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Vitamin D and primary hyperparathyroidism (PHPT)☆

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ABSTRACT

Vitamin D deficiency and 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 25OHD into calcitriol or 24-hydroxylated compounds. Although several studies have reported worsening of PHPT phenotype (larger tumours, higher PTH levels, more severe bone disease) when vitamin D deficiency coexists whereas vitamin D supplementation in PHPT patients with a serum calcium level <3 mmol/L has been shown to be safe (no increase in serum or urinary calcium) and to decrease serum PTH concentration, that many physicians are afraid to give vitamin D to already hypercalcemic PHPT patients. On the other hand, 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.

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 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% 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 1–3% (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]. In most cases (80–85%), PHPT is due to a single benign adenoma although multiple adenoma or hyperplasia of the 4 parathyroid (PT) glands are also quite frequently found [5]. PHPT is also a frequent feature of multiple endocrine neoplasia (MEN) especially MEN1, while the biological and clinical presentation of the rare cases of PT carcinoma (less than 1% of the published series of PHPT) is similar to a severe PHPT [6]. 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 PT gland(s) [7] although alternative medical treatments are possible in case of contra-indication to surgery or anaesthesia [8]. 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 [9].

2. VTD insufficiency/deficiency as a consequence or a cause of PHPT

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 fre-

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quently evoked reason. Studies have shown that the half-life of tritiated 25OHD was shortened in PHPT patients compared to healthy controls and normalized after PTX [10]. 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 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 [11], while Silverberg et al. found no association between the serum levels of 25OHD and calcitriol in 126 PHPT patients [12]. 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 [13] although it is said also to be reduced by PTH [14]. Another reason for a decrease in 25OHD levels in PHPT may be a decreased skin synthesis of cholecalciferol either by a direct stimulatory effect of elevated calcitriol on melanin synthesis [15], or because of a lack of outdoor activity, and thus of exposure to UVB radiation, in those with symptoms (fatigue, muscle weakness, etc.) that are common in PHPT and may be enhanced by vitamin D deficiency (although, as underlined above, most PHPT patients are asymptomatic). Finally, as PHPT patients are usually heavier than matched controls, the hypothesis of decreased 25OHD due to fat sequestration of vitamin D has been suggested [16]. According to the above-mentioned reasons, 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. For example, our group reported that the median 25OHD serum concentration of 72 consecutive patients with PHPT (with a very mild to a very severe clinical and biological presentation), 62.7 years old in mean, was 22.5 nmol/L, 93% of them with a concentration <50 nmol/L [17]. Although not compared to a matched control group, this may seem a very low concentration compared to the mean 43 nmol/L found in the SUVIMAX study in the French general population living, like our patients, in the northern part of France [18]. It is however consistent with the mean levels of 20–30 nmol/L found in the EURONUT-SENECA study on independent older persons living in different Southern European countries [19]. In fact, the rare studies that compared the 25OHD levels of PHPT patients to those of matched controls yielded conflicting results. For example, the mean 25OHD level of 20 PHPT patients from India was 21 nmol/L compared to a mean of 20.8 nmol/L in 14 matched controls [20], whereas Christensen et al. [11] found that 25OHD levels were not different in 147 PHPT patients, 66 patients with FHH and 46 FHH-matched controls. Conversely, Moosgaard et al. [21] reported that the 25OHD level was <50 nmol/L in 81% of 289 PHPT patients (here again the clinical and biological presentation of PHPT ranged from very mild to severe) compared to 60% of 289 matched controls ($p < 0.01$) with a significant inverse correlation between 25OHD and PTH levels in the PHPT patients as also reported in numerous other studies [17,21–25]. Thus, 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.

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 4 PT glands rather than isolated adenomas (although adenomas are also found) [26]. THPT frequently persists after renal transplantation and has also been reported in patients treated with phosphorus for hypophosphatemic rickets [27]. It is thus possible that long-lasting SHPT due to vitamin D deficiency leads to PT hyperplasia and adenoma eventually as suggested previously [28]. It must be said however that, on the 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 VTD-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 [29]. CaSR expression in the PT is up-regulated by calcitriol [30] 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 [31]. 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 [32] or VDR [33] 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 [34]) but not in others [35]. Finally, as the nuclear factor kappaB (NF-κB) pathway seems implicated in the development of PT tumorigenesis [36], and as calcitriol has been reported to inhibit NF-κB pathway in different systems [37], influence of vitamin D deficiency on the PT cells proliferation due to NF-κB activation is another research topic.

