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PERSPECTIVES

Mild Primary Hyperparathyroidism and Metabolism of Vitamin D

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Abstract

Mild primary hyperparathyroidism (PHPT) is a common condition in Western societies, as is vitamin D insufficiency. The prevalence of mild PHPT is high, especially in pre- and postmenopausal women (2-5%), and the incidence seems to be relatively constant at a slightly higher level, compared to the period before automated calcium measurements. As many as 80% of patients with mild (without organ-specific symptoms) PHPT present with 25-hydroxy vitamin D (25OHD) levels below 50 nmol/l (vitamin insufficiency). The reason for the frequent co-existence of vitamin D insufficiency and PHPT is not fully understood and cannot be explained solely by increased PTH-driven conversion to the active vitamin D metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Only three small, prospective studies have been performed within the last ten years on vitamin D repletion in mild PHPT, with ambiguous results. Vitamin D repletion might increase serum calcium levels and in general it is recommended to vitamin D-deplete patients before decision-making for final therapy (surgery). In addition, vitamin D repletion might decrease PTH levels due to binding to the vitamin D receptor in the parathyroid gland, but the results have not been unequivocal. Furthermore, no clear results regarding biochemical markers of bone turnover or bone mineral density have been presented. An increase in renal calcium excretion during vitamin D repletion is a concern and should be carefully monitored. The recommendation of vitamin D repletion in mild PHPT seems logical and reasonable, however, thus far this conclusion is not based on large-scale, randomized controlled studies. Such investigations are highly warranted. *IBMS BoneKEy*. 2011 July;8(7):342-351.

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder and the most frequent cause for disturbance in plasma calcium homeostasis in community-dwelling individuals. The clinical presentation of PHPT has changed dramatically after increased accessibility to biochemical auto-analysers, so today the diagnosis is often made by chance in patients without specific symptoms (1). Operative treatment is recommended in patients with markedly increased calcium levels, typical hypercalcemic symptoms or known complications, *i.e.*, renal stones or osteoporosis. However, the majority of patients in the modern clinic do not present organ-related symptoms and their calcium levels are only slightly increased, or even within the upper limit of normal. Several consensus development conferences have discussed management of these patients with mild, borderline PHPT during the last twenty years (2-4).

In PHPT, parathyroid hormone (PTH) levels are inappropriately increased in relation to circulating calcium concentrations, most often due to a set point error in a parathyroid adenoma (85%) or in parathyroid gland hyperplasia (15%), resulting in a shift to the right in the calcium/PTH relationship (5) (Fig. 1). As many as 20-40% of sporadic parathyroid adenomas may contain somatic mutations in the cyclin-D1/PRAD1 gene (6),

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which is in control of cell division, and thereby may lead to formation of a clone of cells resulting in adenomas. Somatic mutations in the menin (6), BRACA and retinoblastoma genes have also been described (7). PTH and vitamin D levels are closely interrelated, and PTH regulates the rate-limiting step in activation of the pro-hormone 25(OH)-vitamin D (25OHD) to the active 1,25$(OH)_2$-vitamin D (1,25$(OH)_2$D), which again inhibit parathyroid cell proliferation and PTH secretion. Both hormones tend to increase calcium levels in the circulation, by directly or indirectly increasing calcium absorption from the gut, re-absorption via distal tubule cells in the kidney, and finally by releasing calcium stored in bone tissue. Plasma calcium is closely regulated and maintained within narrow limits, and calcium metabolism, in general, is much more complicated than indicated here (5). As indicated in Fig. 1, familial hypocalciuric hypercalcemia (FHH) is an important differential diagnosis to mild PHPT as it is to normo-calcemic hyperparathyroidism (8).

