The Role of Vitamin D Status on Initial Characteristics of Primary Hyperparathyroidism: Current Clinical Experience from a Tertiary Center

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Objective: The aim of this study was to assess vitamin D status and its impact on the initial characteristics of primary hyperparathyroidism (PHPT).

Methods: This study included consecutive participants diagnosed with PHPT aged 18 years and/or older at a tertiary center between November 2017 and December 2023. A total of 195 subjects not taking vitamin D replacement were reviewed retrospectively. The study population was categorized into three groups according to their vitamin D levels at the time of admission: Group 1: vitamin D ≤ 19 ng/mL, Group 2: vitamin D 20-29 ng/mL, and Group 3: vitamin D ≥ 30 ng/mL. Demographic, clinical, biochemical, radiological findings, and postoperative complications were compared between the three groups.

Results: Among 195 patients, 157 (80.5%) were women, and 38 (19.5%) were men. The mean age was 56.4 ± 14.5 years. Sixty-five patients (33.3%) had vitamin D deficiency (VDD), and 48 patients (24.7%) had vitamin D insufficiency. Of the 195 patients, 74 (37.9%) had kidney stones, and 90 (46.2%) had osteoporosis. Fracture frequency was 9.7% (n=19). VDD was associated with higher parathyroid hormone (PTH) levels (p=0.000) and better estimated glomerular filtration rate (p=0.021). When all groups were compared, there were no differences in terms of nephrolithiasis, osteoporosis, and fractures.

Conclusion: The present study revealed that VDD was associated with higher PTH levels and better renal function. However, vitamin D status was not associated with classical target organ involvement in PHPT.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the most frequent endocrine diseases, with a higher predominance in postmenopausal women. PHPT is defined by hypercalcemia and increased or inappropriately normal serum parathyroid hormone (PTH) resulting from the excessive release of PTH in at least one parathyroid gland.[1,2] The most common cause is solitary parathyroid adenoma.[1,2] Three clinical phenotypes are described in PHPT. Symptomatic PHPT presents with overt kidney or bone complications. Asymptomatic PHPT presents no overt signs or symptoms, but patients may be affected by target organ involvement, for example, osteoporosis or nephrolithiasis. Normocalcemic PHPT is defined as both normal albumin-corrected serum calcium levels and increased PTH. Patients in this classification may or may not have renal or skeletal complications.[1,2] In Western countries, most patients are asymptomatic due to increased recognition of PHPT with common biochemical screening tests and earlier diagnosis.[3] In contrast, in some developing countries, the majority of primary hyperparathyroid patients (PHPP) have the classical symptomatic phenotypes with kidney and bone presentations.[4]

25-hydroxyvitamin D (25OHD) deficiency (VDD) and insufficiency (VDI) are still widespread comorbidities in patients with PHPT.[5] The mechanism behind the higher frequency of VDD is multifactorial, including decreased synthesis of vitamin D, accelerated conversion of 25OHD into other vitamin D compounds, increased metabolic clearance rate of vitamin D, shorter half-life of vitamin D, low vitamin D intake, and low vitamin D-binding protein level.[6] Vitamin D status should be considered to explain the different clinical and biochemical presentations of PHPT. There are studies investigating the relationship be-
between vitamin D status and its impact on the initial characteristics in PHPT. Effects of vitamin D status on initial biochemical and clinical characteristics remain controversial. Lower vitamin D is associated with higher serum PTH,[4,6,8,10-14] higher serum calcium,[4,6,8,10-14] lower serum phosphate,[9] increased bone turnover markers,[4,6,8,10-14] lower bone mineral density (BMD),[8,10,11,13] higher rates of pathological fractures,[11,13] and higher calcium excretion.[14] Patients with VDD tend to have larger parathyroid adenoma size or higher weight of excised parathyroid gland.[6,14,16-18] Preoperative VDD is also associated with the development of postoperative hypocalcemia.[19] Measurement and repletion to adequate levels of 25OHD in patients with PHPT are recommended in the current clinical guidelines for PHPT.[2] Vitamin D level should be maintained above 30 ng/mL before surgical or medical treatment.[2] The prevalence of VDD has become less common in recent years due to increased repletion in PHPT.[9,15,20] There is limited available data on vitamin D status and its impact on the initial presentations of PHPT in our country. The aim of this present study is to explore the relationship between vitamin D status and initial characteristics of PHPT.

