

Review

Vitamin D and primary hyperparathyroidism (PHPT)

Vitamine D et hyperparathyroïdie primitive (HPP)

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Abstract

Vitamin D deficiency and primary hyperparathyroidism (PHPT) are two common conditions, especially in postmenopausal women. Vitamin D deficiency is said to be even more frequent in PHPT patients than in the general population due to an accelerated conversion of 25-hydroxy vitamin D (25OHD) into calcitriol or 24-hydroxylated compounds. Although several studies have reported worsening of PHPT phenotype (larger tumours, higher parathyroid hormone [PTH] levels, more severe bone disease) when vitamin D deficiency coexists whereas vitamin D supplementation in PHPT patients with a serum calcium level less than 3 mmol/L has been shown to be safe (no increase in serum or urinary calcium) and to decrease serum PTH concentration, many physicians are afraid to give vitamin D to already hypercalcemic PHPT patients. It is possible that, in some patients, a persistent vitamin D deficiency induces, in the long-term, an autonomous secretion of PTH (i.e. tertiary hyperparathyroidism). The mechanism by which this could occur is unclear however. Finally, as many, otherwise normal, subjects with vitamin D insufficiency may have an increased serum PTH level we believe that those with vitamin D insufficiency should be excluded from a reference population for serum PTH levels. By doing that, we found that the upper normal limit for serum PTH was 25–30% lower than in the whole population.

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Résumé

Le déficit en vitamine D et l'hyperparathyroïdie primitive (HPP) sont deux situations fréquentes, en particulier chez la femme ménopausée. Il est même suggéré que le déficit en vitamine D est encore plus fréquent dans l'HPP que dans la population générale en raison d'une accélération de la conversion de la 25-hydroxy vitamine D en composés di-hydroxylés, 1,25 et 24,25-dihydroxy vitamine D. Bien que plusieurs études aient montré que le phénotype de l'HPP est plus sévère lorsqu'un déficit en vitamine D coexiste (adénomes plus volumineux, hormone parathyroïdienne (PTH) plus élevée, atteinte osseuse plus sévère), et que la supplémentation par la vitamine D chez des patients HPP et insuffisants en vitamine D avec une calcémie inférieure à 3 mmol/L n'induit pas d'élévation de la calcémie ou de la calciurie et permet une baisse de la PTH, la majorité des médecins est effrayé de traiter par vitamine D des patients qui sont déjà hypercalcémiques. De plus, il est possible que chez certains patients, la persistance au long cours d'un déficit profond en vitamine D avec hyperparathyroïdie secondaire soit responsable d'une autonomisation de la sécrétion de PTH (une hyperparathyroïdie « tertiaire »). Enfin, comme de nombreux sujets apparemment en bonne santé ont une insuffisance en vitamine D qui peut induire une stimulation de la sécrétion de PTH, nous pensons que les valeurs de référence pour le dosage de la PTH doivent être établies chez des sujets qui n'ont pas d'insuffisance en vitamine D. En faisant cela, nous avons montré que la limite supérieure des « normes » de PTH était en général 25 à 35% plus basse que ce qu'on obtient en population générale.

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1. Introduction

Primary hyperparathyroidism (PHPT) and vitamin D insufficiency are two frequent conditions. The diagnosis of vitamin D insufficiency is based on the measurement of 25-hydroxy vitamin D (25OHD) in serum/plasma. Depending on the studied

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population, and on the 25OHD cut-off value below which it is defined (50, 75, 80, or 100 nmol/L for example), vitamin D insufficiency is found in approximately 30–50% to almost 100% of cases [1]. According to population-based surveys, PHPT is now considered as the third most frequent endocrinopathy (after diabetes mellitus and thyroid diseases), with a prevalence of approximately 1/1000 in the general population but one to 3% (and sometimes more) in menopausal women depending on the biological diagnostic criteria used [2]. The diagnosis of PHPT is usually based on the measurement of serum calcium and parathyroid hormone (PTH) levels showing a high (or inappropriately high normal) PTH level in the presence of hypercalcemia [3]. Less obvious presentations such as normocalcemic PHPT are more and more frequently detected [4]. It is of note that, due to more systematic measurement of serum calcium, PHPT has shifted from a rare disease with severe bone and/or renal complications to a frequent, mostly asymptomatic disease. The treatment of PHPT consists in the surgical removal of the diseased parathyroid (PT) gland(s) [5] although alternative medical treatments are possible in case of contra-indication to surgery or anaesthesia [6]. It must be underlined that parathyroidectomy (PTX) is not systematically proposed to any PHPT patient and criteria for PTX (based on risk/benefit ratio) are regularly updated during consensus conferences, the latest recommendations having been published in 2009 [7].

