

## VITAMIN D STATUS AND CONSEQUENCES OF LONG TERM SUPPLEMENTATION WITH ORAL NATIVE VITAMIN D<sub>3</sub> ON THE SEVERITY OF PRIMARY HYPERPARATHYROIDISM - THE ROMANIAN EXPERIENCE

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### Abstract

Primary hyperparathyroidism is a common general endocrine disorder everywhere but the clinical presentation differs between western and other countries, probably because of the different prevalence of vitamin D deficiency and its consequences. The study objective was first to compare the prevalence of both vitamin D insufficiency and deficiency between primary hyperparathyroidism (PHPT) patients and controls and to assess the association between 25hydroxi-vitamin D (25OHD) levels and PHPT severity (osteoporosis, fractures, nephrolithiasis, serum and urine calcium, serum PTH, bone turnover markers, bone mineral density (BMD)) and secondly to evaluate the effects of vitamin D repletion. In a cohort of 221 patients with PHPT (mean PTH 317.2 pg/mL; mean Ca 11.4 mg/dL) it was found a significantly lower mean serum 25OHD (13.42 ng/mL vs 17.66 ng/mL) and a significantly higher (34.72%) prevalence of severe vitamin D deficiency (< 10 ng/mL) than in osteoporosis controls (12.83%). Low serum 25OHD was associated with higher serum levels of calcium, PTH and alkaline phosphatase but not with the clinical severity. Supplementing vitamin D in mild primary hyperparathyroidism is safe, as it does not increase serum calcium and significantly reduces iPTH levels.

### Rezumat

Hiperparatiroidismul primar este o boală endocrină frecventă, dar tabloul clinic diferă între țările vestice și alte țări, posibil din cauza prevalenței diferite a deficitului de vitamina D și consecințelor sale. Obiectivul a fost de a compara prevalența insuficienței și deficitului de vitamină D între pacienții cu hiperparatiroidism primar (HPTP) și grupul de pacienți de control, dar și de a evalua asocierea dintre nivelurile serice de 25 hidroxivitamină D (25OHD) și severitatea HPTP (osteoporoză, fracturi, nefrolitiază, calciu seric și urinar, PTH seric, markeri ai *turnover*-ului osos, densitatea minerală osoasă (DMO) și de a evalua efectele repleției de vitamină D. Într-o cohortă de 221 pacienți consecutivi cu HPTP (nivelele medii serice de PTH 317,2 pg/mL, nivelele medii serice de Ca 11,4 mg/dL), s-a constatat o valoare semnificativ mai mică a valorii medii de 25OHD serice (13,42 ng/mL față de 17,66 ng/mL) iar prevalența deficitului sever de vitamină D (< 10 ng/mL) a fost semnificativ mai mare (34,72%) decât în lotul control (12,83%). Valori scăzute ale 25OHD serice s-au asociat cu valori serice crescute ale calciului, PTH și fosfatazei alcaline, dar nu și cu severitatea clinică. Suplimentarea vitaminei D în forma asimptomatică de hiperparatiroidism primar este sigură, nu determină creșterea calcemiei și reduce semnificativ nivelul iPTH.

**Keywords:** primary hyperparathyroidism, vitamin D deficiency, phenotype severity, vitamin D repletion

### Introduction

Primary hyperparathyroidism is a frequent endocrine disease consisting of hypercalcemia and elevated or inappropriately normal levels of PTH. After the introduction on a large scale of auto-analysers in our country, in the last decades, the clinical phenotype of PHPT changed from symptomatic with frequent osteitis *fibrosa cystica* to a mixture of symptomatic and asymptomatic forms, in spite of endemic vitamin D deficiency in Romania [1]. In primary hyperparathyroidism, vitamin D deficiency is more frequent than in the general population because of the increased catabolism of 25OHD stimulated by the increased levels of 1,25-dihydroxyvitamin D<sub>3</sub> [2, 3]. Many studies

showed that vitamin D-deficient patients with PHPT have higher levels of PTH and higher turnover, bigger parathyroid adenomas, reduced bone mineral density (BMD) and a higher prevalence of fractures than vitamin D-sufficient patients [4-9].

