Vitamin D treatment in primary hyperparathyroidism

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Abstract

Background: Primary hyperparathyroidism (PHPT) and vitamin D insufficiency are two very frequent conditions. In cases where the combination of both vitamin D insufficiency and PHPT is diagnosed, vitamin D repletion is an option. However, only limited evidence exists for this treatment.

Objective: The aim of this review is to describe different aspects of concomitant vitamin D deficiency and PHPT and in this setting to evaluate existing evidence on safety and possible outcome of vitamin D treatment.

Methods: Background literature was found based on a search in pubmed.com and scirus.com. Initially 765 articles were identified in pubmed.com and 359 articles in scirus.com. Titles and abstracts of 132 papers were identified to be potentially relevant and were studied as full text articles.

Results: Multiple association studies support the hypothesis that the clinical presentation of PHPT is more severe in patients with vitamin D deficiency. Treatment with vitamin D in PHPT may decrease PTH levels and bone turnover and potentially increase bone mass in various compartments. However, some patients experience increasing plasma or urine levels of calcium, triggering either vitamin D withdrawal or surgery.

Conclusion: Measurement of vitamin D in PHPT is important to evaluate the severity of the disease. The scientific evidence for recommendation of vitamin D treatment in PHPT is weak. Only prospective, randomized and blinded, placebo controlled studies can yield the evidence for vitamin D repletion in PHPT. Furthermore, the effect of vitamin D repletion on other outcomes like quality of life, muscle function and CNS symptoms should be assessed.

Introduction

Primary hyperparathyroidism (PHPT) and vitamin D insufficiency are two very frequent conditions and are both diagnosed as separate clinical entities and together. The diagnostic criteria for PHPT include elevated intact parathyroid hormone (PTH) and inappropriately elevated ionized or total plasma calcium. In borderline cases two or three measurements in vitamin D replete patients may be necessary [1]. PHPT is considered a stable state of equilibrium hypercalcaemia[2-4], therefore the feedback mechanism to regulate calcium metabolism is still in function and is a possible target for medical treatment[5]. The only curative treatment for PHPT is parathyroidectomy (PTX) indicated in moderate and severe cases[6], where evident pathologic parathyroid tissue is removed. Vitamin D insufficiency is diagnosed by measurement of plasma 25-hydroxy vitamin D (25OHD)[7] and levels < 50 nmol/l are widely accepted as insufficient, whereas levels < 25nmol/l indicate vitamin D deficiency[7]. However, others consider levels up to 100 nmol/l as insufficient[8]. Vitamin D should in general be related to PTH levels, and a pragmatic definition of insufficiency is the level of 25OHD below which PTH is increasing[7]. Thus, a hyperbolic relation exists between 25OHD and PTH, also in PHPT [7;9]. In cases where the combination of both vitamin D insufficiency and PHPT is diagnosed, vitamin D repletion is an option. However, only limited evidence exists for this treatment[1].
The aim of this review is to describe different aspects of concomitant vitamin D insufficiency and PHPT and in this setting to evaluate existing evidence on safety and possible outcome of vitamin D treatment.

Methods

Background literature was found based on a search in pubmed.com and scirus.com with the MeSH terms vitamin D and primary hyperparathyroidism as keywords. Initially 765 articles were identified in pubmed.com and 359 articles in scirus.com. Titles and abstracts of 132 papers were identified to be potentially relevant and were ordered as full text articles.

Importance of vitamin D in PHPT

Vitamin D is of major importance for the regulation of calcium homeostasis due to its effects on intestinal calcium absorption and mineralization of calcified tissues. There is increasing evidence of altered vitamin D metabolism in PHPT[10]. Both the half-life of 25OHD [11;12] and the levels of 25OHD are decreased [9;13;14] and numerous possible explanations have been examined. In PHPT, the continuously elevated PTH stimulates the conversion of 25OHD to the active compound 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). However, this conversion can only explain a minor decrease in 25OHD levels, due to the much higher concentration of the substrate[15]. Moreover, there seems to be only a weak correlation between 25OHD and $1,25(OH)_2D$ in PHPT, where the increase in $1,25(OH)_2D$ seems to level off with 25OHD levels coming into the normal range[16]. An increase in both PTH and $1,25(OH)_2D$ stimulates the 24-hydroxylase that converts both 25OHD and $1,25(OH)_2D$ to the less active 24-hydroxylated compounds [17]. This could explain the finding of similar 25OHD levels in former PHPT patients and healthy controls [18]. Another reason for decreased 25OHD could include the weight gain in PHPT [19], which could enhance storage and degradation [20] of vitamin D in fat tissue[21]. Finally, decreased outdoor activity because of muscle weakness and fatigue, may lead to decreased exposure to the UVB radiation necessary for the dermal synthesis of cholecalciferol. Hence, the decreased vitamin D in PHPT may be a consequence of the increased PTH secretion in PHPT. On the other hand vitamin D insufficiency could be involved in the pathogenesis of the disease. Numerous epidemiological studies have been

