Vitamin D Therapy in Patients with Primary Hyperparathyroidism and Hypovitaminosis D

JR Tucci, MD, FACP, FACE, Director, Division of Endocrinology, Department of Medicine, Roger Williams Medical Center, Providence, Rhode Island; Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts; Adjunct Professor of Medicine, The Warren Alpert Medical School of Brown University, Providence, Rhode Island

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Address correspondence to:
Joseph R. Tucci, MD
Roger Williams Hospital
825 Chalkstone Avenue
Providence, RI 02908-4728
Telephone 401-456-2304
Fax 401-456-2016
umgtucci@yahoo.com

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INTRODUCTION:

Hypovitaminosis D is an inclusive term for vitamin D deficiency and insufficiency. It is a problem in all age groups in the general population nationally and worldwide (1,2) and is seen frequently in those with a number of clinical disorders including primary hyperparathyroidism (PHPT) (3,4). There is no universal agreement in defining vitamin D insufficiency with some authors indicating a cutoff point of ≤20 ng/ml (50 nmol/l) for serum 25-OHD (2,5,6) while for many others it is ≤30 ng/ml (75 nmol/l) (1,7-11). In the present study of vitamin D therapy in patients with PHPT, vitamin D insufficiency is defined by a serum level of 21-29 ng/ml (52.5 to 72.5 nmol/l) and vitamin D deficiency by a serum 25-OHD level of ≤20 ng/ml (≤50 nmol/l). In patients with PHPT, subnormal serum 25-OHD levels have been associated with larger parathyroid glands and parathyroid tumors, higher serum PTH, calcium and alkaline phosphatase levels, accelerated bone turnover, and a greater likelihood of abnormal bone and fractures (3,4,12,13). Whereas vitamin D repletion is routinely recommended for patients with hypovitaminosis D, there has been reluctance to restore serum 25-OHD levels to normal in PHPT due to concerns of potentially greater hypercalcemia and hypercalciuria (3,14). In 1997, Zahrani et al indicated that until more data are available, patients with PHPT should moderate their intake of dietary calcium and avoid any calcium or vitamin D supplements (15). Recently, Grey et al reported preliminary observations in 21 patients with PHPT treated with vitamin D (16). Except for two patients who exhibited greater calcium excretion, vitamin D therapy was not associated with adverse clinical or biochemical effects. This report represents a prospective audit of clinical, biochemical, and hormonal data in 56 patients with PHPT and hypovitaminosis D before and during treatment with vitamin D from the years 2002 to 2008.
Subjects and Methods

Patients

Patients with PHPT include 37 females and 19 males. Serum calcium levels ranged from 2.63 to 3 mmol/l and serum 25-OHD from 17.5 to 60 nmol/l. All 56 patients did meet criteria for diagnosis of PHP. Most patients were asymptomatic, but there were 14 patients who did meet criteria for surgery. Subsequent to vitamin D therapy, those 14 patients with pre-existing indications for surgery unrelated to vitamin D therapy did undergo successful surgical treatment of their hyperparathyroidism.

Vitamin D replacement

Patients were treated with 50,000 units (1.25 mg) of ergocalciferol each week for 8 weeks and, subsequently, on the basis of serum 25-OHD levels, doses of vitamin D varied from 800 units daily to as much as 100,000 units monthly in an effort to maintain serum 25-OHD levels at ≥75 nmol/l.

Hormonal and Biochemical Measurements

At baseline, serum calcium, albumin, phosphorus, alkaline phosphatase, creatinine, 25-OHD, and intact PTH were measured. In 42 patients, serum 1,25-OHD levels were also measured. Second voided morning urine specimens were collected for measurement of creatinine, N-telopeptide (NTx), and calcium. At 5 and 10 weeks during and just following the 8 weeks of vitamin D therapy, serum calcium, phosphorus, and 25-OHD levels were measured. Serum intact PTH and urine NTx, creatinine and calcium were also measured at 10 weeks. Approximately 12 weeks
later, while on maintenance therapy with 800 units of vitamin D daily, serum calcium, phosphorus, and 25-OHD were measured and those with subnormal serum 25-OHD levels were then treated with 50,000 units once or twice monthly. Serum calcium, phosphorus, and 25-OHD levels were again measured 12 weeks later at 34 weeks.