In these terms, the biochemical phenotype of PHPT might be progressively worsened by promoting a more marked parathyroid cell proliferation (stimulates parathyroid adenoma growth) and potential detrimental effects on bone mass, so for that reason more recent guidelines encourage vitamin D replacement to a 25OHD level above 20 ng/mL in all monitored patients with PHPT [8, 10]. Older studies of supplementation with vitamin D in PHPT raised concerns of safety

(aggravating hypercalcemia and/or hypercalciuria) but more recent data sustain a safe profile [11-13].

## Materials and Methods

This was a cross-sectional study of clinical characteristics, biochemical findings, bone turnover markers (BTMs), and areal BMD (aBMD) by dual X-ray absorptiometry (DXA) in PHPT patients with vitamin D deficiency or insufficiency, including an investigator-initiated controlled replacement study.

### Patients

The main group consisted in 221 consecutive patients from "C. I. Parhon" National Institute of Endocrinology, Bucharest, Romania with PHPT retrospectively selected from our database between 2006-2012 and 201 age-matched controls with osteoporosis and normal serum calcium.

PHPT was diagnosed in the presence of hypercalcaemia and elevated or inappropriately normal parathyroid hormone (PTH) levels. We defined vitamin D nutrition status by level of serum 25OHD, and when analysing both PHPT group and control group, we used 4 sub-categories: < 10 ng/mL; 10 - 20 ng/mL; 20 - 30 ng/mL; > 30 ng/mL.

From the main cohort of 221 PHPT patients, we selected 55 consecutive patients with mild primary hyperparathyroidism (mean PTH 162 pg/mL; mean Ca 10.88 mg/dL) and vitamin D deficiency (mean 25OHD 12,86 ng/mL) (repletion cohort); the control group consisted in 100 age- and BMI- matched individuals with osteoporosis. Both groups were treated with 1.000 IU cholecalciferol daily for 2 years, and the outcome was to evaluate the efficacy and safety of vitamin D replacement. Data were collected before and after 6 months, one and two years of treatment on: serum calcium, 25-OH D, iPTH, urine calcium excretion, phosphorus, alkaline phosphatase and nephrolithiasis.

### Biochemical parameters

The biochemistry (serum calcium, phosphate, magnesium, alkaline phosphatase and creatinine) were assessed by an automated analyser. 24 hour urine was collected in standard conditions to determine calciuria. Levels of 25OHD, beta crosslaps and osteocalcin were measured by chemiluminescence (Cobas, Roche). Serum intact PTH was measured by electrochemiluminescence automated assays (Cobas, Roche).

### Bone mineral density measurements

Areal BMD was measured by DXA at the lumbar spine, L1 - L4 (LS), femoral neck (FN) and distal radius 1/3 site (R) (GE-Lunar iDXA, USA). At our facility

the *in vivo* precision is 1.2 % at the lumbar spine, 1.5% at the femoral neck and 1.3% at the distal radius.

### Statistical analyses

The results are expressed as mean  $\pm$  SD. The comparison of continuous variables was performed using Student's t-test or Mann-Whitney U test as appropriate, after checking for assumption for distribution normality (Shapiro-Wilk test) and equality of variances (Levene's test).  $\chi^2$  test was used for between-group comparisons for categorical variables. One-way Anova was performed among the variables in order to compare three or more groups of subjects. P values of < 0.05 were considered significant.

All patients were given written informed consent.