2. Vitamin D insufficiency/deficiency as a consequence or a cause of primary hyperparathyroidism

There are potential reasons for PHPT causing vitamin D insufficiency. Increased conversion of 25OHD into calcitriol and/or 24-hydroxylated vitamin D compounds is probably the most frequently evoked reason. However, calcitriol levels and 1-alpha hydroxylase activity are both clearly elevated in PHPT but the serum molar ratio of calcitriol to 25OHD (approximately 1/1000) makes that the excessive synthesis of calcitriol in PHPT is unlikely an explanation for an important decrease in 25OHD serum levels. In line with that, Christensen et al. found a similar mean 25OHD concentration in 147 PHPT patients and 66 patients with familial hypercalcemia-hypocalciuria (FHH) who had similar level of calcemia despite frankly higher PTH and calcitriol levels in the PHPT group [8], while Silverberg et al. found no association between the serum levels of 25OHD and calcitriol in 126 PHPT patients [9]. The high calcitriol levels found in PHPT patients may stimulate the synthesis of 24-hydroxylated compounds as the 24-hydroxylase enzyme is highly inducible by calcitriol [10] although it is said also to be reduced by PTH [11]. Accordingly, 25OHD serum levels should thus be lower in PHPT patients than in controls. However, few studies that reported 25OHD levels in PHPT patients compared the percentage of low values with carefully matched controls. When analyzing these studies, low vitamin D status seems more frequent in the more severe forms of PHPT than in matched controls whereas this is less obvious in mild PHPT [8].

It is well-known that long-lasting secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) may become autonomous, a situation commonly called tertiary

hyperparathyroidism (THPT) which resembles PHPT (hypercalcemia and high PTH levels) albeit usually associated with hyperphosphatemia and characterized by hyperplasia of the four PT glands rather than isolated adenomas (although adenomas are also found) [12]. THPT frequently persists after renal transplantation and has also been reported in patients treated with phosphorus for hypophosphatemic rickets [13]. It is thus possible that long-lasting SHPT due to vitamin D deficiency leads to PT hyperplasia and adenoma eventually as suggested previously [14]. It must be said however that, on one hand, many persons worldwide are almost permanently vitamin D deficient without developing PHPT, and, on the other hand, that not all PHPT patients are vitamin D deficient. Decreased expression of the vitamin D receptor (VDR) and the calcium-sensing receptor (CaSR) in the hyperplastic and adenomatous PT glands is hypothesized to be, at least in part, responsible for the high proliferation of the PT cells and thus the progression of PHPT [15]. CaSR expression in the PT is up-regulated by calcitriol [16] whereas VDR is also stimulated by calcitriol and inhibited by PTH. It is thus likely that, in some patients, profound and sustained SHPT due to vitamin D deficiency induces a desensitization of parathyroid VDR which leads to a decreased expression of CaSR and a shift in the calcium set-point. The reason why some PT but not others may then develop a monoclonal growth leading to a PT adenoma is however unclear. Over-expression of the cyclin *D1/PRAD1* gene has been implicated in the pathogenesis of a significant number of sporadic PT adenomas, while somatic mutations of the *MEN1* gene have been found in some PT adenomas [17]. *VDR* and *CYP27B1* genes have also been hypothesized as candidate tumour suppressor genes conferring to the PT the property of monoclonality. However, no mutation of *CYP27B1* [18] or *VDR* [19] genes have been found in genomic DNA from PT adenomas. *VDR* polymorphism has been related to the frequency of PHPT in some studies (60% of bb in 90 postmenopausal PHPT women compared to 33% in postmenopausal controls [20]) but not in others [21]. Finally, as the nuclear factor kappaB (NF-KB) pathway seems implicated in the development of PT tumorigenesis [22], and as calcitriol has been reported to inhibit NF-KB pathway in different systems [23], influence of vitamin D deficiency on the PT cells proliferation due to NF-KB activation is another research topic.

