Correlation of Plasma 25-Hydroxyvitamin D Levels With Severity of Primary Hyperparathyroidism and Likelihood of Parathyroid Adenoma Localization on Sestamibi Scan

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Objectives: To determine the relationship between preoperative plasma 25-hydroxyvitamin D (25[OH]D) levels and severity of primary hyperparathyroidism (PHPT) and to explore whether presurgical 25(OH)D levels could predict the likelihood of positive results on technetium Tc 99m sestamibi scintigraphy.

Design: Retrospective analysis.

Setting: Tertiary university referral center.

Patients: A total of 421 consecutive patients underwent preoperative sestamibi scintigraphy and parathyroid exploration. Patients with cholecalciferol (vitamin D) deficiency, defined as plasma levels lower than 25 ng/mL, were compared with patients having no vitamin D deficiency. We explored the relationship between 25(OH)D levels and intact parathyroid hormone (iPTH) levels, alkaline phosphatase (ALKP) levels, adenoma weight, binary sestamibi scan results, and postoperative serum calcium levels (at 1 week and 6 months).

Main Outcome Measures: We hypothesized that severity of hypovitaminosis D would correlate with severity of PHPT and predict the likelihood of a positive finding on sestamibi scan.

Results: Concentrations of iPTH and ALKP and parathyroid adenoma weight were significantly higher in patients with lower 25(OH)D levels ($P < .01$ for all). Patients with hypovitaminosis D had a greater percentage decrease in serum calcium levels 1 week and 6 months postoperatively ($P < .05$). Median 25(OH)D levels were lower in patients with positive sestamibi scan results ($P < .001$).

Conclusions: Patients with hypovitaminosis D present with more advanced indices of PHPT. Parathyroid sestamibi scanning is more likely to show positive results for this subset of patients who may then benefit from sestamibi scan–directed surgical intervention.


Primary Hyperparathyroidism (PHPT) is a common disorder characterized by chronically elevated serum calcium and parathyroid hormone (PTH) concentrations and has an estimated incidence of 1 in every 500 women and 1 in every 2000 men older than 40 years. Little is known about the prevalence of cholecalciferol (vitamin D) deficiency in PHPT and the relationship between the severity of PHPT and plasma 25-hydroxyvitamin D (25(OH)D) concentrations. Vitamin D status is usually determined by measuring 25(OH)D plasma levels. Although adverse effects of low plasma 25(OH)D concentration begin to accumulate at levels below 20 ng/mL, and it has been suggested that 25(OH)D levels between 10 and 20 ng/mL constitute vitamin D insufficiency, levels below 10 ng/mL indicate vitamin D deficiency. To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

Recently, low plasma levels of 25(OH)D have been observed not only in institutionalized elderly patients but also in adults of all ages in the United States, Europe, and Japan. Over half of American adults have wintertime hypovitaminosis D, with older adults and persons with dark skin at greatest risk.

Given the increasing frequency of vitamin D insufficiency found in cases of mild PHPT in a recent study, we sought to determine the effect of plasma 25(OH)D level on the severity of PHPT disease. We also sought to determine whether lower basal plasma 25(OH)D levels correlate with the likelihood of positive findings on technetium Tc 99m sestamibi scintigraphy. We postulated that patients with hypovitaminosis D would present with more advanced indices related to PHPT and were therefore more likely to have positive findings on sestamibi scan. To our knowledge, this study represents the largest series of cases used to
evaluate the relationship between plasma 25(OH)D concentrations and the severity of PHPT.

**METHODS**

After obtaining approval from the Johns Hopkins institutional review board, we compiled a database of patients who underwent parathyroid surgery from July 2002 to August 2006. A total of 421 consecutive patients who underwent preoperative sestamibi scintigraphy and parathyroid exploration for PHPT with resection of at least 1 enlarged parathyroid gland were included in this study. Patients with multiple endocrine neoplasia and/or secondary and/or tertiary hyperparathyroidism were excluded from the study. For patients with multigland disease, the weight of the heaviest gland was used for the statistical analysis.

Data reviewed included age, sex, and preoperative laboratory values, including serum calcium (normal range, 8.4-10.5 mg/dL), alkaline phosphatase (ALKP) (normal range, 30-120 U/L), intact parathyroid hormone (iPTH) (normal range, 10-65 pg/mL), and 25(OH)D levels. Adenoma weight, operative notes, pathology reports, and sestamibi scan results were all reviewed. To convert calcium to millimoles per liter, multiply by 0.25; to convert ALKP to microkatals per liter, multiply by 0.0167; to convert calcium to millimoles per liter, multiply by 0.25; to convert iPTH to nanograms per liter, multiply by 0.1053.

**SESTAMIBI SCANS**

All patients underwent an outpatient parathyroid sestamibi scan followed by parathyroid exploration for PHPT. Sestamibi scan reports were reviewed. Confidence for identifying a parathyroid adenoma was assessed semiquantitatively using a 2-point scale: 0 indicated a negative or indeterminate scan finding; and 1 indicated a finding positive for adenoma.