## Results and Discussion

*Main cohort characteristics:* there were 221 PHPT patients (90% females) with mean PTH 317.2 pg/mL; mean Ca 11.4 mg/dL, mean age 61 years (range 17 - 84), mean BMI 26.8 kg/m<sup>2</sup> (range 15 - 43). 7% of the patients had symptomatic hypercalcemia. 63% of the patients had osteoporosis, LS (54%), FN (29%), radius (63%) and 29% had a fragility fracture history; 56% had nephrolithiasis. Mean T-scores was in the osteoporosis range at the LS ( $-2.5 \pm 1.4$  SD) and 1/3 radius ( $-2.6 \pm 1.5$  SD) but was in the osteopenic range at the FN ( $-1.9 \pm 0.8$  SD).

### Vitamin D status in the main cohort

The main cohort had significantly ( $p < 0.001$ ) lower mean serum 25OHD (13.42 ng/mL) vs control group (17.66 ng/mL) and the prevalence of severe vitamin D deficiency (< 10 ng/mL), was significantly higher (34.72% vs 12.83%). The percentage of patients with 25OHD below 20 ng/mL and 30 ng/mL was 85% and 96% respectively compared with 63% ( $p < 0.001$ ) and 82% ( $p < 0.001$ ) of the controls. With regard to the features of PHPT, there were no differences in clinical indices reflecting disease severity (fractures, nephrolithiasis) by vitamin D status (Table I) in a subgroup of 157 patients with complete clinical and biochemical data.

In patients from the main cohort low plasma 25OHD was associated with higher plasma levels of calcium, PTH and alkaline phosphatase (Table I). There were no between-group differences in BMI, age, and markers of bone turnover (many patients were on treatment with bisphosphonates). There were no differences in aBMD at the LS, FN or third distal radius by vitamin D status (data not shown).

**Table I**

	Biochemical and clinical phenotype by vitamin D status			
	25 OH D, ng/ml			p value
	> 30	10 - 30	< 10	
n	6	88	63	
Age, y	65.16 ± 9.76	61.48 ± 9.48	62.28 ± 11.67	NS
BMI, kg/m <sup>2</sup>	25.97 ± 3.2	26.85 ± 4.76	27.09 ± 5.1	NS
25OHD, ng/mL	45.68 ± 23.26	16.15 ± 5.23	7.12 ± 2.11	< 0.0001
sPTH, pg/mL (16 - 62)	133.8 ± 54.2	187.3 ± 159.9	325.9 ± 498.5	0.03
Alk Phos, U/L (35 - 110)	75 ± 35.4	98.9 ± 58.9	162.3 ± 232.7	0.03
sCalcium, mg/dL (8.4 - 10.4)	10.7 ± 0.43	10.99 ± 0.97	11.42 ± 1.29	0.03
sPhosphorus, mg/dL (2.5 - 4.5)	2.86 ± 0.64	2.81 ± 1.32	2.55 ± 1.73	NS
CTX, ng/mL (0.33 - 0.782)	0.7 ± 0.18	0.91 ± 0.83	1.19 ± 1.64	NS
Osteocalcin, ng/mL (15 - 46)	28.54 ± 3.99	43.74 ± 39.74	66.96 ± 88.19	0.07
Nephrolithiasis, %	50	55.68	49.2	NS
Fractures, %	16.66	32.95	19.04	NS

Data are expressed as means ± SD; BMI - Body Mass Index, 25OHD - 25 hydroxvitamin D, PTH - Parathyroid Hormone, Alk Phos - Alkaline Phosphatase, CTX - beta-crosslaps

*The repletion cohort*

The baseline characteristics of the repletion cohort are shown in Table II.

