Vitamin D therapy in patients with primary hyperparathyroidism and hypovitaminosis D

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Abstract

Objective: To determine whether vitamin D repletion of patients with primary hyperparathyroidism (PHPT) and vitamin D deficiency or insufficiency (hypovitaminosis D) has deleterious clinical and/or biochemical effects.

Design: Prospective audit of the effect of vitamin D repletion on biochemical data in 56 patients with PHPT. Patients were treated with 50 000 units of vitamin D2 weekly for 8 weeks with biochemical measurements at 5 and 10 weeks, and subsequently after 12 weeks on 800 units of vitamin D3 daily, and in those with hypovitaminosis D after 12 weeks of up to 100 000 units of vitamin D2 monthly.

Methods: Serum calcium, albumin, phosphorus, 25-OHD, intact parathyroid hormone (PTH) and urine calcium/creatinine (Ca/Cr) ratios were measured before and during vitamin D therapy.

Results: Patients treated with 50 000 units of vitamin D2 weekly for 8 weeks resulted in a significant increase in serum 25-OHD levels from 36.4 to 89.4 nmol/l at 5 weeks (P<0.0001) and 88.6 nmol/l at 10 weeks (P<0.0001). There were no significant changes in serum calcium. At 10 weeks, there was a non-significant decrease in serum PTH and in urine Ca/Cr ratios. None of the patients developed any calcium-related adverse events. Subsequently, patients with subnormal 25-OHD levels on 800 units of vitamin D daily were treated for the next 12 weeks with up to 100 000 units of vitamin D2 monthly with normalization of serum 25-OHD in all but 4 patients.

Conclusion: These data fail to demonstrate any adverse effects of vitamin D repletion in PHPT.

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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 cut-off 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 (52.5–72.5 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 tumours, higher serum parathyroid hormone (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 hypercalcaemia 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 2002–2008.
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 PHPT. 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 39 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 analyser, Siemens Healthcare Diagnostics, Medical Solutions, Tarrytown, NY, USA. Serum 25-OHD level was measured by extraction of D2 and D3 followed by liquid chromatography and tandem mass spectrometry, Mayo Medical Laboratory, Rochester, MN, USA. Serum intact PTH was measured by chemiluminescence immunoassay, Centaur Analyser, Siemens Healthcare Diagnostics, Medical Solutions. Serum 1,25-OHD was determined by precipitation and extraction followed by RIA using a polyclonal antibody, Diasorin Inc., Stillwater, MN, USA. Urine NTx was measured by competitive immunoassay technique on the Vitros ECi analyser, Ortho-Clinical Diagnostics, Inc., Rochester, NY, USA.

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 < 0.05 by a two-tailed test. Linear regression analysis was utilised 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 five having vitamin D insufficiency. Of the 39 patients who had serum 1,25-OHD measurements at baseline, nine had increased serum 1,25-OHD of 163–223 pmol/l while one patient had a low level

| Table 1 Baseline biochemical and hormonal data in patients with primary hyperparathyroidism and normal range of values. |
|--------------------------|--------------------------|--------------------------|
| **Patient data**         | **Mean ± s.d.**          | **Range of values**       | **Normal values**          |
| Patients (M/F)           | –                        | 19/37                    | –                         |
| Age (years)              | 63.6 ± 14.4              | 26–88                    | –                         |
| BMI (kg/m²)              | 29.6 ± 6.4               | 19.4–54.9                | 20–25                     |
| GFR (ml/min)             | 83.1 ± 29.9              | 27–156                   | 80–120                    |
| Serum calcium (mmol/l)   | 2.74 ± 0.10              | 2.63–3.0                 | 2.15–2.63                 |
| Serum albumin (g/l)      | 44.8 ± 2.7               | 38–51                    | 34–47                     |
| Serum phosphorus (mmol/l)| 0.98 ± 0.21              | 0.58–1.58                | 0.87–1.45                 |
| Serum creatinine (mmol/l)| 84.5 ± 26                | 44.2–168                 | 35.4–106.1                |
| Serum alkaline phosphatase (U/l) | 83.7 ± 27.5 | 28–140                   | 25–100                    |
| Serum intact PTH (ng/l)  | 144.7 ± 87.2             | 52–416                   | 14–72                     |
| Serum 25-OHD (nmol/l)    | 36.4 ± 10                | 17.5–60                  | 75–200                    |
| Serum 1,25-OHD (pmol/l)  | 122.4 ± 50.4             | 41–223                   | 53–161                    |
| Urine calcium/creatinine (mmol/mmol) | 0.52 ± 0.29 | 0.09–1.11                | 0.14–0.70                 |
| Urine N-telopeptide (nmol BCE/nmol Cr) | 51.6 ± 37.9 | 16–217                   | 19–65                     |