MATERIALS AND METHODS

Ethical committee approval for this present study was obtained on March 25, 2024, with decision number 2024.137. IRB Z.062. This retrospective cohort study was conducted in a single tertiary center. Consecutive PHPP aged 18 years and/or older not taking vitamin D replacement between November 2017 and December 2023 were included in the study. Patients treated with bisphosphonates and/or denosumab at the time of admission were excluded. A total of 195 subjects with PHPT, verified in accordance with current clinical guidelines, were analyzed retrospectively.[1,2] The diagnosis of PHPT was made by both elevated serum calcium and elevated or unsuppressed serum PTH levels. Abnormal PTH level was defined above 65 pg/mL in this study. Demographic, clinical, and biochemical characteristics of the subjects, including age, gender, body mass index (BMI), history of smoking, laboratory findings [(fasting blood samples for serum calcium, phosphate, PTH, 25OHD), estimated glomerular filtration rate (eGFR), and 24-hour urinary calcium excretion], complications of PHPT (osteoporosis, kidney stone, and fracture history), radiological imaging findings, histopathological findings, and complications after surgery were reviewed. Data of the patients were obtained from the hospital record system. Patients were categorized into three groups according to their serum concentration of vitamin D at the time of diagnosis. Group 1: vitamin D ≤19 ng/mL (VDD), group 2: vitamin D 20-29 ng/mL (VDI), and group 3: vitamin D ≥30 ng/mL (vitamin D sufficiency (VDS)).[1,2] The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR.[21] Neck and urinary tract ultrasonographic examinations were performed by experienced operators. Technetium-99m-labelled sestamibi parathyroid scintigraphy scan imaging was used in the identification of the hyperfunctioning parathyroid gland. BMD values were measured on the lumbar spine (L1-L4), femoral neck, total hip, and 1/3 distal radius using...
a dual-energy X-ray absorptiometry system with a Hologic device. Osteoporosis is defined as a BMD T-score ≤ -2.5 at any of the above-mentioned sites. Parathyroid surgery was performed by experienced parathyroid surgeons according to recommendations of current clinical guidelines for PHPT.[1,2] Demographic, clinical, biochemical, radiological findings, and postoperative complications were compared in the three vitamin D groups.

The electrochemiluminescence immunoassay method was used to measure serum PTH and 25OHD. Adjusted total serum calcium concentration, phosphate, and 24-hour urinary calcium were measured by spectrophotometric assay. Albumin-corrected calcium was calculated using the formula: [(4-albumin)x0.8]+calcium. Serum creatinine concentration and phosphate, and 24-hour urinary creatinine excretion were measured with an enzymatic colorimetric test. These measurements were performed using a Roche Cobas 6000 analyzer device.

Statistical Analysis
IBM SPSS Statistics (version 27, Chicago, USA) program was used to analyze data. Descriptive statistics of variables were represented by percentages (%), frequencies, and means and standard deviations. The distribution of variables was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. A comparative analysis of independent groups studied by quantitative characteristics was carried out using ANOVA (Tukey test), Independent Samples T test, Kruskal-Wallis, and Mann-Whitney U test. Chi-Square test was used in the comparison of independent groups by qualitative characteristics. If the Chi-Square test did not meet the criteria, Fisher’s Exact test was used. The statistical significance level was defined as p<0.05.

RESULTS
A total of 195 patients were analyzed in the study. Among them, 157 (80.5%) were women, and 38 (19.5%) were men with a mean BMI of 26.9±4.6 kg/m². Mean age was 56.4±14.5 years. The current smokers’ rate was 19.5%. Mean 25OHD level was 29.2±18.1 ng/mL. Among participants, 65 (33.3%) had VDD, 48 (24.7%) had VDI, and 82 (42.0%) had VDS. Only 7.2% of patients (n=14) had severe VDD (vitamin D <10 ng/mL). Mean serum calcium concentration adjusted for albumin was 11.4±0.8 mg/dL. Participants had predominantly mild hypercalcemia (81%). Mean phosphate and PTH levels were 2.7±0.5 mg/dL and 169.1±135.8 pg/mL, respectively. Mean 24-hour urinary calcium excretion was 326.5±164.6 mg/day, and eGFR was 100.4±28 ml/min/1.73 m². Of the 195 patients, 74 (37.9%) had kidney stones, and 90 (46.2%) had osteoporosis. Fracture frequency was 9.7% (n=19). Three patients (1.5%) had a history of acute pancreatitis. Mean parathyroid lesion size was 13.8±6.2 mm. A group of 174 patients were operated on for PHPT. One hundred sixty-eight patients were operated with minimally invasive parathyroid surgery and 6 patients with thoracostomy. Baseline characteristics of the 195 patients with PHPT are summarized in Table 1.