**Table II**

Baseline characteristics of 55 patients with PHPT

Characteristic	Mean	SD
Age, y	62.65	11.62
BMI, kg/m <sup>2</sup>	25.43	4.43
Serum PTH (16 - 62 pg/mL)	162.9	156.0
Serum 25OHD	12.86	8.36
Serum calcium (8.5 - 10.4 mg/dL)	10.88	0.83
Serum phosphorus (2.5 - 4.5 mg/dL)	2.73	0.51
Alkaline phosphatase (35 - 110 U/L)	79.54	55.10
Serum creatinine (0.4 - 0.9 mg/dL)	0.71	0.18
Urinary calcium (0.07 - 0.3 g/24h)	0.24	0.11
CTX ng/mL	0.91	0.85
Osteocalcin, ng/mL	44.87	42.94

Mean baseline serum 25OHD was significantly lower vs. control group (12.86 ng/mL vs 18.31 ng/mL, p < 0.001). Vitamin D deficiency/insufficiency prevalence using several cut-offs were as follows: severe vitamin D deficiency (< 10 ng/mL, mean 7.03 ± 2.23) was much higher in PHPT patients

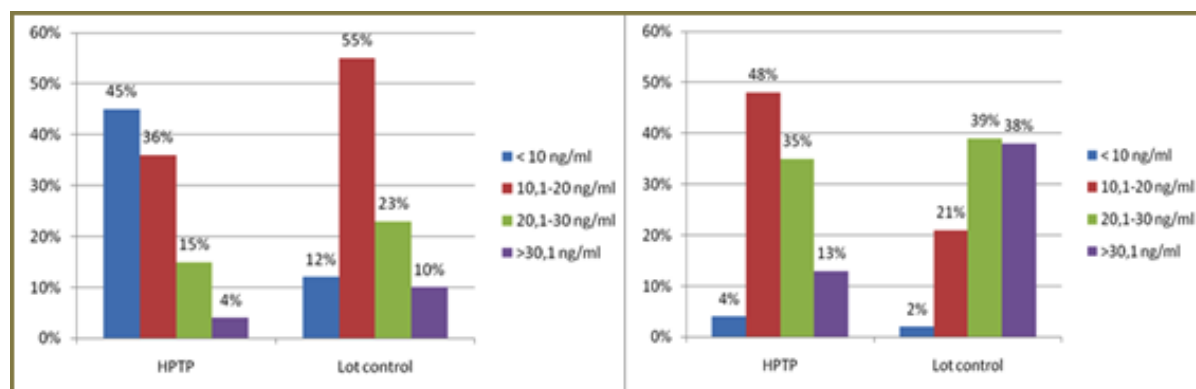
(45%) than in controls (12%); 36% were in 10 - 20 ng/mL group, 15% were in 20 - 30 ng/mL group and only 4% had optimal status (> 30 ng/mL). In the repletion cohort 25-OHD increased significantly, from a baseline of 12.86 ng/mL to 20.44 ng/mL (mean increase 6.14 ± 10.93 ng/mL, p = 0.006) after one year, while control patients had a mean increase of 9.64 ng/mL at 1 year (Table III); the increase in 25OHD in PHPT group was to 22.87 ng/mL (mean increase 8.55 ± 8.99 ng/mL, p = 0.0005) after two years of treatment.

**Table III**

Differential increases in serum 25OHD in PHPT vs control patients under supplementation

Serum 25OHD	PHPT	Control	p
Baseline (ng/mL)	12.86	18.31	p < 0.001
1 yr (ng/mL)	20.44	27.11	p = 0.02
Change (ng/mL)	6.14	9.64	p = 0.08

Changes (%) of vitamin D subcategories in PHPT and control patients at baseline and after 1 year of supplementation can be observed in Figure 1. The increase in serum 25OHD was inversely related to its baseline concentration (r = 0.673) and the slope was quite similar with that in the control group.