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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 ($R=0.25$, $P=0.07$) or between serum PTH and 1,25-OHD levels ($R=0.28$, $P<0.08$). There was an inverse relationship between serum phosphate and 1,25-OHD levels ($R=0.42$, $P=0.01$).

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 (0.25 mmol/l) above the upper limit of normal, osteoporosis, MEN syndrome type 1 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 $36.4 \pm 10$ nmol/l at baseline to $89.4 \pm 33.3$ and $88.6 \pm 29.7$ nmol/l at 5 and 10 weeks respectively ($P<0.0001$). At 5 weeks, serum 25-OHD levels varied from 37.5 to 167.5 nmol/l with 10 patients having vitamin D insufficiency levels of 52.5–72.5 nmol/l and three patients with vitamin D deficiency levels of 37.5–45 nmol/l. At 10 weeks, serum 25-OHD levels varied from 42.5 to 162.5 nmol/l with vitamin D insufficiency in 17 patients with levels of $52.5\text{-}72.5$ nmol/l and vitamin D deficiency in five patients with levels of $42.5\text{-}50$ 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 ($P<0.0001$). There were 12 patients with vitamin D insufficiency $52.5\text{-}72.5$ nmol/l and 10 with vitamin D deficiency $27.5\text{-}50$ nmol/l. In these patients with continuing hypovitaminosis D, 50 000–100 000 units of vitamin D monthly normalised serum 25-OHD levels in all but four who had levels of $62.5\text{-}72.5$ 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 rose 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 two groups were not significantly different. At 10 weeks, there were two 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 varied 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 non-significant decrease of 8% in serum intact PTH from a mean of 145–134 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=0.002). There was also a non-significant decrease in urine calcium creatinine (Ca/Cr) ratios at 10 weeks compared with baseline. Pre-therapy values ranged from 0.09 to 1.11 and at 10 weeks from 0.14 to 1.08. There was no significant difference in urine NTx 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 D3 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 normalisation of serum alkaline phosphatase levels, remineralisation 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 PTH 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 tumour 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 hypercalcaemia, 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 long-term therapy with vitamin D should pertain only to patients with so-called asymptomatic PHPT in whom there are no clear-cut surgical considerations. However, though vitamin D repletion is an 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 hypercalcaemic 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 D3 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. Remineralisation 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 D3 weekly for 1 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 non-significant decrease in urine NTx. Except for increases to over 400 mg (10 mmol) of calcium in 24-h urine 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 hypercalcaemia. 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 D3 were given weekly for 4 weeks followed by 50 000 units monthly. In the present study, 50 000 units of vitamin D2 were given weekly for 8 weeks followed by 800 units of vitamin D3 for up to 12 weeks. Those patients with subnormal serum 25-OHD levels, were then treated with 50 000–100 000 units of vitamin D3 monthly. Despite significant increases in serum 25-OHD with vitamin D administration, there was no significant increase in serum calcium or urinary Ca/Cr ratios. There was a non-significant 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 ≥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 non-skeletal or non-classic effects of vitamin D (1, 24) would support optimisation 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 non-skeletal effects would require long-term studies.

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