Blood chemistries were measured on the ADVIA1650 chemistry analyzer, Siemens Healthcare Diagnostics, Medical Solutions, Tarrytown, NY. Serum 25-OHD level was measured by extraction of D2 and D3 followed by liquid chromatography and tandem mass spectroscopy, Mayo Medical Laboratory, Rochester, MN. Serum intact PTH was measured by chemiluminescence immunoassay, Centaur Analyzer, Siemens Healthcare Diagnostics, Medical Solutions, Tarrytown, NY. Serum 1,25-OHD was determined by precipitation and extraction followed by radioimmunoassay using a polyclonal antibody, Diasorin Inc., Stillwater, Minnesota. Urine N-telopeptide was measured by competitive immunoassay technique on the Vitros ECi analyzer, Ortho-Clinical Diagnostics, Inc., Rochester, NY.

Standard descriptive statistical methods and paired t-tests were used to assess the significance of differences of biochemical and hormonal values before and during vitamin D therapy. Differences were considered statistically significant at a $p$ value of < .05 by a two-tailed test. Linear regression analysis was utilized in assessing the relationship of serum calcium and PTH levels to serum 25-OHD levels and of serum 1,25-OHD to serum 25-OHD, PTH, and phosphate.
Results

Biochemical and hormonal data before initiation of therapy with vitamin D in 56 patients with PHPT are presented in Table 1. Serum calcium levels varied from 2.6 to 3 mmol/l and serum intact PTH from 52 to 416 ng/l. Serum 25-OHD varied from 17.5 to 60 nmol/l with 51 patients having vitamin D deficiency and 5 having vitamin D insufficiency. Of the 39 patients who had serum 1,25-OHD measurements at baseline, 9 had increased serum 1,25-OHD of 163 to 223 pmol/l while one patient had a low level of 41 pmol/l. Regression analysis failed to reveal any relationship between serum 1,25-OHD and 25-OHD levels (R=0.28, p=0.19), serum 25-OHD and calcium levels (R=0.06, p=0.44) serum calcium and PTH levels (R=0.25, p=.07) or between serum PTH and 1,25-OHD levels (R=0.28, p <.08). There was an inverse relationship between serum phosphate and 1,25-OHD levels (R=0.42, p =.01).

During treatment with vitamin D, none of the patients developed any calcium-related complaints or adverse events. Following treatment with vitamin D, fourteen patients were subsequently treated surgically because of pre-existing history of calcium urolithiasis, serum calcium levels consistently more than 1 mg/dl (.25 mmol/l) above the upper limit of normal, osteoporosis, MEN syndrome type I and in one case for personal reasons. The decision to treat surgically was not due to any adverse effects of vitamin D therapy.

Biochemical and hormonal data and vitamin D status before and during therapy with vitamin D are presented in Table 2. With vitamin D therapy there was a significant increase in serum 25-OHD levels rising from 36.4±10 nmol/l at baseline to 89.4±33.3 nmol/l and 88.6±29.7 nmol/l at 5
and 10 weeks, respectively (p < .0001). At 5 weeks, serum 25-OHD levels varied from 37.5-167.5 nmol/l with 10 patients having vitamin D insufficiency levels of 52.5-72.5 nmol/l and 3 patients with vitamin D deficiency levels of 37.5-45 nmol/l. At 10 weeks, serum 25-OHD levels varied from 42.5-162.5 nmol/l with vitamin D insufficiency in 17 patients with levels of 52.5-72.5 nmol/l and vitamin D deficiency in 5 patients with levels of 42.5-50 nmol/l. For the following 12 weeks with a maintenance dose of 800 units of vitamin D daily, there was a significant decrease in serum 25-OHD to 65.7 nmol/l (p < .0001). There were 12 patients with vitamin D insufficiency 52.5-72.5 nmol/l and 10 with vitamin D deficiency 27.5-50 nmol/l. In these patients with continuing hypovitaminosis D, 50,000 to 100,000 units of vitamin D monthly normalized serum 25-OHD levels in all but 4 who had levels of 62.5-72.5 nmol/l.