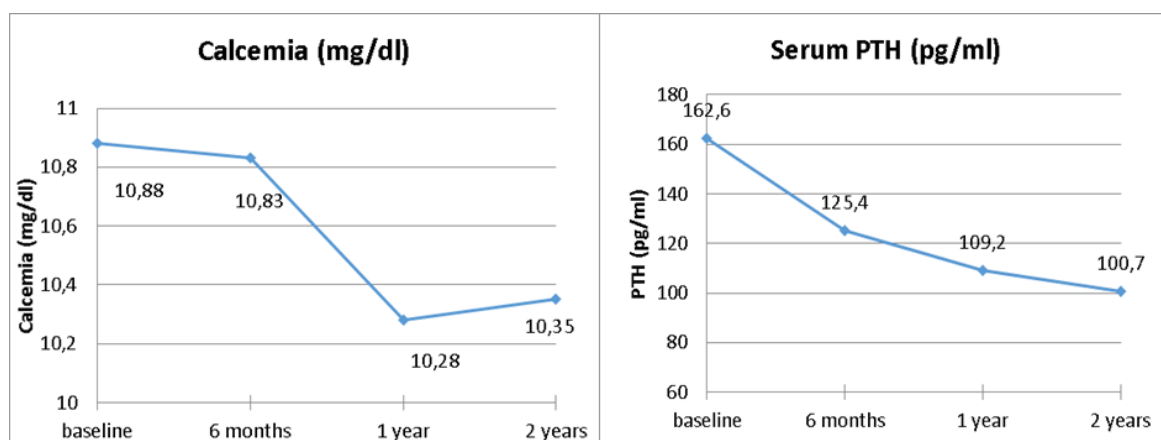


**Figure 1.**

Percentage of vitamin D subcategories in PHPT and control patients at baseline and after 1 year of supplementation

Post-treatment mean serum calcium decreased slightly at 1 year (10.88 mg/dL vs 10.28 mg/dL;  $p = 0.0006$ ) and 2 years (10.35 mg/dL) as seen in Figure 2. The difference in mean serum calcium of PHPT patients became nonsignificant in paired values at two years

versus baseline. A similar trend on PTH levels was observed, with a significantly decrease after one year (mean PTH at one year 162.59 pg/mL vs 109.1 pg/mL,  $p = 0.05$ ) and after two years (mean PTH 100.7 pg/mL,  $p = 0.007$ ) (Figure 2).



**Figure 2.**

Time-related mean concentrations of serum calcium and PTH in PHPT patients under supplementation with vitamin D

Markers of bone turnover did not change in time, probably because many patients were receiving bisphosphonates for osteoporosis. Mean urinary calcium did not significantly differ at 6 months, 1 year and 2 year vs baseline. There were no new cases of nephrolithiasis and serum creatinine remained stable in all patients.

Three important observations were made by this study on more than 200 patients with many symptomatic PHPT: the prevalence of severe vitamin D deficiency is higher than in control and has little impact on the clinical disease severity; two years of replacement with vitamin D in mild PHPT is safe and partly controls biochemical phenotype severity.

Vitamin D deficiency ( $< 20$  ng/mL) and insufficiency are frequent in primary hyperparathyroidism although the prevalence of severe vitamin D deficiency ( $< 10$  ng/mL) is decreasing in western PHPT [14]. A common finding in the latter is that vitamin D deficiency is associated with more severe biochemical hyperparathyroidism as reflected by higher serum PTH levels [4, 5, 15]. However, there were no differences in the clinical presentation of PHPT, such as the frequency of kidney stones or fractures, by vitamin D status [15]. Moreover, low vitamin D in PHPT using current 25OHD thresholds for insufficiency and deficiency did not significantly affect skeletal integrity (volumetric bone density, bone micro-architecture, or strength) as assessed by HRpQCT [16]. Therefore, even if unexpected, it seems that vitamin D deficiency as currently defined ( $< 20$  ng/mL) has little if any detrimental effect on bone health in mild/asymptomatic PHPT [16]. Our study fills the gap in the knowledge of the effects of severe