3. Vitamin D deficiency and the presentation of PHPT: effect of vitamin D supplementation in PHPT patients

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 [17,21–25], lower bone mineral density (BMD) especially at sites rich in cortical bone, and/or higher bone turnover [12,38,39], and even an increased risk of fracture [40] in PHPT patients with vitamin D deficiency compared to those with a "normal" vitamin D status. Although some studies did not find this relationship between vitamin D deficiency and more severe bone disease in PHPT [41,42], the results of the above-mentioned studies [17,21–25,12,38–40] may argue for a beneficial effect of vitamin D supplementation in PHPT patients with a low 25OHD serum level. 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 [43–45] suggesting that ensuring an optimal post-PTX vitamin D (and nutritional calcium) status is mandatory. However, what most physicians remember from their medical studies is that vitamin D deficiency may cause rickets on the 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 5 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

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

Study 1st author [ref]	Patients	Vitamin D treatment	Main results
Kantorovitch [46]	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 [47]	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-h calciuria, but two patients became hypercalciuric (>400 mg/day)
Grubbs [48]	112 PHPT patients	400,000 IU ergocalciferol over a 1-month period	No change in serum calcium levels
Tucci [49]	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 [50]	27 PHPT patients	8–16 μg calcifediol/day for 1 year	Mean 25OHD of 71 nmol/L at 1 year. No change in serum calcium. Transient decrease in serum PTH. One-third of the patients became hypercalciuric

BMD, bone mineral density.

BMD [46]. The "princeps" study was however published by Grey et al. 5 years later [47]. In this study, 21 PHPT patients with a serum calcium level <3 mmol/L and a 25OHD level <50 nmol/L were given 50,000 IU vitamin D3/week for 1 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. [48] and Tucci [49] 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 1 year, serum calcium did not change while serum PTH decreased transiently, but one-third of the patients became hypercalciuric [50]. This may be due to the use of calcifediol (25OHD) instead of vitamin D2 or vitamin D3 as in [46–49] 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 [47–49]. 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 <50 nmol/L. They also recommended to better define the optimal 25OHD levels for individuals with PHPT by including randomized trials with vitamin D supplementation. In addition, we propose to quantify the calcium intakes of the patients during the day(s) of urine collection when 24-h calciuria is measured in vitamin D-treated PHPT patients, data that are lacking in the above-mentioned studies [45–50].

4. Vitamin D and the diagnosis of PHPT

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 (normocalcemic PHPT), or even high normal calcemia and PTH. In this context, the reliability of the reference values for serum PTH is of great importance. Contrary to the 25OHD reference values which must be "health-based" [51] with still non consensual cut-offs defining an optimal vitamin D status, the reference values for serum PTH levels are "population-based". This means measuring the PTH concentrations in a reference population and using either the parametric (mean ± 2SD) or the non-parametric method depending on the distribution of the variable to propose reference values. Exclusion criteria for this population are highly important and, in addition to common exclusion criteria (known chronic disease, obesity, tobacco and alcohol excess, etc.), should include any cause for an altered PTH secretion. This includes hypo- or hypercalcemia, low GFR (<60 mL/min/1.73 m^2?), drugs known to influence PTH secretion (anticonvulsant, lithium, phosphorus, thiazide, loop diuretic, bisphosphonate, etc.), very low calcium intakes. Thus, why should we include (otherwise normal) subjects with vitamin D insufficiency as it is widely demonstrated that PTH levels may be increased in these patients and that their PTH usually decreases when they are given vitamin D [51]? This point is important because vitamin D insufficiency is very frequent in the general population [51–53], and thus should be prevalent in an otherwise apparently healthy group recruited to establish reference values for PTH. However, excluding vitamin D insufficient subjects from the reference group requires measuring the 25OHD level beforehand in all subjects, a practice which complicates the establishment of reference values, and which was not considered in most studies which provided serum PTH reference values for different immunoassays [54–58]. Nevertheless, we have demonstrated that excluding subjects with low serum 25OHD levels (<20 ng/mL of DiaSorin RIA-equivalent) from a reference population decreased the upper normal limit for serum PTH by 25–35% depending on the assay considered, compared to the initial reference populations [59,60] (Fig. 1). We have then verified that our PTH reference values which take vitamin D status into account did not induce a decrease in diagnostic specificity [61]. We must acknowledge that our "new" reference values were derived from an initial reference population of healthy Caucasian subjects aged 60–79 years, with a normal body mass index (BMI) and an almost normal renal function (estimated creatinine clearance >50 mL/min in all subjects) and thus, that they may be not applicable to other populations as discussed in [62]. Indeed, several other determinants of PTH levels should also be tested such as age and GFR [63], nutritional calcium