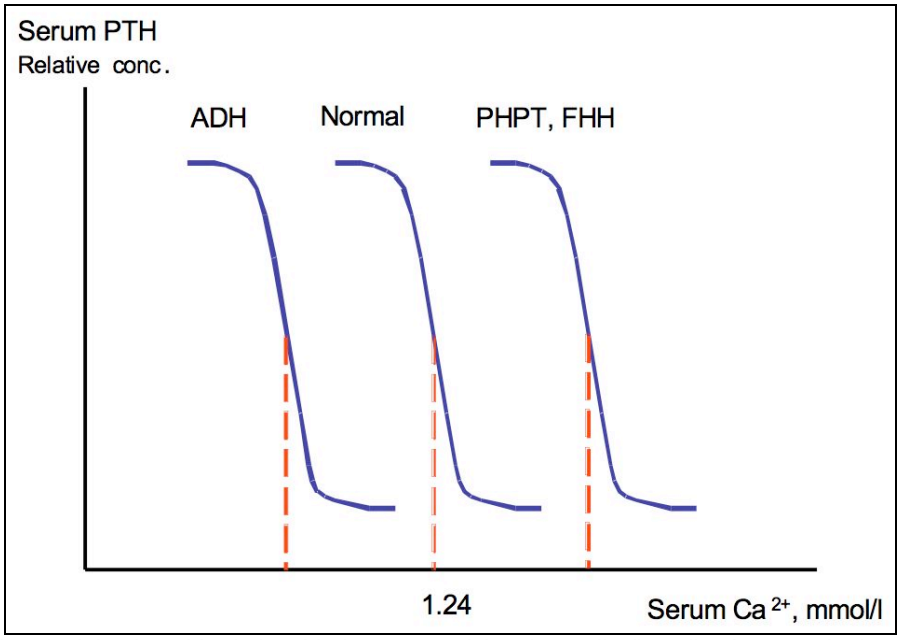

Fig. 1. The in principle sigmoid relationship between calcium in media (in cell cultures or in the circulation *in vivo*) and PTH secretion is demonstrated. The PTH set point is defined as a calcium concentration that corresponds to a fifty percent reduction in PTH. The set point is increased in PHPT and familial hypocalciuric hypercalcemia (FHH) – a drift to the right. A shift to the left is seen in autosomal dominant hypocalcemia (ADH) due to a gain-of-function mutation in the calcium-sensing receptor.

Vitamin D deficiency is another common condition, although this has improved, especially in Western communities, as socioeconomic conditions have raised (9). It is of major interest in this regard that the clinical presentation of PHPT in areas with vitamin D deficiency is much more severe than what is seen in the modern Western clinic. Severe vitamin D deficiency may mask calcium levels in PHPT, resulting in diagnostic inaccuracy (9), hence this is why vitamin D repletion might be of relevance in relation to patient work-up and stratification of treatment in accordance with international guidelines (4).

In this *Perspective*, we discuss mild PHPT from the vantage point of the most recent workshops on treatment of this disorder, with special focus on concomitant low plasma 25OHD levels and evidence for recommendation of vitamin D repletion in PHPT.

Mild PHPT: Epidemiology and Clinical Presentation

After introduction of automated serum calcium determinations at the beginning of the 1970s, a dramatic rise in patients devoid of symptoms was seen in both sexes (10), which, however, later seemed to level off. In

the Rochester Epidemiology Project, patients with PHPT living in the Rochester area and referred to the Mayo Clinic have been followed since the early '70s and thus far results have been published up to 2001 (11). Immediately after introduction of automated biochemical panel analyses, the adjusted incidence rate for the period from 1974-1982 was 82.5 per 100,000 person years, declining to 29.1 in the period from 1983-1992, and further declining to 21.6 per 100,000 person years in the latest reported period through 2001 (11). It is of interest that the discontinuation of the automated calcium measurements by 1996 did not seem to have an impact on diagnostic incidence or clinical phenotype, as most of the diagnosed patients with PHPT remained asymptomatic (11). Most of the patients in the project were observed without surgery. However, only minimal effect of the guidelines from the first, NIH-initiated consensus conference on management of mild PHPT (2) was observed (11). Thus, the incidence of PHPT is higher today than in the '60s and '70s, however, it is not as high as in the first years following multiple channel chemistry. The reason for the change in incidence remains unknown.

