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ORIGINAL ARTICLE

The impact of vitamin D deficiency on clinical, biochemical and metabolic parameters in primary hyperparathyroidism

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Abstract
Background: It has been suggested that vitamin D deficiency is associated with worse clinical outcomes in primary hyperparathyroidism (PHPT). We aimed to evaluate the relationship between vitamin D deficiency and clinical, biochemical and metabolic parameters in PHPT patients.
Methods: A total of 128 patients with biochemically confirmed PHPT were included. Patients were categorized as vitamin D deficient if 25-OH vitamin D was <50 nmol/L, or normal if vitamin D was ≥50 nmol/L. Biochemical parameters, bone mineral densitometry (BMD), and urinary tract and neck ultrasonography were assessed.
Results: In the study group, 66 (51.6%) patients had vitamin D deficiency and 60 (48.4%) had normal vitamin D levels. Nephrolithiasis and osteoporosis were found in 26.6% and 30.5% of subjects, respectively. The prevalence of metabolic syndrome (MetS), obesity (BMI ≥30 kg/m^2) and hypertension (HTN) were higher in the vitamin D deficient group when compared to the normal group ($p = 0.04$, $p = 0.01$ and $p = 0.03$, respectively). There was no difference regarding the presence of nephrolithiasis and osteoporosis between the groups. The mean adenoma size was similar in both groups.
Conclusions: Vitamin D deficiency was not associated with osteoporosis, nephrolithiasis, adenoma size or biochemical parameters in PHPT. However, vitamin D deficiency may be a risk factor for developing HTN and MetS in PHPT.

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PALABRAS CLAVE
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Síndrome metabólico;
Obesidad;
Hipertensión

El impacto de la deficiencia de vitamina D en los parámetros clínicos, bioquímicos y metabólicos en el hiperparatiroidismo primario

Resumen

Antecedentes: Se ha sugerido que la deficiencia de vitamina D se asocia a peores resultados clínicos en el hiperparatiroidismo primario (HPTP). Nuestro objetivo es evaluar la relación entre la deficiencia de vitamina D y los parámetros clínicos, bioquímicos y metabólicos en pacientes con HPTP.

Métodos: Se incluyeron 128 pacientes con HPTP confirmado bioquímicamente. Los pacientes fueron categorizados de acuerdo con sus niveles de vitamina D, siendo deficientes si los niveles de 25-OH vitamina D eran <50 nmol/l, o normales si los niveles de vitamina D eran ≥50 nmol/l. Se evaluaron los parámetros bioquímicos, la densitometría mineral ósea (DMO) y la ecografía del tracto urinario y del cuello.

Resultados: En el grupo de estudio, 66 (51,6%) pacientes tenían niveles deficientes de vitamina D y 60 (48,4%) mostraban niveles normales de vitamina D. Se detectaron nefrolitiasis y osteoporosis en 26,6 y 30,5% de los sujetos, respectivamente. La prevalencia del síndrome metabólico (SM), la obesidad (IMC ≥30 kg/m^2) y la hipertensión (HTA) fueron mayores en el grupo con niveles deficientes de vitamina D en comparación con el grupo con niveles normales (p = 0,04, p = 0,01 y p = 0,03, respectivamente). No hubo diferencias en cuanto a la presencia de nefrolitiasis y osteoporosis entre los grupos. El tamaño medio del adenoma fue similar en ambos grupos.

Conclusiones: La deficiencia de vitamina D no se asoció a la osteoporosis, la nefrolitiasis, al tamaño del adenoma ni a los parámetros bioquímicos en el HPTP. Sin embargo, la deficiencia de vitamina D puede ser un factor de riesgo para el desarrollo de HTA y SM en el HPTP.