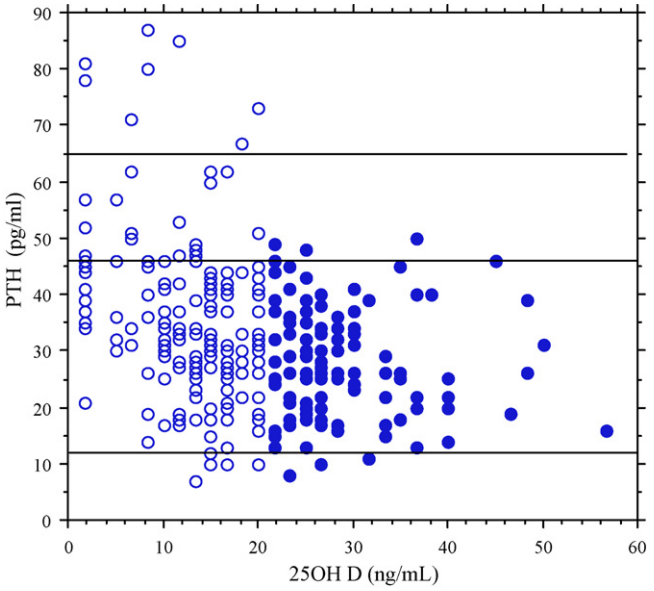

Fig. 1. Scatter plot of the 25OHD and PTH concentrations (Allegro Intact PTH assay) measured in 280 healthy Caucasian subjects, 140 men and 140 women, aged 60–79 years living in the Paris, France, area. In this population, the 95% confidence interval of the PTH levels was 12–65 pg/mL and is represented by the lower and the upper horizontal lines. Among these subjects, only 113 (40.4%) had a serum 25OHD concentration >20 ng/mL (50 nmol/L) when expressed in DiaSorin RIA-equivalent. The 97.5th percentile of the PTH levels in these 113 subjects was 46 pg/mL (i.e. 29.2% lower than in the whole population) and is represented by the middle horizontal line.

intake of the population [64], race [65], BMI [61]. Indeed, the PTH levels will usually be higher in mean if the subjects are older, have a decreased GFR, and/or poor calcium intakes, are black or have more fat mass. Note however that 25OHD is also usually lower in the elderly than in the young, the black than the Caucasian, the obese than the thin, and that it will be necessary to test whether these differences persist when all subjects are vitamin D-replete. 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." We also believe that "dynamic" PTH reference intervals obtained in normal subjects according to the above-mentioned inclusion/exclusion criteria, in whom serum calcium is acutely modified (i.e. increased by infusion of $CaCl_2$ or calcium gluconate) as proposed by Lepage et al. [66] may significantly improve the diagnostic sensitivity for PHPT by improving the evaluation of the adequacy between serum PTH and calcium concentrations.

As stressed above, using PTH reference values which take vitamin D status into account will probably decrease the upper limit of normal by 25–35% when compared to what is generally obtained when vitamin D status is not considered. The evident consequence is that above-normal PTH concentrations will be found more often in clinical practice. On the 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. Only if none of these causes are identified, and especially if calcemia is in the upper half of the normal values, the diagnosis of normocalcemic PHPT may be suspected [3].