There were no significant changes in serum calcium or phosphorus at 5 or 10 weeks versus baseline levels. At 5 weeks, in one patient serum calcium rose from 2.93 to 3.08 mmol/l. At 5 weeks in patients with normal serum 25-OHD levels, serum calcium ranged from 2.6 to 3.08 mmol/l. In those with subnormal 25-OHD levels, serum calcium varied from 2.6 to 2.95 mmol/l. Mean serum calcium levels in these 2 groups were not significantly different. At 10 weeks, there were 2 patients in whom serum calcium rose from 2.8 to 3.03 mmol/l and 2.83 to 3.05 mmol/l. At 10 weeks, in patients with normal serum 25-OHD levels, serum calcium ranged from 2.6 to 3.03 mmol/l while in those with subnormal 25-OHD levels, serum calcium varied from 2.6 to 3.05 mmol/l. In these two groups, mean serum calcium levels were not significantly different. Regression analysis failed to reveal any relationship between serum calcium and serum 25-OHD levels before and during vitamin D therapy. At 10 weeks, there was a nonsignificant decrease of 8% in serum intact PTH from a mean of 145 ng/l to 134 ng/l. Serum 25-OHD and PTH levels
were not correlated ($R=0.08, p=0.41$) but serum calcium and PTH levels were correlated ($R=0.41, p=.002$). There was also a nonsignificant decrease in urine Ca/Cr ratios at 10 weeks compared to baseline. Pre-therapy values ranged from .09 to 1.11 and at 10 weeks from 0.14 to 1.08. There was no significant difference in urine N-telopeptide at 10 weeks versus pre-therapy levels.

**Discussion**

Hypovitaminosis D is a common clinical finding in the general population and in a variety of clinical disorders including PHPT (1-4). In 1971, Woodhouse et al reported two patients with PHPT, one with severe osteitis fibrosa cystica, and the other with subperiosteal cortical erosions (17). Treatment with a single injection of 50,000 units of vitamin D$_3$ followed by 1500 units daily for up to 16 months in the patient with osteitis fibrosa cystica and 500 units of vitamin D daily in the second patient for 11 months resulted in normalization of serum alkaline phosphatase levels, remineralization of bone, and healing of subperiosteal cortical bone erosions. The authors postulated that vitamin D deficiency may occur as a consequence of an increase in parathyroid hormone secretion. The available data now suggest that in PHPT there is increased catabolism and inactivation of vitamin D related to increases in 1,25-OHD that are attributable to the hyperparathyroidism (18,19). Halloran et al reported that chronic 1,25 OHD administration in rats reduces serum 25-OHD levels by an increase in its clearance and in biliary excretion of degradation metabolites (20). Subsequently, Clements et al reported a shortened elimination half-time of infused 25-OHD in patients with PHPT with reversion toward normal following parathyroidectomy (18). These results were thought to be consistent with increased hepatic inactivation and biliary excretion of metabolites.
Silverberg et al found that 53% of their patients with PHPT had serum 25-OHD levels of <50 nmol/l (3). Those patients with the lowest serum 25-OHD levels had the highest serum PTH levels and more pronounced changes in biochemical, densitometric, and histomorphometric indices of skeletal metabolism. Carnevale et al reported serum 25-OHD levels of ≤30 nmol/l in 27% of their patients with PHPT (21). Rao et al reported that suboptimal vitamin D nutrition stimulates parathyroid adenoma growth with a significant inverse relationship between serum 25-OHD levels and parathyroid gland weight (4). Their data confirmed earlier reports that parathyroid tumor weight was a significant determinant of disease severity as reflected by serum PTH, calcium and alkaline phosphatase levels. These authors indicated that while limiting intake of vitamin D and calcium has often been advised in the hope of avoiding a worsening hypercalcemia, such an approach would lead to increased PTH secretion, higher bone turnover, and greater cortical bone loss. They concluded that patients with PHPT need at least as much vitamin D as patients without hyperparathyroidism and possibly more and that a certain level of calcium intake would be appropriate to prevent greater bone resorption.

