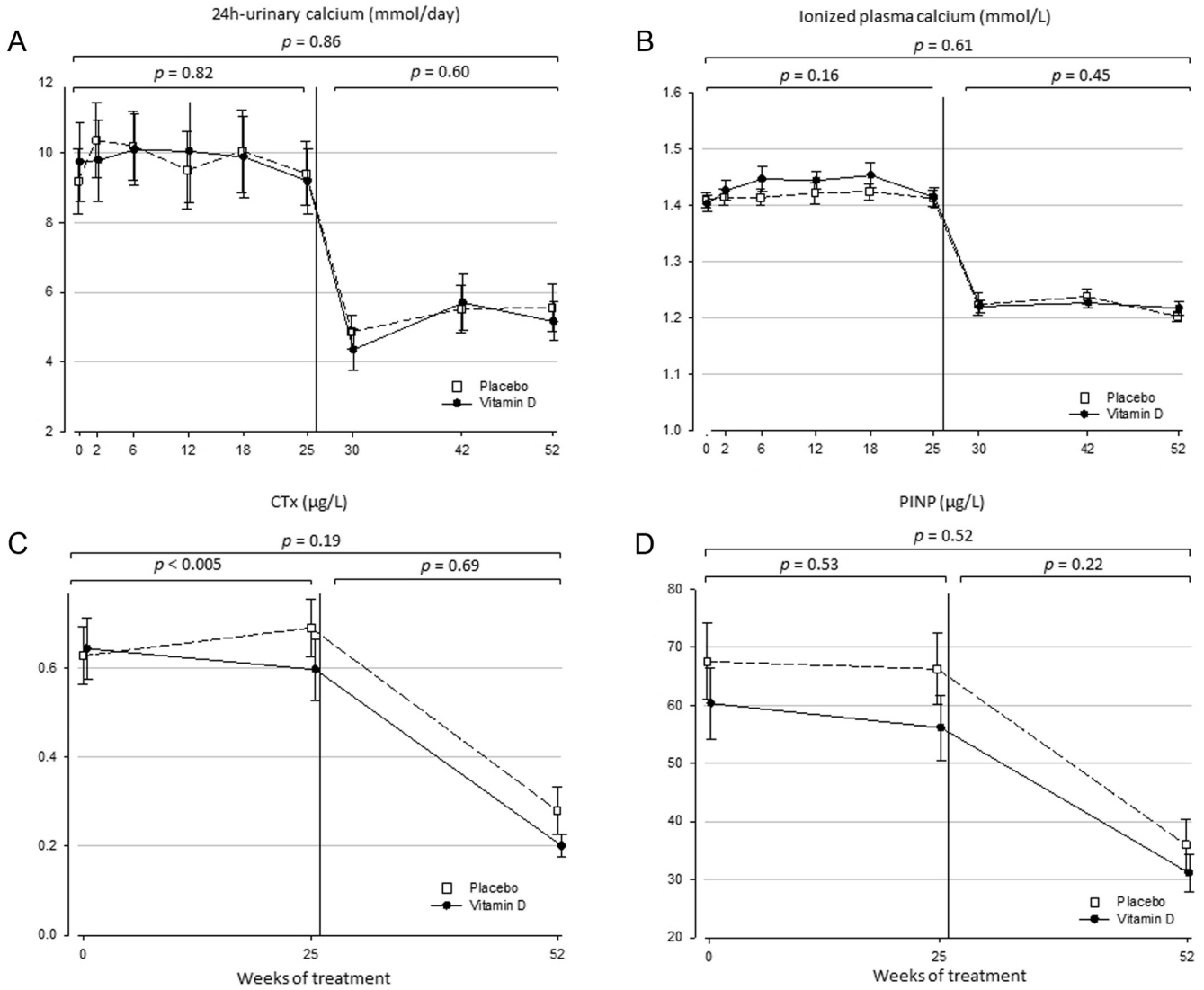

Figure 3. Changes in 24h-UCa (A), plasma ionized calcium (B), CTx (C), and PINP (D) in patients randomized to 52 weeks of treatment with vitamin D (black circles) or placebo (white squares). The vertical line at week 26 indicates the time of PTX. In A and B, the *P* values indicate between-group differences by ANOVA for the preoperative period, the postoperative period, or the whole 52 weeks of the study. In C and D, the *P* values are assessed by a 2-sample *t* test.

not contain this amount of calcium, and calcium tablets without vitamin D were used as supplementation.