The comparison of vitamin D groups [group 1: ≤19 ng/mL (VDD), group 2: 20-29 ng/mL (VDI), and group 3: ≥30 ng/mL (VDS)] is shown in Table 2. Patients who were in group 1 tended to have higher serum PTH levels than group 2 and group 3 (p=0.000) (Fig. 1). PTH levels did not differ between group 2 and group 3. Mean serum calcium and phos-

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (n=65)</th>
<th>Group 2 (n=48)</th>
<th>Group 3 (n=82)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>52.5±14.7</td>
<td>58.0±16.3</td>
<td>58.5±12.7</td>
<td>0.064&lt;sup&gt;k&lt;/sup&gt;</td>
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<tr>
<td>Gender, n (%)</td>
<td></td>
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<tr>
<td>Female</td>
<td>52 (78.8)</td>
<td>38 (80.9)</td>
<td>67 (81.7)</td>
<td>0.903&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male</td>
<td>14 (21.2)</td>
<td>9 (19.1)</td>
<td>15 (18.3)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²), mean±SD</td>
<td>27.6±5.6</td>
<td>25.8±4.3</td>
<td>27.0±3.8</td>
<td>0.208&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>14 (21.2)</td>
<td>8 (17.0)</td>
<td>16 (19.5)</td>
<td>0.858&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Albumin-corrected calcium (mg/dL), mean±SD</td>
<td>11.5±1.0</td>
<td>11.3±0.7</td>
<td>11.3±0.8</td>
<td>0.280&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phosphate (mg/dL), mean±SD</td>
<td>2.6±0.5</td>
<td>2.7±0.6</td>
<td>2.8±0.5</td>
<td>0.069&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>PTH (pg/mL), mean±SD</td>
<td>221.2±207.9</td>
<td>149.3±76.9</td>
<td>138.5±52.3</td>
<td>0.000&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>24-h urinary calcium excretion (mg/24h), mean±SD</td>
<td>351.4±188.3</td>
<td>312.9±158.8</td>
<td>314.4±146.9</td>
<td>0.377&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²), mean±SD</td>
<td>109.7±31.8</td>
<td>91.9±26.8</td>
<td>99.1±24.1</td>
<td>0.021&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kidney stone, n (%)</td>
<td>26 (39.4)</td>
<td>16 (34.0)</td>
<td>32 (39.0)</td>
<td>0.817&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Osteoporosis, n (%)</td>
<td>26 (39.4)</td>
<td>22 (46.8)</td>
<td>42 (51.2)</td>
<td>0.356&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fracture, n (%)</td>
<td>5 (7.6)</td>
<td>4 (8.5)</td>
<td>10 (12.2)</td>
<td>0.608&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acute Pancreatitis, n (%)</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
<td>2 (2.4)</td>
<td>&gt;0.05&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parathyroid lesion size (mm), mean±SD</td>
<td>15.6±7.4</td>
<td>13.2±6.4</td>
<td>12.9±4.5</td>
<td>0.116&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Postoperative complication, n (%)</td>
<td>8 (13.6)</td>
<td>3 (7.3)</td>
<td>9 (12.2)</td>
<td>0.612&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
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</table>