publishes showing associations between decreased vitamin D levels and increased incidence of various diseases [8;22]. At the cellular level, vitamin D binds to the vitamin D receptor (VDR) and affects the cell cycle in different ways leading to increased cell differentiation [23;24]. Further, vitamin D has been shown to decrease parathyroid cell proliferation and PTH secretion via VDR on the parathyroid cells [25-27]. Thus, long standing vitamin D deficiency might lead to parathyroid hyperplasia or adenoma development, as also seen in various forms of secondary hyperparathyroidism [7]. The increase in the amount of parathyroid tissue could lead to a refractory state of secondary hyperparathyroidism as described earlier by *Parfitt* and others [2;28] or to evident PHPT. Especially in the nodular parathyroid hyperplasia the density of VDR is reduced [28].

Low levels of Vitamin D in PHPT

During the last decade, many studies have evaluated the prevalence and severity of vitamin D deficiency in PHPT (Table 1). Generally, there is a large variation in symptoms and severity at the time of diagnosis. The clinical spectrum covers cases from mild, mostly asymptomatic patients to very severe cases with classical symptoms and marked bone affection.[29]. Today most patients in the developed world are diagnosed by coincidence without showing specific symptoms[29] whereas the severe, symptomatic cases typically are diagnosed in the developing countries [29].The range of vitamin D levels in PHPT varies equally. Interestingly, a study of patients with PHPT from various geographic regions demonstrated an inverse relationship between 25OHD-levels and the degree of PTH elevation. Thus, in western populations with 25OHD-levels in the 50 nmolar range, PTH levels were only slightly elevated, whereas PTH was 15 to 20 fold increased in India and China with very low 25OHD-levels [14]. Nutrition status, national food fortification programs, latitude and socioeconomic factors may contribute to some of the differences in 25OHD-levels[7]. *Silverberg et al* [30] described in a study from 1999 the associations of preoperative 25OHD-levels to other clinical variables. The 124 PHPT patients were divided into tertiles according to low, mid or high 25OHD-levels. The tertile of patients with the lowest plasma 25OHD (N=41, 25OHD < 40 nmol/l) had significantly higher plasma levels of PTH and alkaline phosphatase and lower levels of plasma phosphorus levels compared with the other tertiles. However, plasma and urinary calcium did not vary by tertile of 25OHD. Similar studies have been performed at other centers in the US, Europe and Asia [9;13;31-39]. The number of patients included, vitamin D levels and definitions of vitamin D insufficiency and deficiency varies (Table 1). However, all the larger studies described that higher plasma PTH is associated with lower 25OHD. Low plasma 25OHD levels were also often associated with higher plasma calcium, plasma alkaline phosphatase and adenoma weight. In a few studies low 25OHD-levels were significantly associated with low plasma phosphorus, low forearm and femoral neck BMD, high urinary calcium, postoperative hypocalcaemia and an increase in postoperative PTH. Low vitamin D levels have also been related to cardiovascular function in mild PHPT, where a recent cross sectional study showed an inverse relationship between 25OHD and left ventricular hypertrophy, a well known risk factor for cardiovascular disease and mortality [40]. This relationship was, however, not found in a Scandinavian randomized study on treatment of mild PHPT, potentially due to a higher level of vitamin D in Scandinavia compared to USA [41].

To summarize, these associations support the hypothesis that the clinical presentation of PHPT is more severe in patients with low 25OHD-levels[10]. Moreover, the clinical phenotype including classical hyperparathyroid manifestations and cardiovascular morbidity is still observed in relation with vitamin D deficiency in PHPT, especially in non-western communities.