An NIH consensus conference relating to the management of asymptomatic PHPT in 2002 delineated guidelines for those patients who should be treated surgically and those who could be followed safely without surgical intervention (22). Any longterm therapy with vitamin D should pertain only to patients with so-called asymptomatic PHPT in whom there are no clearcut surgical considerations. However, though vitamin D repletion is accepted therapy for the general population, in 1999 Silverberg et al felt that vitamin D administration in patients with PHPT can be “difficult if not dangerous because of potential hypercalcemic and hypercalciuric effects of vitamin D” (3). Accordingly, vitamin D therapy was not recommended for such patients.
Kantorovich et al reported biochemical and hormonal data in three patients with PHPT who were treated with 100,000 units of vitamin D$_2$ weekly for 5 weeks (23). Serum calcium levels before and after therapy were 11 and 10.9 mg/dl (2.75 and 2.73 mmol/l), 10.5 and 10.9 mg/dl (2.63 and 2.73 mmol/l), and 10.7 and 10.4 mg/dl (2.68 and 2.6 mmol/l) with serum PTH levels falling in two of the three patients. Remineralization of bone occurred and the subperiosteal cortical bone erosions healed.

Recently, Grey et al reported biochemical data in 21 patients with mild PHPT with serum calcium levels ≤12 mg/dl (≤3 mmol/l) and serum 25-OHD levels <20 ng/ml (<50 nmol/l) who were treated with 50,000 units of vitamin D$_3$ weekly for one month followed by 50,000 units monthly for 12 months (16). With therapy, there was no significant change in serum calcium levels, with no serum calcium rising above 12 mg/dl (3 mmol/l). There was a significant decrease in serum intact PTH levels by 24% at 6 months and by 26% at 12 months. There was a nonsignificant decrease in urine N-telopeptides. Except for increases to over 400 mg (10 mmol) of calcium in 24-hour urines in two patients, mean values were unchanged. These authors concluded that repletion of body stores of vitamin D in patients with mild PHPT and hypovitaminosis D may be safe with no evidence of worsening hypercalcemia. However, they suggested larger studies to assess safety and efficacy of such therapy.

The data herein reported support the observations of Grey et al (16) that vitamin D therapy is, indeed, safe in patients who have coexistent mild PHPT with serum calcium levels of up to 3 mmol/l and hypovitaminosis D. None of the patients treated with vitamin D developed any calcium-related symptoms or adverse events. The therapeutic regimens did differ somewhat in
that in the study of Grey et al 50,000 units of vitamin D$_3$ were given weekly for 4 weeks followed by 50,000 units monthly. In the present study, 50,000 units of vitamin D$_2$ were given weekly for 8 weeks followed by 800 units of vitamin D$_3$ for up to 12 weeks. Those patients with subnormal serum 25-OHD levels were then treated with 50,000 to 100,000 units of vitamin D$_2$ monthly. Despite significant increases in serum 25-OHD with vitamin D administration, there was no significant increase in serum calcium or urinary calcium creatinine ratios. There was a nonsignificant decrease in serum PTH levels. In 23 patients monthly doses of up to 100,000 units of vitamin D were necessary to restore or maintain serum 25-OHD levels at $\geq$75 nmol/l. These findings do not support the generally accepted position that therapy with vitamin D is dangerous in PHPT. When one considers the potential long-term deleterious skeletal effects of untreated hypovitaminosis D, particularly in patients with PHPT (4,12), such a position now seems untenable. Also, the increasing evidence of positive nonskeletal or nonclassic effects of vitamin D (1,24) would support optimization of vitamin D levels in patients with PHPT especially in those in whom a decision has been made for indefinite monitoring rather than definitive surgical therapy. However, demonstration of any positive skeletal or nonskeletal effects would require long-term studies.
DECLARATION OF INTEREST:

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

FUNDING:

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REFERENCES


Table 1 – Baseline biochemical and hormonal data in patients with PHP and normal range of values.