The prevalence of PHPT in peri- and postmenopausal Scandinavian women is well-described in mammography-based epidemiological studies (12;13). Out of a total population of 5,202 women aged 55-77 years, 109 women proved to have PHPT, of whom two out of three had calcium levels within the upper normal range, with inappropriately high PTH levels (12). As part of a stratified treatment program, 59 out of 60 women undergoing surgery demonstrated pathological parathyroid tissue, with a mean weight of almost 600 mg (12). In a subsequent study, sick leave and morbidity were investigated. Forty-eight case-control pairs from the study were investigated for morbidity and sick leave for the preceding 5-year period before diagnosis (14). Proven cases not known to have PHPT before going to the screening program had an odds ratio of more than 12 for being on more than 50% sick leave benefit, as compared to women without PHPT. The main reason for sick leave was musculoskeletal and cardiovascular diseases (14).

In a recent, similar population-based study of 1,900 premenopausal, 40-50-year-old women, the prevalence of PHPT was found to be 5.1% (96 patients were identified) (13). Compared to controls (women without PHPT from the same screening), cases had lower bone mass, higher weight (BMI), and reduced quality of life, especially in the physical functioning, vitality, and general health domains of the generic SF-36 questionnaire (13), corroborating the impact of PTH on target tissues even in patients found by a screening program.

The background for the three international workshops on treatment of mild PHPT thus far has been the remarkable shift in clinical presentation of PHPT during the last decades of the old millennium (2-4). Most patients present now without specific symptoms. However, as illustrated above, patients might have significant morbidity, especially related to bone tissue, the cardiovascular system, and neuropsychological aspects (1;15-18). The question remains, however, whether surgical intervention in mild asymptomatic PHPT significantly alters morbidity and prognosis. Thus far, only three prospective, randomized studies have appraised the benefit of surgery versus medical observation, without significant clinical improvements of active intervention with observation time up to two years (19-23).

Vitamin D and Mild PHPT

Because of the observation that the clinical phenotype and severity in PHPT decrease in relation to an increase in vitamin D intake, a direct association between 25OHD levels and classical symptoms and complications has been hypothesized (9;24). Comparing plasma 25OHD and PTH levels with clinical presentation in a global perspective has indicated that symptoms and complications of PHPT are much more prevalent and pronounced in areas with vitamin D deficiency, as compared to regions with higher or sufficient levels (24-26). Moreover, weight of removed parathyroid tissue by

surgery in PHPT seems to be inversely related to the level of 25OHD (27;28).

Plasma 25OHD levels in most series of mild PHPT seem to be in the low normal range (21;29), however, with an association between low 25OHD and target tissue affection. Thus, biochemical markers of bone turnover seem to be higher and bone mass lower in patients with the lowest vitamin D levels (29;30). In the Scandinavian Study of Primary Hyperparathyroidism (SIPH), a prospective and randomized study of the effect of surgery in mild PHPT, we found an inverse correlation between 25OHD and PTH levels, as also found by others (30) (Fig. 2). Plasma 25OHD levels have been related to neurocognitive function in epidemiological, case-control studies (31), and patients with mild PHPT seem to have reversible impairments in cognition (15). Moreover, quality of life is decreased in mild PHPT (13;20), but seems not to improve following surgical treatment (19;20;23). However, thus far no studies have substantiated the impact of low 25OHD levels on quality of life or cognition in mild PHPT.