Vitamin D treatment in PHPT

Older studies and studies with active vitamin D

Since the studies and description of parathyroid function by Fuller Albright [42;43] in the 1930s and 1940s a comprehensive amount of research has been performed, increasing our understanding of the complex interaction and homeostasis of calcium metabolism. However, it was not until the 1960s the importance of vitamin D in parathyroid disease was reported in a case with concomitant osteomalacia and PHPT [44]. Further, *Woodhouse and others* [45-47] studied vitamin D treatment in patients with PHPT. Targets of interest were both treatment of osteitis fibrosis cystica and severe postoperative hypocalcaemia. The patients described in these early reports were often severely vitamin D deficient, suffered from marked bone disease and at high risk of hypocalcaemic tetany after removal of large parathyroid adenomas. Hence, achieving a preoperative suppression of PTH and reduction of postoperative hypocalcaemia was of greater significance than merely repletion of vitamin D. The studies are summarized in Table 2.

In a study by *Boyle et al* [47] preoperative treatment with 2 µg 1-alpha-hydroxylated cholecalciferol daily in six PHPT patients was evaluated. The duration of treatment varied, but interestingly there was a preoperative decrease in alkaline phosphatase in three patients without change in plasma calcium. There was no severe postoperative tetany, but three patients did require postoperative intravenous calcium supplementation. In a later study [46], the enthusiasm was more modest. Preoperative treatment with 1-alpha-hydroxylated cholecalciferol daily in five days in a group of six PHPT patients with pronounced bone disease was compared with a group of six similar PHPT patients. It was impossible to detect any advantageous effect in the pretreated group and in addition, plasma calcium in half of the pretreated patients increased preoperatively. Based on this, preoperative treatment with 1-alpha-hydroxylated cholecalciferol was not in general recommended. *Lind et coworkers* performed a small randomized controlled study of 31 patients with mild PHPT randomized to 1 µg 1-alpha-hydroxylated cholecalciferol daily for 6 months versus placebo[48], followed by another 12 months open phase study (18 patients) of a 2 µg/day dose [49].The study showed only a modest increase in calcium levels with the lower dose but a marked increase in plasma calcium with the higher dose. Of interest, only a transient reduction in PTH levels was observed, indicating no substantial inhibition of PTH-levels by a small to moderate dose of active vitamin D in mild PHPT. In contrast, plasma PTH decreased in a study with intravenous treatment with increasing daily doses (0.5 – 2 micrograms) of active vitamin D [50].

In a study from 1985 of short term vitamin D treatment, *LoCascio et al* [51] compared daily oral treatment with 50 µg cholecalciferol in one month to 6 PHPT patients and 5 healthy adults. In the healthy adults 25OHD increased from 45 nmol/l to 340 nmol/l without changes in any other plasma levels. In the PHPT patients there was a slight decrease in PTH and a marked increase in 25OHD and 1,25-OHD along with slight increases in calcium and phosphate levels. This study was followed by a randomized double-blind cross-over study [52] evaluating treatment with 24,25-dihydroxyvitamin D3 (24,25$(OH)_2$D) versus placebo. In this cross-over study 19 PHPT patients were randomly assigned to 25 µg 24,25$(OH)_2$D tablets daily in 3 months followed by placebo or treatment with the reverse sequence. There was no significant difference after treatment with respect to PTH, plasma and urinary calcium. Only plasma 24,25$(OH)_2$D increased significantly, however, neither 25OHD nor 1,25$(OH)_2$D changed.

After these initial studies, treatment with vitamin D2 or D3 in PHPT was not reported for several years. These early, small but often randomized controlled studies in general indicated no overall beneficial effect of active vitamin D on PTH secretion but involved a risk of increasing calcium levels. Neither could any positive effects of treatment with 24,25-dihydroxyvitamin D3 be demonstrated.

Systematic studies from the last decade

During the last decade vitamin D has become a favorite topic for many studies. Vitamin D affects a wide range of tissues through its receptor VDR, which has been found in almost every tissue examined [53;54]. The increasing interest for vitamin D insufficiency and its prevention or treatment in various diseases has augmented the need for further controlled trials. In PHPT, the interest still mainly focus on beneficial gains of suppressing PTH and reducing postoperative "hungry bones" and thereby the risk of hypocalcaemia. However, safety issues regarding plasma levels and urinary excretions of calcium seem to exceed the interest in beneficial gains [55;56].