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>Mean ± SD</th>
<th>Range of Values</th>
<th>Normal Values</th>
</tr>
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<tbody>
<tr>
<td>Patients (M/F)</td>
<td>--</td>
<td>19/37</td>
<td>--</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63.6±14.4</td>
<td>26 – 88</td>
<td>--</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>29.6 ± 6.4</td>
<td>19.4 – 54.9</td>
<td>20 - 25</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>83.1±29.9</td>
<td>27 - 156</td>
<td>80 - 120</td>
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<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.74±0.10</td>
<td>2.63 – 3.0</td>
<td>2.15 – 2.63</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>44.8 ± 2.7</td>
<td>38 -51</td>
<td>34 - 47</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/l)</td>
<td>0.98 ± 0.21</td>
<td>0.58 – 1.58</td>
<td>0.87 – 1.45</td>
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<tr>
<td>Serum creatinine (nmol/l)</td>
<td>84.5±26</td>
<td>44.2 – 168</td>
<td>35.4 – 106.1</td>
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<tr>
<td>Serum alkaline phosphatase (U/l)</td>
<td>83.7±27.5</td>
<td>28 - 140</td>
<td>25 - 100</td>
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<tr>
<td>Serum intact PTH (ng/l)</td>
<td>144.7±87.2</td>
<td>–52 - 416</td>
<td>14 - 72</td>
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<tr>
<td>Serum 25-OHD (nmol/l)</td>
<td>36.4±10</td>
<td>–17.5 - 60</td>
<td>75 - 200</td>
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<tr>
<td>Serum 1,25 OHD (pmol/l)</td>
<td>122.4±50.4</td>
<td>41 – 223</td>
<td>53 - 161</td>
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<tr>
<td>Urine calcium/creatinine (mmol/mmol)</td>
<td>0.52 ± 0.29</td>
<td>0.09 - 1.11</td>
<td>0.14 - 0.70</td>
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<tr>
<td>Urine N-telopeptide (nmol BCE/nmol Cr)</td>
<td>51.6±37.9</td>
<td>16 - 217</td>
<td>19 - 63</td>
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</table>
### Table 2 – Biochemical and hormonal data before and during therapy with vitamin D

<table>
<thead>
<tr>
<th></th>
<th>50,000 U/week x 8</th>
<th>800 U/day</th>
<th>50,000 to 100,000 U/month</th>
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<tbody>
<tr>
<td></td>
<td>Pre Rx</td>
<td>5 weeks</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Serum Ca</td>
<td>2.74±.10</td>
<td>2.71±.11</td>
<td>2.73±.13</td>
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<tr>
<td>Serum PO₄</td>
<td>0.98±0.21</td>
<td>0.99±.22</td>
<td>0.92±.2</td>
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<tr>
<td>Serum 25-OHD</td>
<td>36.4±10</td>
<td>89.4±33.3</td>
<td>88.6±29.7</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>144.7±87.2</td>
<td>--</td>
<td>133.5±97.9</td>
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<tr>
<td>Urine Ca/Cr</td>
<td>0.52±.29</td>
<td>--</td>
<td>0.44±.28</td>
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<tr>
<td>Urine NTx/Cr</td>
<td>51.6±37.9</td>
<td>--</td>
<td>54.2±51</td>
</tr>
</tbody>
</table>

Serum Ca baseline vs 5, 10, 22, 34 weeks NS (nonsignificant)

Serum PO₄ baseline vs 5 and 10 weeks NS

Serum 25-OHD
- baseline vs 5, 10, 22, 34 weeks p<.001
- 22 weeks vs 10 weeks p<.001
- 22 weeks vs 34 weeks p<.0001

Serum PTH baseline vs 10 weeks NS

Urine Ca/Cr baseline vs 10 weeks NS

Urine NTx/Cr baseline vs 10 weeks NS