**STATISTICAL ANALYSIS**

Demographic and clinical characteristics were summarized using descriptive statistics. Categorical data were summarized with frequencies and percentages, and continuous data with medians and ranges because many of the measures were not normally distributed. Vitamin D deficiency was defined as a plasma level lower than 25 ng/mL, and patients with 25(OH)D deficiency were compared with patients with normal 25(OH)D levels using χ² tests for categorical data and Wilcoxon rank sum tests for continuous data. Linear regression analysis was used to assess the association of vitamin D levels with other preoperative and postoperative measures. Logistic regression analysis was used to test the statistical significance of the observed relationships between vitamin D deficiency and positive sestamibi scan results, after adjusting for age and sex. Analysis was performed using SAS version 9.1.3 software (SAS Institute, Cary, North Carolina). All reported P values are 2-sided, and P < .05 was considered significant.

**RESULTS**

We performed a retrospective analysis of 421 patients who underwent preoperative sestamibi scintigraphy and parathyroid exploration for PHPT. The demographic and clinical characteristics of the 421 patients are summarized in Table 1. A total of 83.5% of patients had a single enlarged gland removed, while 16.5% had more than 1 en-

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**Table 1. Demographic and Clinical Characteristics of 421 Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (23 to 95)</td>
</tr>
<tr>
<td>Men</td>
<td>114 (27.1)</td>
</tr>
<tr>
<td>Adenoma weight, mg</td>
<td>565 (30 to 10 780)</td>
</tr>
<tr>
<td>25(OH)D, ng/dL</td>
<td>21 (4 to 73)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>92 (28 to 292)</td>
</tr>
</tbody>
</table>

**Table 2. Demographic and Clinical Characteristics by Vitamin D Deficiency**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin D &lt; 25 ng/dL</th>
<th>≥ 25 ng/dL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>233 (61.0)</td>
<td>140 (39.0)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>61 (25 to 93)</td>
<td>62 (23 to 88)</td>
<td>.29</td>
</tr>
<tr>
<td>Men</td>
<td>57 (24.5)</td>
<td>46 (30.9)</td>
<td>.17</td>
</tr>
<tr>
<td>Adenoma weight, mg</td>
<td>647 (30 to 10 360)</td>
<td>430 (50 to 6100)</td>
<td>.002</td>
</tr>
<tr>
<td>25(OH)D, ng/dL</td>
<td>16 (4 to 24)</td>
<td>32 (25 to 73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>95 (41 to 292)</td>
<td>86 (28 to 169)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; PostOp, postoperative measurement; PreOp, preoperative measurement.

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The extent of parathyroid exploration and gland removal was based on intraoperative iPTH level analysis.

A high prevalence of hypovitaminosis D was found among these patients (61.0%). The median plasma level of 25(OH)D for the entire study group was 21 ng/mL (range, 4-73 ng/mL). Consistent with the diagnosis of PHPT, serum calcium and iPTH levels were elevated. Characteristics of the patients by 25(OH)D group are summarized in Table 2. Median serum calcium, iPTH, and ALKP levels were significantly higher in the group with lower 25(OH)D plasma levels (Figure 1). A significant inverse correlation between serum 25(OH)D level and both iPTH level and serum ALKP activity was also observed (Figure 2).

Patients with lower 25(OH)D levels exhibited significantly higher adenoma weight (Table 2). Also, there was an inverse correlation between serum 25(OH)D level and resected gland weight (P < .001) (Figure 3). These results were also adjusted for age and sex and continued to show a statistically significant inverse correlation (P < .01).

Patients in the vitamin D deficiency group had lower serum calcium levels 6 months postoperatively. They also exhibited a significantly greater percentage drop in their calcium levels at 1 week and 6 months compared with their preoperative levels (P < .05 for both) (Figure 4).

Patients with lower 25(OH)D levels were almost 8 times as likely to present with a positive finding (vs suspicious or negative) on sestamibi scan (odds ratio, 7.86; 95% confidence interval, 4.78-12.93) (P < .001) after adjusting for age and sex. The median values of 25(OH)D levels were higher for patients with negative sestamibi scan findings than for patients with positive sestamibi scan findings (29.0 vs 18.0) (P < .001) (Figure 5).