3. Vitamin D deficiency and the presentation of primary hyperparathyroidism

Whether a cause or a consequence of PHPT (or both), vitamin D deficiency has been clearly associated with a more severe phenotype of PHPT in many studies which reported higher PTH levels and larger tumours [24–29], lower bone mineral density (BMD) especially at sites rich in cortical bone, and/or higher bone turnover [9,30,31], and even an increased risk of fracture [32] in PHPT patients with vitamin D deficiency compared to those with a “normal” vitamin D status. Furthermore, PHPT patients with vitamin D deficiency have worse post-PTX outcomes such as SHPT, delayed bone recovery, or “hungry bone syndrome”, than those with a normal vitamin D status [33–35]

Table 1
Summary of the studies where primary hyperparathyroidism (PHPT) patients were given vitamin D (or calcifediol).

Study 1st author [ref]	Patients	Vitamin D treatment	Main results
Kantorovitch [37]	5 PHPT patients with 25OHD < 25 nmol/L	50,000 IU ergocalciferol twice weekly for 5 weeks	No increase in serum calcium Decrease in PTH levels Increase in hip or spine BMD
Grey [38]	21 PHPT patients serum calcium < 3 mmol/L 25OHD < 50 nmol/L (mean 27.5 nmol/L)	50,000 IU cholecalciferol weekly for 4 weeks, followed by 50,000 IU cholecalciferol monthly for 11 months	Increase in serum 25OHD to a mean 77.5 nmol/L No increase in serum calcium or phosphorus Decrease (–26%) in serum PTH Decrease in serum total alkaline phosphatase No increase in mean 24-hour calciuria, but two patients became hypercalciuric (> 400 mg/day)
Grubbs [39]	112 PHPT patients	400,000 IU ergocalciferol over a one-month period	No change in serum calcium levels
Tucci [40]	56 PHPT patients with 25OHD < 3 mmol/L	50,000 IU ergocalciferol weekly for 8 weeks followed by a “stabilization” dosage ranging from 800 IU/day to 100,000 IU/month	No change in serum calcium, phosphate, and PTH levels No change in urinary calcium
Isidro [41]	27 PHPT patients	8–16 µg calcifediol/day for one year	Mean 25OHD of 71 nmol/L at one year No change in serum calcium Transient decrease in serum PTH One-third of the patients became hypercalciuric

BMD: bone mineral density.

suggesting that ensuring an optimal post-PTX vitamin D (and nutritional calcium) status is mandatory.

4. Effect of Vitamin D supplementation in primary hyperparathyroidism patients

The results of the above-mentioned studies [24–35] may argue for a beneficial effect of vitamin D supplementation in PHPT patients with a low 25OHD serum level. However, what most physicians remember from their medical studies is that vitamin D deficiency may cause rickets on one hand, and that vitamin D may be potentially toxic on the other hand, vitamin D intoxication being a severe medical condition characterized by symptomatic hypercalcemia and hypercalciuria. It is thus not easy to convince the medical community to give vitamin D to already hypercalcemic PHPT patients, even if they are also vitamin D-deficient. Trials of vitamin D in PHPT patients with coexisting vitamin D deficiency, aiming to evaluate the risk/benefit ratio of this treatment, are thus of paramount importance. An encouraging report of five PHPT patients with low 25OHD serum levels who were given 50,000 IU vitamin D2 twice weekly for 5 weeks showed no increase in serum calcium and an increase in spine and/or hip BMD [36]. The “princeps” study was however published by Grey et al. 5 years later [37]. In this study, 21 PHPT patients with a serum calcium level less than 3 mmol/L and a 25OHD level less than 50 nmol/L were given 50,000 IU vitamin D3/week for one month and 50,000 IU/month for the following 11 months. At the end of the study, 25OHD levels had increased by almost 200%, whereas no increase in serum calcium or phosphate, and a decrease in serum PTH (–26%) and total alkaline phosphatase were recorded. The group mean calciuria did not change but two individual patients became hypercalciuric. Since then, Grubbs et al. [38], and Tucci [39]

reported no change in serum calcium in PHPT patients who received large doses of vitamin D2. Very recently, Isidro et al. reported that, in 27 PHPT patients who received 8–16 µg calcifediol/day for one year, serum calcium did not change while serum PTH decreased transiently, but one-third of the patients became hypercalciuric [40]. This may be due to the use of calcifediol (25OHD) instead of vitamin D2 or vitamin D3 as in [36–39] but it is somewhat surprising regarding the 25OHD levels reached in these patients (71 nmol/L in mean), which were quite similar (or even lower) than in the previous studies [37–39]. These studies, summarized in Table 1, are consistent with the recommendation of the expert panel [3] to measure routinely 25OHD levels in any PHPT patient and to treat with vitamin D if the serum 25OHD level is less than 50 nmol/L. They also recommended performing randomized trials with vitamin D supplementation to better define the optimal 25OHD levels for individuals with PHPT.