Introduction

Vitamin D deficiency has been reported to be more common in patients with PHPT when compared to healthy subjects and suggested to be associated with worse disease outcomes.[1–3] In addition, a limited number of studies reported higher alkaline phosphatase (ALP), calcium, and parathyroid hormone (PTH) levels and larger parathyroid adenoma (PA) size in PHPT patients with vitamin D deficiency.[3–7] However, these findings were not confirmed in all clinical studies.[4,7]

In addition to the classic bone and kidney complications of PHPT, several metabolic consequences of disease have been reported.[8,9] Hypertension, glucose intolerance, diabetes mellitus, dyslipidemia and obesity were reported to be related to PHPT.[8,10] Direct effects of parathyroid hormone (PTH) on adipocyte differentiation, insulin resistance and lipogenesis induced by increased intracellular calcium in adipocytes were suggested mechanisms of obesity and glucose intolerance in PHPT.[11,12] Vitamin D deficiency has also been suggested to be related to cardiometabolic disorders including hypertension, type 2 diabetes, dyslipidaemia, obesity, metabolic syndrome and cardiovascular diseases.[13,14] Several mechanisms were postulated to explain the interactions between vitamin D deficiency and metabolic diseases.[15–17] However, the causal relationship between vitamin D deficiency, obesity and related disorders has not been clearly identified. Low grade inflammation, lipogenesis induced by increased PTH synthesis and direct effects of vitamin D deficiency on adipogenesis were suggested as pathogenic factors for obesity and metabolic disorders.[11,18] On the other hand, volumetric dilution or sequestration of vitamin D in adipose tissue has been accepted as the most reasonable explanation for the link between obesity and vitamin D deficiency.[15,17]

In the present study, we aimed to investigate the impact of vitamin D deficiency on the clinical features and biochemical and metabolic parameters of PHPT.

Materials and methods

Patients

In this study, 128 patients with newly diagnosed PHPT at the Ankara University Faculty of Medicine Endocrinology Clinic were included. The PHPT diagnosis depended on both hypercalcaemia and high/inappropriately non-suppressed levels of PTH. Thiazide/lithium-induced hyperparathyroidism and familial hypocalciuric hypercalcaemia were excluded by measuring 24-h urinary calcium excretion and reviewing the medical history. Ninety-one patients underwent parathyroidectomy and adenoma was proven by histopathology. Patients who used agents which may affect calcium, vitamin D and bone metabolism (calcium, vitamin D, bisphosphonates, denosumab, corticosteroid, antidepressant, antiepileptic, selective oestrogen receptor modulator, teriparatide) and/or had a condition that may affect vitamin D/calcium metabolism (cancer, sarcoidosis, stage 4–5 chronic renal failure, active liver disease, malabsorption syndromes, immobilization, bariatric surgery, Cushing's

syndrome) were excluded. Pregnant women were not included. The body mass index (BMI) was defined as the weight in kilograms divided by the square height in meters. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria.[19] All patients were screened with urinary tract ultrasonography if they did not have medical history of nephrolithiasis/nephrocalcinosis or surgery for nephrolithiasis. Informed consent was obtained from all patients. The study was approved by the Ankara University ethics committee.

Ultrasonography

Neck ultrasonography was performed using high-resolution, B-mode, grey-scale US (Hitachi EUB 7000 HV machine with a 6–13 MHz linear transducer). The PA was measured in three dimensions, and the greatest dimension was categorized as <15 mm and ≥15 mm.

Eighty-six PAs that were not proven by histopathology and thirty-three PAs that were not treated surgically were identified by US. If a lesion with atypical sonographic findings suggestive of adenoma or multiple lesions suggestive of adenoma were observed, a sestamibi parathyroid scan or parathyroid hormone wash-out procedure was performed to prove PA. Parathyroid adenomas were not detected on US in nine patients (7.0%). Adenoma size was defined as the greatest diameter as measured by ultrasonography.