BMD and TBS

At baseline, TBS and total BMD of the spine, hip, and distal forearm were similar in the 2 groups (Table 2). During the 25 weeks with preoperative vitamin D supplementation, BMD of the lumbar spine increased by 2.5% ($P = .01$) in the vitamin D group compared with the placebo group. Postoperatively, there was an increase of spine BMD in both the vitamin D group (2.6%) and the placebo group (3.7%) with no significant difference between groups ($P = .30$). The TBS of the spine was without differences between groups. However, in the entire group of patients, TBS increased significantly after PTX (Table 2). At the total hip and femoral neck, preoperative BMD change did not differ between groups. After PTX, BMD increased significantly within the vitamin D group at the total hip (2.6%) and femoral neck (2.1%) without changes in the placebo group. Between groups, these changes were only borderline significant at the femoral neck ($P = .08$) and total hip ($P = .09$). At the distal forearm, no between-group differences were seen, although there was a significant preoperative BMD decrease within the placebo group ($P < .01$).

Safety and adverse events

In general, both the vitamin D and placebo tablets were well tolerated and the compliance to study medication was high (96%) with no difference between groups. In total, we recorded 2 serious adverse events and 13 adverse events. None of the events were suspected to be caused by

Table 2. BMD and TBS as Measured at Baseline and After 25 and 52 Weeks of Treatment With Vitamin D or Placebo in Patients With PHPT