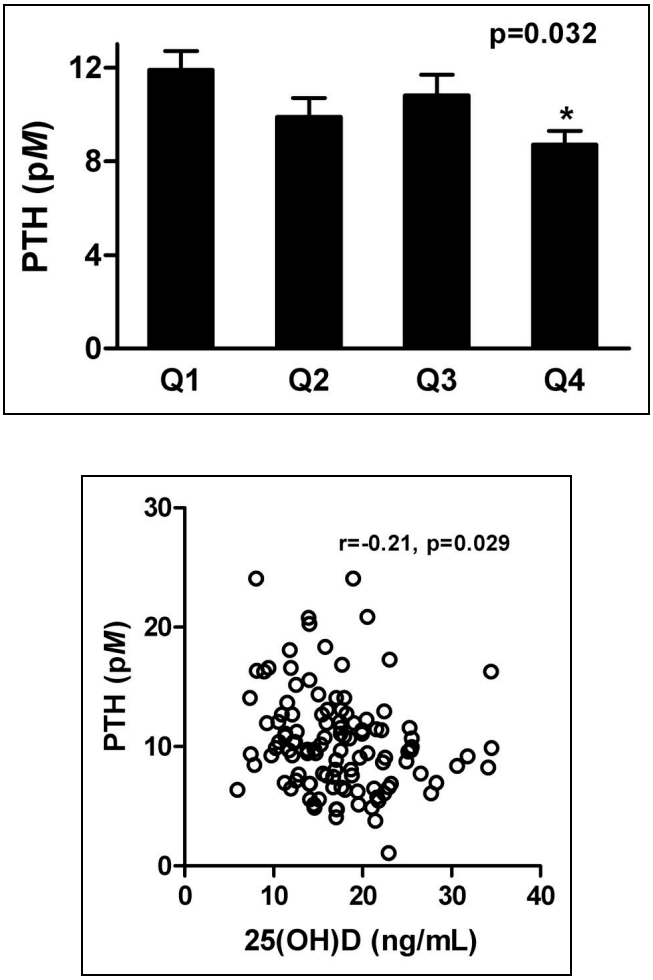

Fig. 2. The relationship between 25OHD and PTH levels in 116 patients with mild PHPT at baseline from the Scandinavian Study of Primary Hyperparathyroidism, unpublished data *(SIPH Study Group, 2011)*. Top: PTH concentrations in relation to vitamin D quartiles; p-value denotes the result of the Anova analysis. * Indicates the significant difference between Q1 and Q4, Mann Whitney Test. Bottom: Corresponding significant correlation between vitamin D and PTH levels as in the top part of the figure (Pearson's correlation test).

The increased cardiovascular risk is well-recognized as well in mild PHPT (17) and with echocardiography correlates. The cardiac growth-promoting effect of PTH in

mild PHPT has also been demonstrated by a direct correlation between PTH levels and left ventricular mass (22;32). With respect to vitamin D, a recent cross-sectional study of patients with mild PHPT showed an inverse correlation between 25OHD levels and left ventricular mass index, a finding we could not confirm in our recent prospective, randomized study (22), and which might be ascribed to the tight correlation between PTH and 25OHD levels (Fig. 2).

Vitamin D Repletion in Mild PHPT

Low 25OHD levels in PHPT cannot be ascribed solely to the effect of PTH on renal α-hydroxylase and thereby augmented conversion to active $1,25(OH)_2D$. The half-life of 25OHD is decreased in PHPT and reverts to normal following parathyroidectomy (33). The primary reason for low 25OHD levels in PHPT seems to be increased hepatic inactivation of 25OHD followed by clearance of metabolites. Therefore, if vitamin D intake is low, a condition of PHPT will increase the depletion of vitamin D stores (34). In this respect, it is of interest that there might be a pathogenetic association between low 25OHD levels and PHPT. The active vitamin D metabolite ($1,25(OH)_2D$) binds directly to its receptor (VDR) also in parathyroid cells followed by pro-apoptotic and anti-proliferative effects, hence, this is why vitamin D inhibits PTH secretion and cell proliferation (35;36). Thus, theoretically, low vitamin D levels might predispose to parathyroid hyperplasia and adenoma formation. *In vitro* and *ex vivo* studies of parathyroid tissue have demonstrated that the inhibition of PTH secretion and cell proliferation holds for normal parathyroid tissue. However, in tissue from PHPT patients, even high doses of calcitriol ($1,25(OH)_2D$) did not have the same effect (35), in agreement with an early clinical study on active vitamin D treatment. Lind and 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 (37). The study showed a modest increase in calcium levels, but only a transient reduction in PTH levels, indicating no specific inhibition of PTH secretion by a moderate dose of active vitamin D in mild PHPT. Thus, treatment with vitamin D or vitamin D repletion in PHPT might be a logical approach and a subject for further studies. Several minor clinical studies have looked recently into these aspects, but thus far no larger prospective and randomized studies on the effect of vitamin D treatment/repletion in mild PHPT have been published.