In a study by *Kantorovich* [57] vitamin D and PTH were analyzed in 229 patients referred for osteoporosis evaluation. In 15 patients vitamin D was decreased (< 37 nmol/l) and PTH elevated (> 6.8 pmol/l). These patients were treated with 1250 microgram ergocalciferol twice weekly for ten weeks. In 10 of the patients PTH returned to normal and they were considered to have secondary hyperparathyroidism. In the latter 5 patients vitamin D increased significantly (21 to 52 nmol/l), but PTH remained elevated (11.2 to 10.9 pmol/l) and they were categorized as having PHPT indicating a prevalence of 2.2% of coexisting PHPT and vitamin D insufficiency in their population. Vitamin D repletion improved significantly BMD at both the femoral neck and lumbar spine, without any increase in plasma calcium. The authors conclude that diagnosis of PHPT can be obscured by vitamin D insufficiency, and when treated, can be followed by a substantial increase in bone mass, despite unchanged PTH levels. However, two of the patients were normocalcaemic both before and after vitamin D treatment and may be classified as having refractory secondary hyperparathyroidism[2;28]. Only in one of the remaining three hypercalcaemic patients the PHPT diagnosis was confirmed histopathologically after surgical removal of a parathyroid adenoma. Furthermore, the intervention part of this non-controlled study is very small and the data should be interpreted with caution. In conclusion, the results are of interest pointing to the difficulties in delimiting the diagnosis of PHPT and the potential benefit of vitamin D repletion.

In 2005 Grey [58] reported an open study of vitamin D treatment in 21 patients with mild PHPT (S-calcium < 3 mmol/l) and vitamin D insufficiency (25OHD < 50 nmol/l). In this non-controlled study, the patients were treated with 1250 microgram (50 000 IU) D_3 tablets weekly for one month followed by 1250 microgram D_3 per month for one year. There was an increase in 25OHD from 28 to 76 nmol/l after 6 months accompanied by a significant PTH decrease from 12.4 to 9.4 pmol/l (25%). These results remained unchanged at the end of the study. There was a significant decrease in alkaline phosphatase and no overall increase in 24 h urinary calcium excretion. However, in three patients measurements of 24 h calcium excretion exceeded 10 mmol, but there were no reports of kidney stones during the observation period. Three patients discontinued vitamin D treatment within the first month and three patients went to PTX within the observation period. Data from these patients were included. There was no change in bone mass at the lumbar spine or femoral neck. The study concludes that vitamin D repletion in patients with mild PHPT is safe and is followed by a decrease in PTH levels and markers of bone turnover. However, an increase in calcium excretion in some patients is a concern[58]. Unfortunately, the study was not controlled and it needs to be followed by randomized and placebo controlled clinical trials.

In a larger scale, *Grubbs et al* [55] in 2008 reported a prospective study based on a clinical database, where demographics and pre/postoperative biochemistry were entered. The purpose of the study was to address the safety and potential clinical benefit of preoperative vitamin D supplementation in PHPT patients undergoing surgery. PHPT patients (n=301) were divided into three groups. Patients in group 1 (n=118, plasma calcium 2.68 mmol/l) with vitamin D levels > 75 nmol/l went directly to surgery. Patients in group 2 (n=112, plasma calcium 2.73 mmol/l) all had vitamin

D levels < 75 nmol/l and were treated preoperatively with ergocalciferol 1250 microgram pr. tablet. The range of treatment was 2-210 days and the cumulative dose was 600 - 37 500 microgram. Patients in group 3 (n=71, plasma calcium 2.75 mmol/l) all had vitamin D levels < 75 nmol/l but did not receive any vitamin D treatment. In group 2 vitamin D increased from 45 to 115 nmol/l preoperatively (p<0.0001), PTH decreased from 18.4 to 17.2 nmol/l (p=0.014) and calcium decreased from 2.73 to 2.68 mmol/l (p=0.008). Six patients (5%) had a mean increase in plasma calcium of 0.16 mmol/l during the treatment without symptoms. The mean gland size in group 2 was smaller than in group 3 (p = 0.04) but larger than in group 1 with the highest baseline vitamin D status (p=0.004). The study has several limitations. By design, the study was historic, dose and duration of treatment was far from standardized, information of symptoms was not collected, BMI differed significantly between the groups as did mean creatinine clearance. The strength of the study is the high number of patients in all groups, the prospective collection of data and the total amount of data described. The authors conclude that vitamin D treatment is safe, but does not assess the effect on postoperative PTH elevation, overall cure-rate or risk of recurrent disease.