DEXA

Dual energy X-ray absorptiometry was performed on the lumbar spine, femoral neck, and total hip with the Hologic Discovery QDR™ series DXA systems, USA. Osteoporosis was defined according to WHO criteria as femoral or lumbar density 2.5 standard deviations below that of a young adult.[20]

Biochemistry

25-Hydroxyvitamin D (25OHD) was measured with high performance liquid chromatography using a Shimadzu device and an Immuchro-HPLC kit. Parathyroid hormone (PTH) was measured using the chemiluminescence method with a Beckman Coulter AU5800 (Brea, California, USA). Serum creatinine, albumin and phosphorus were measured with a Beckman Coulter DXI 800. Fasting blood glucose and insulin were measured after at least 8 h overnight fasting with Roche P800 and Cobas e411 (Roche Diagnostics, Switzerland). Corrected calcium (cCa) was calculated using the equation: $cCa = [(4 - albumin) \times 0.8] + Ca$.

Statistical analysis

Statistical analysis was performed with SPSS version 11.5 (BM Corp, NY, USA). Categorical data were presented as counts and percentages. Continuous variables with a normal distribution were presented as mean ± SD. Variables with a non-normal distribution were presented as median (minimum–maximum). Categorical data were compared using the Chi-square or Fisher's exact tests. Group data with a normal distribution were compared using Student's *t* test or analysis of variance. Nonparametric data were compared using the Mann–Whitney *U* or Kruskal–Wallis tests. The associations between continuous variables were determined by Pearson or Spearman correlation analysis according to distribution. A *p*-value <0.05 was considered statistically significant.

Table 1 Median levels of 25-hydroxyvitamin D according to comorbidities and complications in PHPT patients.

	25-hydroxyvitamin D level (nmol/L)	*p*-Value
Gender		
Male	56.3 (21.8–150.7)	0.77
Female	47.5 (10.0–206.8)	
Hypertension		
Present	40.0 (10.0–152.0)	0.15
Absent	54.0 (10.0–206.8)	
Type 2 diabetes		
Present	40.0 (13.5–136.0)	0.82
Absent	47.8 (10.0–206.8)	
Metabolic syndrome		
Present	40.8 (10.0–150.8)	0.52
Absent	52.8 (10.0–206.8)	
Dyslipidaemia		
Present	43.3 (10.0–200.0)	0.69
Absent	52.8 (10.0–206.8)	
Obesity		
Present	37.5 (13.0–127.0)	0.03
Absent	55.0 (10.0–206.8)	
Osteoporosis		
Present	48.5 (10.0–200.0)	0.35
Absent	43.3 (10.0–206.8)	
Nephrolithiasis		
Present	51.8 (12.8–150.8)	0.50
Absent	43.3 (10.0–200.0)	

Results

The study group included 128 patients [106 female (82.8%) and 22 (17.2%) male]. Among them, 66 patients (51.6%) had vitamin D deficiency (<50 nmol/L) and 60 (48.4%) had normal vitamin D levels (≥50 nmol/L). Twenty-one patients (17%) had severe vitamin D deficiency. Prevalence of hypertension (HTN), type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) were 20.3% ($n = 36$), 14.1% ($n = 18$) and 32.8% ($n = 42$), respectively. Nephrolithiasis and osteoporosis were found in 26.6% ($n = 34$) and 30.5% ($n = 39$) of subjects, respectively. None of the patients had a history of fracture. Vitamin D levels according to comorbidities and complications in PHPT patients are given in Table 1.

Mean BMI was similar in both vitamin D groups ($p = 0.1$). Obesity, metabolic syndrome and hypertension were more common in the vitamin D deficient group when compared to the normal vitamin D group ($p < 0.01$, $p = 0.04$ and $p = 0.03$, respectively). Type 2 diabetes was more common in the

Table 2 Comparison of clinical, metabolic and biochemical parameters of PHPT in the normal and vitamin D deficient groups.