In an open study of vitamin D repletion in patients with mild PHPT, asymptomatic and with serum calcium levels < 3.00 mmol/l and co-existing 25OHD levels < 50 nmol/l, Grey and coworkers investigated 25 patients (23 women) in a one-year study (38). The patients were evaluated by their referring physician to be suited for conservative treatment, and received cholecalciferol tablets 50,000 IU weekly for four weeks, thereafter monthly for a total of 12 months. Calcium supplements were not prescribed (four of the women received antiresorptive drugs). Data were available for 21 patients, as three women discontinued treatment within the first month, and another requested parathyroidectomy after three months of repletion. With this regime, 25OHD levels increased in all patients above 50 nmol/l after 6 months and remained steady for the following six months up to one year of repletion. No significant increase in mean serum calcium levels was observed and no patients experienced levels above 3.00 mmol/l. Plasma PTH decreased significantly by 25% after six months, and remained at this level throughout the study. After 12 months of repletion, a significant decrease in total alkaline phosphatase was observed, however, not after six months and no significant decrease in bone resorption markers was demonstrated. In agreement with the modest changes in biochemical markers of bone turnover, no significant improvement in bone mass assessed by DEXA was demonstrated. During the study, three patients experienced calcium excretion > 10 mmol/24 h, but mean calcium excretion in the 17 patients who completed the study was not higher than at baseline and none developed renal stones during the study period. The study concluded that vitamin D repletion in patients with mild PHPT was safe, however, an increase in calcium

excretion in some patients was a concern (38).

Recently, Tucci performed a prospective audit of 56 patients with mild PHPT (39), of whom 14 met the NIH criteria for surgery (2). At baseline, 51 of the patients had 25OHD levels below 50 nmol/l; the mean level was 36.4 nmol/l (range 17.5-60 nmol/l). The patients were treated with 50,000 IU vitamin D_2 weekly for eight weeks, followed by individual repletion of 800 IU daily to 100,000 IU monthly in order to keep 25OHD levels above 75 nmol/l. The patients were followed for up to 34 weeks, and no significant change was observed concerning calcium and PTH levels, or in the measured biochemical markers of bone turnover. In this audit, calcium excretion did not increase and none of the patients developed calcium-related symptoms or side effects. The study concluded that patients with the combination of mild PHPT and vitamin D deficiency (or insufficiency) should be given vitamin D repletion – that it was safe and without side effects. However, demonstration of positive classical or non-classical effects of vitamin D repletion in mild PHPT demands long-term studies (39).