5. Vitamin D and the diagnosis of primary hyperparathyroidism

As indicated above, the diagnosis of PHPT is based on the concomitant finding of high serum calcium and PTH levels. In our clinical practice, probably because of the growing practice of biological testing in osteoporosis patients to exclude secondary causes of low bone mass and/or fracture, we are however more and more frequently confronted with difficult diagnoses presenting with mild hypercalcemia and normal PTH, normocalcemia and high PTH (normo-calcemic PHPT), or even high normal calcemia and PTH. In this context, the reliability of the reference values for serum PTH is of great importance. PTH reference values are established in an apparently healthy population. The problem is that vitamin D status of the various reference populations recruited to establish PTH normal values

Table 2

Comparison of parathyroid hormone (PTH) reference values (ng/L) provided by the manufacturers of 10 commercial kits with reference values obtained in our units in a population of 240 healthy subjects (120 men, 120 women) with a serum 25-hydroxy vitamin D (25OHD) greater than 30 ng/mL and an eGFR (MDRD formula) greater than 60 mL/min/1.73 m². With all these PTH assays, our upper normal limit is lower than those from the manufacturer. The difference is sometimes marginal (Architect, or Vitros assay), but sometimes huge (Access 2). It is mostly in the 25–35% range. The obvious consequence is that, depending on the reference values that are used with a given assay, a patient may be considered as having a PTH level that is either normal or high.

Assay	Manufacturer's reference values	Our laboratories' reference values
<i>2nd generation assays</i>		
Architect (Abbott)	15–68	16–65
Immulite (Siemens)	12–65	0.5–50
Vitros (Ortho-clinical)	7.5–53	11–48
Liaison N-tact (DiaSorin)	17.3–73	21–68
TiPTH (Scantibodies)	14–66	8–50
Elecsys (Roche Diagnostics)	15–65	14–50
DiaSorin IRMA (DiaSorin)	13–54	7–36
Access 2 (Beckman-Coulter)	12–88	10–47
<i>3rd generation assays</i>		
CA-PTH (Scantibodies)	5–39	7–31
Liaison 3 ^e G (DiaSorin)	5.5–38	5–26

had not usually been taken into account [41–45]. As vitamin D deficiency/insufficiency is highly frequent in the general population on one hand [46], and as it may induce an increase in PTH secretion on the other hand [47], including only vitamin D sufficient subjects in the reference population may have a significant impact on PTH normal values [48]. We have recently compared the PTH reference values provided by the manufacturers of 10 commercial PTH kits with those obtained in our units in 240 healthy persons with a serum 25OHD levels greater than 30 ng/mL and an estimated glomerular filtration rate greater than 60 mL/min/1.73m² [49]. As shown in Table 2, our upper normal value was lower than the manufacturer's ones. The difference was marginal with some kits but huge (up to nearly 50%) with other kits. It was in the range of 25–35% for most kits. We thus fully agree with the expert panel who published the last recommendations for the diagnosis of PHPT [3] stating that "... Further studies are required to establish reference intervals for second- and third-generation PTH assays using large population cohorts that are comprised of vitamin D-replete subjects and also to stratify according to age, sex, race, GFR, and possibly BMI".

As stressed above, using PTH reference values, which take vitamin D status and renal function into account will probably decrease the upper limit of normal of most PTH assays by 25–35% when compared to what is generally used. The evident consequence is that above-normal PTH concentrations will be found more often in clinical practice. On one hand, this will improve the diagnostic sensitivity of PTH measurements as serum PTH will be more frequently elevated in patients with PHPT, but on the other hand, this will also induce an increase in the detection of high serum PTH in otherwise normocalcemic patients. In most cases, this will reflect SHPT for which a cause must be searched. Above all, it will be of paramount importance

to prescribe vitamin D supplementation in order to increase the 25OHD serum level when it is initially low (even marginally). In our experience, and due the measurement uncertainty of the 25OHD assay [50], obtaining a serum level of 40 ng/mL or more is necessary to be confident with the fact that the high PTH level was not due to vitamin D insufficiency. Only if no causes of SHPT are identified, and especially if calcemia is in the upper half of the normal values, the diagnosis of normocalcemic PHPT may be suspected. In this situation, we usually perform an intravenous calcium load test to evaluate how PTH decreases when ionized calcium increases far above normal.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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