	25-OH-vitamin D (ng/dl)		*p*-Value
	<50 nmol/L	≥50 nmol/L	
Age, years	55.5 ± 14.7	60.5 ± 13.1	0.04
Female/male, n (%)	58/8	48/14	0.11
Creatinine, μmol/L	63.6 ± 15.0	66.3 ± 17.7	0.52
GFR mL/min/1.73 m²	94.1 ± 20.2	89.9 ± 19.8	0.23
<60, n (%)	3 (4.5)	5 (8.1)	0.48
>60, n (%)	63 (95.5)	57 (91.9)	
BMI, kg/m²	28.4 ± 4.7	26.9 ± 3.5	0.10
<30, n (%)	42 (63.6)	51 (82.3)	0.01
>30, n (%)	24 (36.4)	11 (17.7)	
Lumbar spine T score	−1.6 ± 1.6	−1.9 ± 1.2	0.20
Femoral neck T score	−1.3 ± 1.3	−1.4 ± 1.0	0.53
Total hip T score	−1.0 ± 0.9	−1.1 ± 1.0	0.40
Forearm T score	−1.9 ± 1.6	−1.6 ± 1.7	0.66
HTN, n (%)	24 (36.4)	12 (19.4)	0.03
T2DM, n (%)	13 (19.7)	5 (8.1)	0.05
MetS, n (%)	27 (40.9)	15 (24.2)	0.04
FBG, mmol/L	5.1 (3.4–8.4)	50.1 (3.7–10.2)	0.60
HDL, mmol/L	1.2 (0.6–2.2)	1.3 (0.6–2.1)	0.25
LDL, mmol/L	3.1 (1.3–6.4)	3.2 (1.3–5.4)	0.47
TG, mmol/L	1.3 (0.4–3.6)	1.4 (0.5–3.2)	0.87
TSH, mIU/L	1.6 (0.01–18.8)	1.4 (0.08–16.4)	0.70
PTH, ng/L	138 (65–700)	135 (72–1229)	0.80
cCa, mmol/L	2.6 (2.5–3.8)	2.6 (2.6–3.4)	0.40
24-h urinary calcium, mg/day	311 (100–922)	282 (98–1300)	0.40
Nephrolithiasis, n (%)	15 (22.7)	19 (30.6)	0.30
Osteoporosis, n (%)	17 (26.4)	22 (36.0)	0.29
Adenoma size ≥15 mm, n (%)	30 (45.5)	30 (48.3)	0.25

cCa: corrected calcium; FBG: fasting blood glucose; HDL: high density lipoprotein; HTN: hypertension; LDL: low density lipoprotein; MetS: metabolic syndrome; T2DM: type 2 diabetes mellitus; PTH: parathyroid hormone; TG: triglyceride.

vitamin D deficient group when compared to the normal group, but this finding was not statistically significant ($p = 0.058$). Prevalence of osteoporosis and nephrolithiasis were similar in both groups ($p = 0.29$, $p = 0.30$, respectively). Serum PTH, Ca, 24-h urinary calcium level were not different in the two groups. The comparison of normal and deficient vitamin D groups is summarized in Table 2. Adenoma size was not associated with the vitamin D level ($p = 0.32$).

The vitamin D level was not correlated with PTH, Ca, P, ALP and 24-h urinary Ca ($p = 0.84$, $p = 0.70$, $p = 0.43$, $p = 0.73$ and $p = 0.45$, respectively). BMI was negatively correlated with the vitamin D level ($r = -0.27$, $p = 0.008$). Lumbar spine, total hip, femoral neck and distal radius *T* scores were not associated with vitamin D levels, respectively ($p = 0.20$, $p = 0.06$, $p = 0.54$ and $p = 0.97$ respectively). The mean age of patients with OP was 59 ± 12.7 years. After adjusting for age and BMI, the vitamin D level was not related to osteoporosis or the *T* score of any sites. There was a negative association between BMI and osteoporosis (OR: 0.84; 95% CI: 0.749–0.956). BMI was correlated with the total hip, lumbar spine, and femoral neck *T* scores (*r*: 0.41, $p = 0.01$; *r*: 0.32, $p = 0.01$, *r*: 0.35, $p = 0.02$, respectively) but not with distal radius ($p = 0.74$).

The median PTH level was not different between obese and non-obese groups [136.0 ng/L (73.9–602.0) vs. 136.8 ng/L (65.1–1229)]. The prevalence of nephrolithiasis was similar in obese and non-obese patients ($p = 0.59$). The prevalence of osteoporosis was 30.1% ($n = 28$) in non-obese and 20.0% ($n = 20$) in obese patients ($p = 0.026$).