vitamin D deficiency ( $< 10$  ng/mL) on the clinical and biochemical severity of PHPT as it included also data from a group of 63 such patients, which may have increased our probability to observe between-group differences. In the main cohort the percentage of patients with 25OHD below 20 ng/mL was 85% and those with profound deficiency ( $< 10$  ng/mL) were 35% (from 221 patients). Therefore, our data confirm the observations from other studies which also found an increased prevalence of vitamin D deficiency (32% - 81%) with a large range (14.4 - 30.4 ng/mL) of mean 25OHD levels [4, 5, 17]. It has long been accepted that coexisting vitamin D deficiency produces a more severe PHPT phenotype, characterised by higher PTH levels, greater adenoma weight, lower BMD, higher bone turnover and increased fracture risk [6, 7]. This is why current guidelines recommend measurement and repletion of vitamin D in these patients [8, 10, 18]. Indeed, in our patients also low plasma 25OHD was associated with higher plasma levels of calcium, PTH and alkaline phosphatase. There were no between-group differences ( $< 10$  vs 10 - 30 vs  $> 30$  ng/mL) in BMI, age, age at menopause, markers of bone turnover and aBMDs at any site. Moreover, there were no between-group differences in overt signs of symptomatic disease, such as nephrolithiasis or fracture. This data is quite similar to those recently reported in western PHPT with very few patients (4 from 100 patients) with severe vitamin D deficiency [15].

Several studies suggest that PHPT in patients with vitamin D deficiency is associated with a more aggravated hormonal and biochemical profile (higher levels of PTH, calcium and bone turnover markers)

and propose that preserving vitamin D sufficiency may prevent the progression of PHPT [4, 11]. Our results suggest that vitamin D repletion does not promote an increase in serum calcium, and determines even a significant decrease in serum PTH (38% at 2 years), but no influence on urine calcium was observed. Grey *et al.* showed in a small group of 21 PHPT patients over 1 year treatment that vitamin D repletion does not exacerbate hypercalcemia, PTH decreased by 26%, and also bone turnover markers tended to be lower [4]. Similar to our study, Rao *et al.* also stated on 40 PHPT patients monitored over 54 months that prolonged vitamin D supplementation is safe and significantly decreased PTH levels by 21% [8]. PHPT patients have relative hypercalciuria and kidney stones occur in 10% - 20% of patients [13]. Nevertheless, urine calcium excretion is a poor predictor of stone formation, and in consequence regular monitoring of urinary calcium excretion should no longer be recommended in patients with PHPT [19]. Rolighed L *et al.* reported in a randomized controlled trial on 46 PHPT patients treated with 2800 IU cholecalciferol for 26 weeks before parathyroidectomy, a significantly decrease in PTH (17%) while serum/urinary calcium remained unchanged [18]. A recent meta-analysis was performed to evaluate the consequences of vitamin D replacement on biochemical and bone parameters in subjects with mild PHPT and associated vitamin D deficiency. A total of 547 patients were examined and results were that vitamin D replacement improved serum 25OHD level with unchanged serum iPTH level and without aggravation of pre-existing hypercalcemia or hypercalciuria [12]. In our study, although 25-OHD increased significantly from baseline, and the increase was inversely related to its initial concentration, 48% of the patients in PHPT group had 25OHD values > 20 ng/mL compared to the control group (76%). This may suggest that higher doses or longer repletion periods would be necessary to obtain sufficiency in 25OHD.

The data from our study reinforce the notion that vitamin D repletion for two years in patients with mild PHPT may be adequate and safe. This approach may be helpful in patients with asymptomatic PHPT and in patients who are not willing to undergo surgery, have negative localization studies or have other medical contraindications.

Our study has several limitations: the evaluation of bone microarchitecture was not available; the use of bisphosphonates by many patients limited the interpretation of bone turnover markers, both in the main and the repletion cohort; the repletion study was not randomized.

## Conclusions

In patients with primary hyperparathyroidism there is an increased prevalence of vitamin D deficiency,

using several cut-offs, greater than in an age-matched control group with osteoporosis. Low serum 25OHD levels, even those in the range of severe deficiency, do not influence clinical disease severity, but favour a more severe biochemical phenotype (mostly higher PTH levels). Replacing vitamin D in mild primary hyperparathyroidism is safe, does not increase serum calcium and effectively reduces PTH levels.

## Conflict of interest

No potential conflicts of interest were disclosed.

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