We found a high prevalence of hypovitaminosis D among patients with PHPT seen at our institution. Patients with lower plasma levels of 25(OH)D (<25 ng/mL) presented with more advanced indices of PHPT and were
more likely to have a positive finding on parathyroid sestamibi scan. Bone turnover may be increased in PHPT. Low vitamin D status in patients with PHPT is associated not only with higher plasma iPTH levels but also with higher ALKP activity, reflecting the increased severity of the disease in this group of patients. Median preoperative plasma calcium levels were only slightly higher for patients with lower vitamin D levels but did reach statistical significance. Patients with PHPT and low vitamin D status tend to have a higher adenoma weight. The cause of this association is uncertain but likely multifactorial. Earlier reports confirmed that parathyroid tumor weight is a significant determinant of disease severity, as reflected by serum levels of iPTH, calcium, and ALKP.11,12

A possible explanation for our findings of more severe presentation of the disease is that with 25(OH)D deficiency, the PTH gene, which is abnormally active in PHPT, might be less constrained due to the loss of the regulatory influence of 25(OH)D. Rao et al13 have suggested that chronic vitamin D deficiency may accelerate parathyroid adenoma growth and thereby exacerbate bone turnover and bone loss.

Rao et al13 have proposed that 25(OH)D insufficiency can reach levels low enough to stimulate parathyroid hormone production and cause substantial effects on biochemical indices indicative of mild PHPT. Similar to our data, Silverberg et al14 found mean (SD) 25(OH)D levels to be 21 (11) ng/mL in 124 patients with PHPT, with 53% of patients having 25(OH)D deficiency defined as plasma 25(OH)D levels less than 25 ng/mL. These findings may be partially explained by the typically 25(OH)D-deficient American diet. Silverberg et al14 also observed that patients with plasma levels of 25(OH)D in the lower group had higher plasma iPTH levels, higher plasma ALKP concentrations, and higher bone turnover. However, their results differed from ours in multiple aspects. In another study, Silverberg et al14 described only 55 patients who underwent parathyroidectomy for mild PHPT, and they found no correlation between vitamin D status and parathyroid gland weight, preoperative localization on sestamibi scan, or the postoperative surgical outcome.

Our results are also relevant to the management of PHPT. In a patient who is not undergoing surgery, limiting dietary intake of vitamin D and calcium are often advised in the hope of minimizing the risk of hypercalcemia. However, moderate restriction of vitamin D intake will not reduce plasma calcium levels but will lead
to increased PTH secretion, higher bone turnover, and greater acceleration of cortical bone loss. In the present study, patients with hypovitaminosis D had significantly lower serum calcium levels 1 week and 6 months after surgery than they had prior to surgery (Figure 4), suggesting that surgical intervention in this subset of patients would be beneficial and that surgical consultation should be considered. One might be inclined to treat patients with PHPT and low plasma levels of 25(OH)D with vitamin D. However, the potential hypercalcaemic and hypercalciuric effects of vitamin D can be dangerous. Therefore, these patients are more likely to benefit from surgical intervention.14,15 At present in the United States, more than 80% of patients with PHPT present with a myriad of subclinical signs and symptoms, a condition often referred to in the literature as asymptomatic PHPT. Therefore, if vitamin D deficiency becomes even more widespread in the United States, the phenotype of PHPT could change, with more symptomatic disease emerging again.

The present study has several shortcomings. First, we evaluated only the indices associated with PHPT and did not evaluate the symptoms associated with the disease. Also, we cannot determine whether the parathyroid disease caused the observed vitamin D deficiency or whether the vitamin D deficiency resulted in worsening of PHPT. Nevertheless, our findings are relevant to the management of PHPT.

In summary, our observations suggest that vitamin D deficiency is common among patients with PHPT, and patients with hypovitaminosis D present with laboratory indices suggestive of more advanced disease. In addition, patients with lower basal plasma 25(OH)D levels were more likely to have positive findings on sestamibi scans. Parathyroid sestamibi scanning may be more useful in this patient population by helping to identify those who would benefit from an attempt at directed surgical intervention as opposed to standard 4-gland exploration.

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Author Contributions: Drs Tufaro and Zieger had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kandil, Tufaro, Carson, Lin, Somervell, Farrag, Dackiw, Zeiger, and Tufano. Acquisition of data: Kandil, Tufaro, Caron, Lin, Somervell, Farrag, Dackiw, Zeiger, and Tufano. Analysis and interpretation of data: Kandil, Tufaro, Carson, Lin, Somervell, Farrag, Dackiw, Zeiger, and Tufano. Drafting of the manuscript: Kandil, Tufaro, Caron, Lin, Somervell, Farrag, Dackiw, Zeiger, and Tufano. Critical revision of the manuscript for important intellectual content: Kandil, Tufaro, Caron, Lin, Somervell, Farrag, Dackiw, Zeiger, and Tufano. Administrative, technical, and material support: Tufaro, Caron, Lin, Somervell, Farrag, Dackiw, Zeiger, and Tufano. Study supervision: Tufaro and Zieger.

Financial Disclosure: None reported.

Previous Presentation: This study was presented at the American Head and Neck Society Annual Meeting; April 27-29, 2007; San Diego, California.

Figure 5. Relationship between preoperative serum levels of 25-hydroxyvitamin D (25[OH]D) and technetium Tc 99m sestamibi scintigraphy findings. To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

REFERENCES