	Mean Values (95% CI)			Percent Changes (%)		
	Baseline, wk 0	Preoperative, wk 25	End of Study, wk 52	Preoperative, wk 0–25	Postoperative, wk 26–52	Total Change, wk 0–52
Lumbar spine BMD, g/cm^2						
Placebo (n = 20)	0.93 (0.86–1.01)	0.92 (0.85–0.99)	0.95 (0.88–1.03)	−1.5 (−2.7 to −0.2)[a,b]	3.7 (2.0–5.4)[d]	1.9 (0.03–3.8)[b]
Vitamin D (n = 20)	0.89 (0.84–0.94)	0.90 (0.85–0.95)	0.92 (0.87–0.98)	1.0 (−0.5 to 2.5)[a]	2.6 (1.0–4.1)[c]	3.3 (1.3–5.3)[c]
All (n = 40)	0.91 (0.87–0.96)	0.91 (0.87–0.95)	0.94 (0.89–0.98)	−0.3 (−1.3 to 0.7)	3.1 (2.0–4.2)[d]	2.6 (1.3–3.9)[d]
Total hip BMD, g/cm^2						
Placebo (n = 20)	0.89 (0.81–0.96)	0.89 (0.82–0.97)	0.90 (0.82–0.98)	0.7 (−0.8 to 2.1)	0.8 (−0.9 to 2.6)	1.5 (−0.6 to 3.5)
Vitamin D (n = 20)	0.80 (0.75–0.86)	0.81 (0.75–0.86)	0.83 (0.77–0.88)	0.2 (−0.9 to 1.3)	2.6 (1.4–3.9)[d]	2.8 (1.8–3.8)[d]
All (n = 40)	0.84 (0.79–0.89)	0.85 (0.80–0.90)	0.86 (0.81–0.91)	0.4 (−0.4 to 1.3)	1.7 (0.6–2.8)[c]	2.1 (1.0–3.3)[d]
Femoral neck BMD, g/cm^2						
Placebo (n = 20)	0.75 (0.69–0.82)	0.75 (0.68–0.81)	0.75 (0.68–0.83)	−0.6 (−2.2 to 1.0)	0.1 (−1.8 to 2.0)	0.1 (−1.8 to 2.0)
Vitamin D (n = 20)	0.67 (0.62–0.72)	0.67 (0.63–0.72)	0.69 (0.64–0.73)	0.0 (−1.3 to 1.3)	2.1 (0.9–3.4)[c]	2.2 (0.9–3.4)[c]
All (n = 40)	0.71 (0.67–0.75)	0.71 (0.67–0.75)	0.72 (0.68–0.76)	−0.3 (−1.3 to 0.7)	1.1 (−0.1 to 2.3)	1.1 (0.0–2.3)
Total distal forearm BMD, g/cm^2						
Placebo (n = 20)	0.47 (0.43–0.52)	0.47 (0.42–0.51)	0.48 (0.43–0.53)	−1.2 (−2.0 to −0.4)[c]	2.2 (−1.8 to 6.2)	0.9 (−2.7 to 4.4)
Vitamin D (n = 20)	0.45 (0.40–0.50)	0.45 (0.40–0.49)	0.45 (0.40–0.49)	−0.4 (−1.9 to 1.2)	0.5 (−0.4 to 1.5)	−0.1 (−1.6 to 1.5)
All (n = 40)	0.46 (0.43–0.49)	0.46 (0.43–0.49)	0.46 (0.43–0.50)	−0.8 (−1.6 to 0.01)	1.4 (−0.6 to 3.4)	0.4 (−1.5 to 2.3)
Proximal 1/3 of distal forearm BMD, g/cm^2						
Placebo (n = 20)	0.59 (0.52–0.66)	0.58 (0.52–0.65)	0.58 (0.52–0.64)	−1.0 (−2.2 to 0.3)	0.3 (−1.5 to 2.2)	−1.0 (−2.8 to 0.9)
Vitamin D (n = 20)	0.59 (0.53–0.65)	0.58 (0.53–0.64)	0.58 (0.53–0.64)	−1.1 (−2.7 to 0.4)	0.1 (−1.2 to 1.5)	−1.3 (−3.0 to 0.4)
All (n = 40)	0.59 (0.55–0.63)	0.58 (0.54–0.63)	0.58 (0.54–0.62)	−1.0 (−2.0 to −0.1)[b]	0.2 (−0.8 to 1.3)	−1.1 (−2.4 to 0.1)
Mid-distal forearm BMD, g/cm^2						
Placebo (n = 20)	0.49 (0.45–0.53)	0.50 (0.45–0.54)	0.48 (0.44–0.53)	2.8 (−5.8 to 11.5)	−2.3 (−7.1 to 2.5)	−1.2 (−2.4 to −0.1)[b]
Vitamin D (n = 20)	0.46 (0.41–0.52)	0.46 (0.41–0.51)	0.46 (0.41–0.51)	−0.3 (−1.9 to 1.3)	0.4 (−0.4 to 1.3)	−0.1 (−1.7 to 1.4)
All (n = 40)	0.48 (0.44–0.51)	0.48 (0.45–0.51)	0.47 (0.44–0.51)	1.4 (−3.1 to 5.9)	−0.9 (−3.3 to 1.5)	−0.7 (−1.6 to 0.2)
Ultradistal forearm BMD, g/cm^2						
Placebo (n = 20)	0.35 (0.32–0.39)	0.35 (0.31–0.38)	0.35 (0.32–0.38)	−1.3 (−2.9 to 0.3)	1.0 (−0.7 to 2.6)	−0.5 (−1.8 to 0.9)
Vitamin D (n = 20)	0.31 (0.27–0.35)	0.31 (0.28–0.35)	0.32 (0.28–0.35)	0.6 (−2.1 to 3.3)	1.4 (−0.6 to 3.5)	2.0 (−0.9 to 4.9)
All (n = 40)	0.33 (0.31–0.36)	0.33 (0.30–0.35)	0.33 (0.31–0.36)	−0.4 (−1.9 to 1.1)	1.2 (0.0–2.4)	0.7 (−0.8 to 2.2)
TBS (L1–L4)						
Placebo (n = 19)	1.24 (1.19–1.30)	1.26 (1.21–1.31)	1.28 (1.23–1.33)	1.1 (−0.7 to 2.8)	2.1 (0.1–4.0)[b]	3.1 (0.6–5.7)[b]
Vitamin D (n = 18)	1.25 (1.16–1.33)	1.27 (1.18–1.35)	1.28 (1.20–1.36)	0.9 (−1.5 to 3.3)	1.7 (−0.8 to 4.2)	2.5 (−0.6 to 5.7)
All (n = 37)	1.25 (1.20–1.29)	1.26 (1.22–1.31)	1.28 (1.24–1.32)	1.0 (−0.5 to 2.4)	1.9 (0.3–3.4)[b]	2.8 (0.9–4.8)[c]

[a] Between-group differences, $P < .05$.