PHPT: Primary hyperparathyroidism; SD: Standard deviation; BMI: Body mass index; PTH: Parathyroid hormone; 25OHD: 25-hydroxyvitamin D; h: hour; eGFR: Estimated glomerular filtration rate. <sup>a</sup>ANOVA / <sup>2</sup>Kruskal-Wallis (Mann-Whitney u test) / <sup>4</sup>Chi-Square test (Fisher’s test).
has been noted in our study. We think that the frequency of VDD will be less prevalent in PHPT if vitamin D replacement becomes widespread with the recommendation of current clinical guidelines for PHPT in our country. Lower vitamin D levels are associated with more severe biochemical presentation. Liu et al. [12] reported that serum PTH and calcium levels were significantly higher in PHPP with lower vitamin D status. Some authors similarly showed that a lower vitamin D level was associated with higher PTH and calcium levels. [4,8,12,13] A study reported that vitamin D treatment for 1 year reduced PTH levels by 26% without exacerbating hypercalcemia. [23] Other studies confirmed the reduction in PTH levels with vitamin D repletion. [14,16] Serum calcium level also remained stable after vitamin D replacement. [16] These study results might be associated with the presence of mild hypercalcemia in the majority of PHPP. [1,2] There were studies that showed opposite results about the association between serum PTH and vitamin D levels. [5] In our study population, those with vitamin D levels below 20 ng/mL had higher PTH levels. We found no correlation between vitamin D status and serum calcium levels. It was thought that this finding might be related to earlier diagnosis.

PHPP with VDD present more severe skeletal manifestations at the time of diagnosis. [8,12,15,24] Signs of severe bone disease in PHPT include increased bone turnover markers, [4,6,8,12-14] lower BMD, [8,10,11,13] and increased fracture risk. [11,15] Brown tumors and osteolytic bone lesions are now very rare complications of PHPT in developed countries. [15] A study from India reported that most of the PHPP who presented with osteitis fibrosa cystica had severe VDD. [13] However, a recent study from India reported that VDD was associated with only increased serum alkaline phosphatase levels. [6] Walker et al. [9] reported that 39% of subjects had osteoporosis and 15% had a history of fragility fracture. They showed no difference between vitamin D levels and the presence of osteoporosis and fracture. [9] In their study, the vitamin D effect was only limited to corre-
tical 1/3 radius.\cite{9} Their findings may be explained by the mean age being younger in the vitamin D deficient group than in the vitamin D insufficient and sufficient groups.\cite{9} Furthermore, there was male predominance in these two groups.\cite{9} Other studies found no significant correlation between vitamin D status and bone signs.\cite{10} We observed that 46.2% of patients had osteoporosis, and 9.7% had a fragility fracture. Vitamin D status was not related to age, gender, presence of osteoporosis, and fragility fracture in our cohort. The lower fracture rate in our cohort may be associated with short-term VDD due to early diagnosis of PHPT and the presence of a few patients with severe VDD. Previous studies reported that patients with severe bone disease had prolonged PHPT coexisting with VDD.\cite{11,12} The amount of nutritional daily calcium intake of the cases may be higher in our cohort. We also did not investigate the silent vertebral fractures with radiographic imaging modalities in patients who did not have a fracture history. In addition, we found a low smoking rate in our study population.

Hypercalcemia, nephrolithiasis, and chronic kidney disease are classical renal involvements of PHPT.\cite{1,2,12,25} One study reported elevated urinary calcium excretion in PHPP with VDD.\cite{14} In contrast to these findings, vitamin D was higher in patients with nephrolithiasis than in those without nephrolithiasis.\cite{15} There were studies that found no differences between vitamin D status and the presence of nephrolithiasis or hypercalcemia.\cite{9,10,25} In the comparison of PHPP according to their vitamin D status, we demonstrated no difference in nephrolithiasis and 24-hour urinary calcium excretion. Lower vitamin D was associated with better renal function in some studies.\cite{9,10} We found that PHPP with VDD had higher eGFR. Rolighed et al.\cite{26} found that daily supplementation with 2800 IU vitamin D was safe and associated without any change in urinary calcium and serum creatinine. In our study, renal functions did not differ in the vitamin D sufficient group from the deficient and insufficient groups. We think that vitamin D repletion could be safe in PHPP with VDD and VDI.

There is an inverse relationship between the size/weight of parathyroid adenoma and vitamin D levels.\cite{8,14,15} VDD stimulates the proliferation of parathyroid cells, which may cause larger parathyroid adenoma size.\cite{17,18} In most of the studies, the excised parathyroid gland weight was evaluated.\cite{8,14,17,18} We evaluated the greatest size of the parathyroid lesion on ultrasonography examination because we did not have the weight of the parathyroid gland on pathology reports. In our study results, there was no relationship between parathyroid adenoma size and vitamin D levels. Ayçiçek et al.\cite{3} confirmed our findings. In their study, the mean parathyroid adenoma size was similar in the vitamin D deficient and vitamin D sufficient groups. These findings may be related to the quicker diagnosis of PHPT in recent years compared to previous years.