In 2009, *Tucci et al* [59] reported a study of ergocalciferol treatment in 56 PHPT patients (plasma calcium 2.74 ± 0.10 mmol/l) with low plasma 25OHD (17-60 nmol/l). Most of the patients had mild and asymptomatic PHPT. Fourteen patients meeting indications for surgery according to the 2002 criteria[60] were operated successfully after vitamin D treatment. There was no significant correlation between plasma 25OHD and PTH or between PTH and calcium at baseline. Initial doses of 1250 microgram ergocalciferol weekly was evaluated after 8 weeks and altered to individual treatment doses from 20 microgram daily to 2500 microgram monthly in an effort to maintain 25OHD levels > 75 nmol/l. Plasma 25OHD increased significantly from 36 to 89 nmol/l at 5 weeks and 10 weeks (p<0.0001). However, only an insignificant 8% PTH decrease from 15.2 to 14.1 nmol/l was observed. At 10 weeks levels of PTH were not correlated to 25OHD (p=0.41) but PTH was positively correlated to calcium (R = 0.41, p=0.002). None of the patients developed symptoms related to increased calcium and there were no adverse events. No significant changes in urinary calcium/creatinine excretion or in the urinary bone resorption marker NTx were observed. With ergocalciferol doses up to 2500 microgram monthly the study could not substantiate any risk of vitamin D_2 treatment in PHPT. The study support that optimization of vitamin D levels in patients with PHPT is safe even with high doses.

Latest *Isidro et al* [56] aimed to assess biochemical effects of one-year calcifediol (25OHD) treatment in 27 patients with asymptomatic PHPT (plasma calcium 2.70 ± 0.13 mmol/l) and concomitant vitamin D deficiency (plasma 25OHD < 50nmol/l, mean 28.7 ± 8 nmol/l). There was an inverse correlation between PTH and 25OHD at baseline. Twenty of the patients completed the one-year treatment period. Plasma 25OHD levels increased significantly after 3 months (62.9 ± 25 nmol/l, P < 0.01), 6 months (62.7 ± 26.8 nmol/l, P < 0.01), and following one year of treatment (71.5 ± 32.5 nmol/l, P < 0.01). PTH decreased significantly during the first 6 months (plasma iPTH at baseline: 19.7 ± 14.2 pmol/l versus plasma iPTH after 6 months 13.8 ± 10.0 pmol/l, p=0.03). However, the decrease was no longer significant following one year of treatment (plasma iPTH at baseline: 19.7 ± 14.2 pmol/l versus plasma iPTH after 12 months: 17.2 ± 14.6, NS). Plasma calcium levels remained unchanged throughout the treatment period. Attention was attracted to the 24h-urinary calcium excretion which increased significantly after 3 and 12 months (p < 0.05), but not after 6 months . In three patients calcifediol were withdrawn due to 24 h urinary calcium excretion > 10 mmol and in six patients calcifediol were reduced after one year. In addition, calcifediol was withdrawn in another two patients due to plasma calcium above 2.9 mmol/l after 3 months. Plasma phosphorous and alkaline phosphatase did not change significantly during the study, emphasizing the non-significant alterations in PTH at the level of target organs. It remains unclear

whether the increase in urinary calcium and the decrease in PTH could be temporary or permanent in these patients. The author suggests monitoring of urinary calcium excretion on PHPT patients while on vitamin D treatment.

Evidence for Vitamin D treatment in PHPT

Within the last decades several studies have focused on repletion of vitamin D insufficiency in PHPT, and often with inclusion of patients with mild and asymptomatic disease not meeting international criteria for surgery. The larger investigations are typical prospective but un-controlled studies or historical register studies. In these studies alteration over time in management, clinical assessment or laboratory analyses may affect results and randomized, placebo-controlled and blinded studies are strongly needed. Until now it has been reported that treatment with vitamin D may or may not decrease PTH levels and bone turnover and potentially increase bone mass in various compartments. However, some patients experience increasing plasma levels of calcium, triggering either vitamin D withdrawal or surgery. The increase in some patients of the renal excretion of calcium is a concern and it has to be monitored, although kidney stones have not been described in these overall short term studies. Based on single cases it has been suggested that repletion may improve the diagnostic accuracy in some patients. However, this has to be evaluated in more details.
The guidelines from the third international workshop on management of mild PHPT recommend vitamin D repletion[6]. However as described above the scientific evidence for this recommendation is weak. Only prospective, randomized and blinded, placebo controlled studies can yield the evidence for vitamin D repletion or treatment in PHPT. Furthermore, the effect of vitamin D repletion on other outcomes like quality of life, muscle function and CNS symptoms should be assessed.

Conclusion

Measurement of vitamin D in PHPT is important to evaluate the severity of the disease. The causality of the frequent coexistence of vitamin D insufficiency and PHPT is not fully understood. Treatment with vitamin D in PHPT may lead to a PTH decrease. However, there is no randomized controlled trial to prove any beneficial effect. For safety reasons, it is recommended to monitor plasma and urinary calcium during treatment.

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