Discussion

In this study, we could not demonstrate an association between the severity of clinical and biochemical features of PHPT and vitamin D deficiency. The prevalence of vitamin D deficiency was 51.6% and severe deficiency was 17%. Osteoporosis and nephrolithiasis frequencies were similar in the normal and vitamin D deficient groups. Serum corrected calcium, phosphorus, PTH, ALP levels, glomerular filtration rate and urinary calcium excretion were not associated with the vitamin D level. Obesity, MetS and HTN were more frequent in vitamin D deficient group when compared to normal vitamin D group. Type 2 DM was also more frequent in vitamin D deficient patients, although the difference was not statistically significant.

Previously, a relationship between vitamin D deficiency, low BMD, and severe bone disease was suggested in PHPT patients.[1,2,21] However, this finding was not confirmed in all studies.[4,7,22,23] A study by Walker et al. revealed that

the relationship between vitamin D deficiency and BMD in PHPT patients was limited to the distal radius.[4] In the study by Carnevale et al., the effect of vitamin D levels on BMD was found to be negligible, while PTH level, age and BMI were significantly correlated with BMD in women with PHPT.[22] Vitamin D status was associated with bone specific ALP and PTH, but not with BMD in a study by Viccica et al.[7] In a recent study, Walker et al. evaluated the effect of low vitamin D on volumetric BMD, bone microarchitecture and strength measured with quantitative computed tomography.[24] The authors observed that vitamin D deficiency was not related to any skeletal integrity parameters and hypothesized that the potential anabolic effects of high PTH might compensate for the negative effects of vitamin D deficiency on bone.[24] Furthermore, another study by the same group demonstrated an association between low vitamin D levels, higher volumetric BMD and vertebral integrity, supporting the possibility of positive impact of high PTH levels at the spine.[25]

The association between the vitamin D level and nephrolithiasis has also been controversial.[7,23,26] In a recent study, Reid et al. investigated the predictors of nephrolithiasis, osteoporosis and mortality in 611 patients with PHPT.[23] Vitamin D deficiency was not related with the risk of nephrolithiasis or osteoporosis. Consistent with the findings of Walker et al. and Reid et al., vitamin D deficiency was not correlated with osteoporosis or nephrolithiasis in our study group, although our cohort had a relatively high prevalence of vitamin D deficiency and severe deficiency.

None of the patients in our study group had a history of fracture. Recent studies show that the symptomatic course of PHPT has shifted to an asymptomatic disease, which presents as hypercalcemia and subclinical organ involvement.[27,28] This shift was caused by early detection of PHPT via routine calcium examinations during patient assessment. A study from Turkey reported that the vast majority of PHPT cases who underwent surgery were asymptomatic at the time.[29] Factors such as older age, longer disease duration and prior fractures increase the risk of fracture in PHPT patients.[30,31] Only newly diagnosed cases at our outpatient clinic were included in our study. Shorter disease duration due to immediate referral of patients to the Endocrinology Outpatient Clinic may be one of the causes of the lack of bone fragility in our group. Also, the mean age of patients with OP was relatively young. As a limitation, underestimation of silent fractures on X-ray in asymptomatic PHPT, especially mild vertebral fractures with 20–25% vertebral height reduction, cannot be ruled out in our study, as many factors such as BMI and patient-specific factors decrease the reliability of screening.[32] The false negative rate of X-ray in identifying vertebral fractures was reported as up to 30% in the literature.[33] Our study was not designed to assess the fracture risk, so we did not perform further imaging studies. Finally, a history of peripheral fractures was taken from the patients. So the reliability for non-vertebral, non-hip fractures may be low in our study group.

Vitamin D deficiency was also suggested to be related to the biochemical severity of PHPT.[4,7] Higher levels of PTH, ALP, Ca and lower levels of P have been reported to be correlated with low vitamin D concentrations, but results from clinical studies are inconsistent.[3–7] Our results did not confirm any relationship between the vitamin D level and biochemical severity of disease.