Preoperative VDD and VDI are associated with the development of transient hypoparathyroidism.\cite{19} One retrospective study showed that vitamin D supplementation in PHPT undergoing parathyroid surgery reduced hypercalcemia and the duration of hospitalization.\cite{27} In this study, bilateral neck exploration was also associated with increased postoperative hypocalcemia risk.\cite{27} Most of the postoperative complications were temporary hypocalcemia in our study. We found no correlation between vitamin D status and postoperative complications. Our findings may be related to a targeted surgical approach to the parathyroid lesion with experienced surgeons. We also began vitamin D replacement before the surgical approach in PHPP with VDD and VDI.

Some limitations exist within our study. It was a single-center study. Our study had a small sample size. We also did not have a control group. Calcium intake may play a role in the bone and kidney characteristics of the PHPP. We could not evaluate the amount of nutritional daily calcium intake of the cases. In addition, we did not assess bone turnover markers and silent fractures of the subjects. Finally, we did not have the excised weight of the parathyroid adenoma. Despite these limitations, we think that our study is important to show current vitamin D status and its effects on biochemical and clinical characteristics in PHPT. It seems that although VDD was a common condition in PHPP, vitamin D status was not associated with classical target organ involvement in PHPT. We think that our study results are related to earlier diagnosis and treatment in our country. Based on our study results, we suggest that PHPP with VDD and VDI should be treated with vitamin D replacement before the management plan for PHPT.

### Conclusion

This present study showed that VDD was still a common condition in PHPP in our country. VDD was associated with higher PTH levels and better renal function. Furthermore, we found no difference between vitamin D status and PHPT-related classical skeletal and kidney complications.

### Ethics Committee Approval

This study approved by the Koç University Ethics Committee (Date: 25.03.2024, Decision No: 2024.137.İRB2.062).

### Informed Consent

Retrospective study.

### Peer-review

Externally peer-reviewed.

### Conflict of Interest

None declared.

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Primer Hiperparatiroidinin Başlangıç Özelliklerinde D Vitamini Durumunun Rolü: Uygun Büyük Merkezden Güncel Güncel Klinik Deneyim

Anaç: Bu çalışmanın amacı, D vitamini durumunu ve bunun primer hiperparatiroidinin (PHPT) başlangıç özellikleri üzerindeki etkisini daha iyi değerlendirmektir.

Gereç ve Yöntem: Bu çalışma, Kasım 2017 ve Aralık 2023 tarihleri arasında üçüncü basamak bir merkezdeki 18 yaş ve/veya üzeri PHPT tanısı olan 464 hastanın (235 kadın, 229 erkek) derlemesi bulunmaktadır. Çalışma popülasyonu başvurdu anındaki D vitamini düzeylerine göre 3 gruba kategoriye edildi. Grup 1: D vitamini ≤19 ng/mL, grup 2: D vitamini 20-29 ng/mL, ve grup 3: D vitamini ≥30 ng/mL. Demografik, klinik, biyokimyasal, radyolojik bulgular ve operasyon sonrası komplikasyonlar üç grup arasında karşılaştırıldı.

Bulgular: Yuz vardır %80.5'lik kadın, %19.5'lik erkekti. Ortalama yaş 56.4±14.5 idi. Alınmış beş hastadan (%33.3) D vitamini eksikliği (DVE) ve 48 hastada (%24.7) D vitamini yetersizliği vardı. Yuz vardır %7.9'lu iki gruba olarak katıldı. DVE daha yüksek paratiroid hormon (PTH) seviyesi (p<0.000) ve daha iyi tahmini glo- merüler terasyon hız (p=0.021) ile ilişkilidir. Tüm grublar karşılaştırıldığında böbrek taşı, osteoporoz ve kırık dağılımı açısından fark yoktu.

Sonuç: Mevcut çalışma DVE'nin daha yüksek PTH seviyesi ve daha iyi bıbrek fonksiyonu ile ilişkili olduğunu ortaya çıkardı. Ancak, D vitamini durumu PHPT'de klasik hedef organ tutulumuyla ilişkili değişdi.

Anatara Sözcükler: D vitamini durumu; eGFR; paratiroid hormon; primer hiperparatiroidi.