Finally, another recent open and non-randomized study aimed to investigate the effect of vitamin D supplementation in 27 patients (three men) with mild PHPT (serum calcium < 2.90 mmol/l, six patients were treated with bisphosphonates prior to the study and continued throughout) and concomitant vitamin D deficiency (25OHD < 50 nmol/l) (40). The patients were supplemented with calcifediol ($25OHD_3$) 480-960 IU daily for one year, adjusted in order to keep serum calcium < 2.90 mmol/l and calcium excretion < 10 mmol/24 h. However, supplementation was withdrawn in three patients due to an increase in calcium levels, and in another 9 patients due to high calcium excretions. All patients increased their 25OHD levels during the study, and after 12 months, 13 out of 17 had levels above the recommended 50 nmol/l in mild PHPT (4). Initially, PTH levels decreased, but were without significant change after one year of supplementation compared with baseline (40). In agreement with this, no changes in biochemical markers of bone turnover were observed. Of concern was the gradual increase in 24 h calcium excretion; as mentioned, a third of the patients had significant calciuria (> 10 mmol/24h) at completion of the study, which the authors concluded in the paper to be a concern (40).

To summarize these recent prospective studies on repletion of vitamin D in mild PHPT (Table 1), no large-scale randomized, controlled studies have been published. Repletion with vitamin D in order to increase 25OHD to the recommended level might increase calcium levels in some patients, raising indications for surgery. PTH levels during treatment have been ambiguous, in accordance with unclear alterations in biochemical markers of bone turnover and therefore no observed significant alterations in bone mass. Two of the three studies performed raised concern in relation to hypercalciuria, but the observation time has been too short for potential development of renal concrements.

Table 1. Recent prospective studies on vitamin D repletion in mild PHPT.

Study	Design	Number of patients	Medication	Duration	Goal for 25OHD	Effect Ca++	Effect PTH	Side effects
Grey (38)	Open	25 (23 women)	Cholecalciferol	12 months	> 50 nmol/l	NC	↓	Ca-excretion ↑
Tucci (39)	Audit	56 (37 women)	Cholecalciferol	Up to 34 weeks	> 75 nmol/l	NC	NC	NC
Isidro (40)	Open	27 (24 women)	Calcifediol	12 months	> 50 nmol/l	NC (↑)	NC	Ca-excretion ↑

NC: No significant change; Effect Ca++ and Effect PTH denote significant effects of vitamin D repletion on calcium and PTH levels at the end of the study.

Evidence for Vitamin D Treatment in PHPT

The guidelines from the Third International Workshop on management of mild PHPT recommend vitamin D repletion in general (4). However, the scientific evidence for this recommendation is weak, as described above. Thus, the workshop stated the issue as a blueprint for further research in upcoming years.

It was recommended to assess vitamin D status in all patients with mild PHPT, as seen in the modern Western clinic, and the best test is measurement of 25OHD (8). If vitamin D insufficiency is defined as 25OHD levels below 50 nmol/l (8), the prevalence of vitamin D insufficiency in mild PHPT might be as high as 80%, as seen in newer studies (22;29;30). At the time of the workshop, only a single recent study was published (38). Nevertheless, the workshop recommended correction of vitamin D depletion before other management decisions (8).

As mentioned above, vitamin D repletion in mild PHPT might increase renal calcium excretion. It has been stated that in patients with mild PHPT who have not yet formed stones, a high urinary calcium excretion was not associated with development of concrements (3). Therefore, it was not recommended to follow calcium excretion with conservative management of mild PHPT, in order to define an indication for surgical treatment (3;4). However, this statement did not take vitamin D repletion into account. The studies published thus far have not been performed in a time frame long enough to rule out potential development of stones, hence this is why monitoring of urinary calcium excretion during vitamin D repletion is recommended in general.

Conclusion

In the modern clinic mild PHPT and vitamin D insufficiency are common conditions. As many as 80% of those who present with mild PHPT have 25OHD levels below 50 nmol/l, but the causality of the frequent co-existence of vitamin D insufficiency and PHPT is not fully understood. In general, it is recommended that vitamin D repletion be performed before decision-making for observation versus surgical treatment. Thus far, no randomized controlled trials have been published proving a beneficial effect of vitamin D repletion in mild PHPT. Such studies are highly warranted. For safety reasons, it is recommended that serum and urinary calcium be monitored during repletion, because calcium levels might rise and calcium excretion is a concern.

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