[b–d] Within-group differences: [b] $P < .05$, [c] $P < .01$, [d] $P < .001$.

the study medication, and none of the adverse events were statistically more frequent in either of the groups. Biochemical criteria for withdrawal of any study participants were never close to be fulfilled (plasma creatinine >170 μmol/L or plasma Ca^{2+} >1.70 mmol/L). The highest measured value of Ca^{2+} was 1.65 mmol/L (in both groups).

Discussion

To the best of our knowledge, the present study is the first randomized, double-blind, controlled trial on preoperative vitamin D supplementation to PHPT patients with vitamin D insufficiency. Preoperative optimization of vitamin D status decreased the levels of PTH and CTx with a concomitant increase in lumbar spine BMD. Importantly, our data do not suggest safety concerns, because plasma and urinary calcium as well as renal function did not change. Postoperatively, vitamin D-treated patients also had lower PTH and alkaline phosphatase levels compared with controls, suggesting a reduced remodeling activity, although total hip and spine BMD increased in all patients.

Our findings support the results from vitamin D treatment in uncontrolled trials (19, 20). A decrease in PTH levels by optimization of vitamin D status may be of clinical importance due to the association between PTH levels, disease severity, and postoperative bone hunger (9, 13, 30, 31). This was confirmed in our study with preoperative reduction in the resorptive bone marker CTx. The CTx decrease probably reflects a decreased remodeling activity in vitamin D-treated patients. The trabecular bone remodeling in PHPT is generally characterized by increased turnover but preserved coupling between resorption and formation (32). The total remodeling period takes 4 to 5 months (32, 33), and this duration may explain the lack of preoperative decrease in bone formation markers. From these results, it is conceivable that the BMD increase in trabecular dominated sites mainly arises from a reduction in bone resorption. Although most of the bone loss in PHPT is reversible (34, 35), the downregulation of bone remodeling activity may also reduce the risk of bone hunger in the postoperative phase, because this is considered to be a manifestation of high turnover. The preoperative reduced bone resorption by vitamin D was in the present study followed by postoperative reduced levels of PTH and alkaline phosphatase. However, a profound clinical appearance of hungry bone syndrome is not common in these mild or asymptomatic patients.

In our study, TBS improved significantly after PTX, without group differences. However, the BMD response to vitamin D supplementation could not be detected by TBS. Additional studies are needed to determine the value of TBS in patients with vitamin D insufficiency because the evidence for its clinical use has not been fully elucidated (36).

In otherwise healthy individuals, a positive correlation exists between 25OHD and $1,25(OH)_2D$ levels (37). We showed a similar positive correlation in PHPT with increased $1,25(OH)_2D$ levels in response to vitamin D treatment. Levels of DBP did not change. Accordingly, calculation of free 25OHD levels did not provide additional information. In a previous study, renal calcium excretion correlated with $1,25(OH)_2D$ levels, suggesting that calcium intake should be limited in PHPT patients with high $1,25(OH)_2D$ levels (38). Our data do not support such a relationship. Although we did not vary calcium intake as part of our investigation, $1,25(OH)_2D$ levels did not correlate with 24h-UCa. In multiple regression analyses, the only significant predictors of 24h-UCa were plasma calcium and PTH levels, suggesting that the filtered load of calcium determines calcium excretion in PHPT.

The major strength of our study is the randomized double-blind design. The inclusion of patients was more difficult than expected. Several patients refused participation because they did not want to postpone surgery for 6 months. Furthermore, the strength is limited according to the relatively small number of participants because we did not achieve 50 included patients as intended after the power calculation. However, the primary endpoint did reach statistical significance, and it is our impression that no major differences were present between included participants and those who rejected participation. Accordingly, our sample seems representative for PHPT patients with mild to moderate disease and vitamin D insufficiency.

Conclusion

Daily supplementation with a high vitamin D dose safely improves vitamin D status and decreases PTH in PHPT patients without increasing plasma or urinary calcium. The vitamin D treatment is accompanied by reduced bone resorption and improved BMD before operation. Postoperatively, vitamin D treatment reduced PTH and alkaline phosphatase. The study supports a wider use of vitamin D supplementation in PHPT patients.

Acknowledgments

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The study is funded by Horslev Foundation, Denmark.
Disclosure Summary: The authors have nothing to disclose.

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