An inverse relationship between adenoma size and vitamin D status was suggested in previous reports.[3,34] In the study by Rao et al., PA weight was found to be inversely associated with 25-hydroxyvitamin D levels, but not 1,25-dihydroxyvitamin D levels.[34] This finding was explained by the expression of 1α-hydroxylase enzyme in parathyroid cells, which could cause parathyroid cell proliferation and induce PTH secretion during 25-hydroxyvitamin D deficiency.[34] We did not include the PA weight as a parameter, because 29% of our study group did not undergo surgery and the PA weight was not available in most pathology reports. Additionally, radio-guided occult lesion localization was performed occasionally and this procedure might affect the adenoma weight and size in the surgical specimen. We evaluated the greatest dimension on ultrasonography and could not demonstrate an association between vitamin D status and adenoma size. However, our method has limitations in defining the size of adenoma appropriately.

Metabolic consequences including glucose intolerance, hypertension, dyslipidaemia and cardiovascular disease have been reported to be more common in PHPT.[9,35] However, the causal relationship between PHPT, obesity and related metabolic consequences is not yet understood. The proposed mechanisms included possible PTH-induced adipocyte differentiation, the effect of elevated intracellular calcium on enhanced insulin resistance and lipolysis inhibition.[12,36] Conversely, obesity was suggested as a risk factor for developing PHPT via vitamin D deficiency.[8] In our study, hypertension, MetS and obesity were more common in the vitamin D deficient group when compared to the normal group, whereas PTH levels were similar in both groups. Limited sun exposure in obese patients, volumetric vitamin dilution in overweight patients and vitamin D sequestration by adipose tissue were all suggested as possible contributing factors between vitamin D deficiency and obesity.[15,17] Additionally, vitamin D deficiency was suggested to promote adipocyte differentiation directly via the inhibitory effects of active vitamin D on adipogenesis, or indirectly by increasing PTH level.[16] Renin-angiotensin-aldosterone system activation by vitamin D deficiency due to decreased vitamin D receptor (VDR) production was also suggested as a possible explanation for the association between vitamin D deficiency and hypertension.[37]

A possible link between vitamin D deficiency, CVD risk and CVD-related mortality was previously suggested, but the causality remained unexplained.[38,39] It was hypothesized that vitamin D deficiency may not have a direct, rather an indirect role in CVD fatality via its immunological effects.[38] RAA system activation and atherogenesis caused by alterations in proinflammatory and anti-inflammatory molecules were proposed as possible mechanisms by which vitamin D deficiency may be related to CVD.[40] Finally, MetS and its components are confounders of CVD and vitamin D deficiency was suggested to be associated with CVD indirectly by its effects on these confounders.[39] In this study, we did not evaluate the CVD risk, but our results showed that vitamin D deficiency in PHPT patients was correlated with MetS, hypertension and obesity.

The major limitation of our study was the single measurement of the vitamin D level. The estimated duration of PHPT

and vitamin D deficiency was not available. The number of female patients was significantly higher than the number of male patients in both groups, but the female-to-male ratio was similar in both groups. Also, the effect of sun exposure and dietary calcium intake could not be evaluated. Patients who were not taking vitamin D supplements were included in this cross-sectional study, so the effect of supplementation on parameters could not be evaluated.

In conclusion, vitamin D deficiency was not associated with biochemical or clinical severity of PHPT, although the prevalence of vitamin D deficiency was greater than 50% in our study population. The frequency of obesity, hypertension and metabolic syndrome were higher in the vitamin D deficient group when compared to the normal group. Further research is needed to explain the underlying mechanisms of relationship between metabolic parameters and vitamin D deficiency in PHPT patients.

Authors' contributions

All authors contributed to the conception, design and data collection of this study. Analyses were performed by GŞA, BİA and MŞ. GŞA, BİA and MŞ were responsible for the literature review and writing the draft. All authors supervised the study, reviewed and approved the final version.

Ethical approval

The study was approved by the Ankara University Faculty of Medicine Ethics Committee. Informed consent was obtained from all participants.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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