References

[1] M. Holick, Vitamin D deficiency, N. Engl. J. Med. 357 (July (3)) (2007) 266–281.
[2] E. Lundgren, E.G. Hagström, J. Lundin, K. Winnerbäck, L.J. Ross, S. Ljunghall, J. Rastad, Primary hyperparathyroidism revisited in menopausal women with serum calcium in the upper normal range at population-based screening 8 years ago, World J. Surg. 26 (August (8)) (2002) 931–936.
[3] R. Eastell, A. Arnold, M.L. Brandi, E.M. Brown, P. D'Amour, D.A. Hanley, D.S. Rao, M.R. Rubin, D. Goltzman, S.J. Silverberg, S.J. Marx, M. Peacock, L. Mosekilde, R. Bouillon, E.M. Lewieki, Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop, J. Clin. Endocrinol. Metab. 94 (February (2)) (2009) 340–350.
[4] S.J. Silverberg, E.M. Lewiecki, L. Mosekilde, M. Peacock, M.R. Rubin, Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop, J. Clin. Endocrinol. Metab. 94 (February (2)) (2009) 351–365.
[5] E. Szabo, E. Lundgren, C. Juhlin, S. Ljunghall, G. Akerström, J. Rastad, Double parathyroid adenoma, a clinically nondistinct entity of primary hyperparathyroidism, World J. Surg. 22 (July (7)) (1998) 708–713.
[6] C. Marcocci, F. Cetani, M.R. Rubin, S.J. Silverberg, A. Pinchera, J.P. Bilezikian, Parathyroid carcinoma, J. Bone Miner. Res. 23 (December (12)) (2008) 1869–1880.
[7] R. Udelsman, J.L. Pasieka, C. Sturgeon, J.E. Young, O.H. Clark, Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop, J. Clin. Endocrinol. Metab. 94 (February (2)) (2009) 366–372.
[8] A. Khan, A. Grey, D. Shoback, Medical management of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop, J. Clin. Endocrinol. Metab. 94 (February (2)) (2009) 373–381.
[9] J.P. Bilezikian, A.A. Khan, J.T. Potts, Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop, J. Clin. Endocrinol. Metab. 94 (February (2)) (2009) 335–339.
[10] M.R. Clements, M. Davies, D.R. Fraser, G.A. Lumb, E.B. Mawer, P.H. Adams, Metabolic inactivation of vitamin D is enhanced in primary hyperparathyroidism, Clin. Sci. (Lond.) 73 (December (6)) (1987) 659–664.
[11] S.E. Christensen, P.H. Nissen, P. Vestergaard, L. Heickendorff, L. Rejnmark, K. Brixen, L. Mosekilde, Plasma 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and parathyroid hormone in familial hypocalciuric hypercalcemia and primary hyperparathyroidism, Eur. J. Endocrinol. 159 (December (6)) (2008) 719–727.
[12] S.J. Silverberg, E. Shane, D.W. Dempster, J.P. Bilezikian, The effects of vitamin D insufficiency in patients with primary hyperparathyroidism, Am. J. Med. 107 (December (6)) (1999) 561–567.
[13] A.J. Brown, A. Dusso, E. Slatopolsky., Vitamin D, Am. J. Physiol. 277 (August (2 Pt 2)) (1999) F157–F175.
[14] H.L. Henry, A.W. Norman, Vitamin D: metabolism and biological actions, Annu. Rev. Nutr. 4 (1984) 493–520.
[15] J. Hosoi, E. Abe, T. Suda, T. Kuroki, Regulation of melanin synthesis of B16 mouse melanoma cells by 1 alpha, 25-dihydroxyvitamin D3 and retinoic acid, Cancer Res. 45 (April (4)) (1985) 1474–1478.
[16] M.J. Bolland, A.B. Grey, G.D. Gamble, I.R. Reid., Association between primary hyperparathyroidism and increased body weight: a meta-analysis, J. Clin. Endocrinol. Metab. 90 (March (3)) (2005) 1525–1530.
[17] P. Boudou, F. Ibrahim, C. Cormier, E. Sarfati, J.C. Souberbielle, A very high incidence of low 25 hydroxy-vitamin D serum concentration in a French population of patients with primary hyperparathyroidism, J. Endocrinol. Invest. 29 (June (6)) (2006) 511–515.
[18] M.C. Chapuy, P. Preziosi, M. Maamer, S. Arnaud, P. Galan, S. Hercberg, P.J. Meunier, Prevalence of vitamin D insufficiency in an adult normal population, Osteoporos Int. 7 (5) (1997) 439–443.
[19] R.P. Van der Wielen, M.R. Löwik, H. van den Berg, L.C. de Groot, J. Haller, O. Moreiras, W.A. van, Staveren, Serum vitamin D concentrations among elderly people in Europe, Lancet 346 (July (8969)) (1995) 207–210.
[20] C.V. Harinarayan, N. Gupta, N. Kochupillai, Vitamin D status in primary hyperparathyroidism in India, Clin. Endocrinol. (Oxf.) 43 (September (3)) (1995) 351–358.
[21] B. Moosgaard, P. Vestergaard, L. Heickendorff, F. Melsen, P. Christiansen, L. Mosekilde, Vitamin D status, seasonal variations, parathyroid adenoma weight and bone mineral density in primary hyperparathyroidism, Clin. Endocrinol. (Oxf.) 63 (November (5)) (2005) 506–513.
[22] D.S. Rao, M. Honasoge, G.W. Divine, E.R. Phillips, M.W. Lee, M.R. Ansari, G.B. Talpos, A.M. Parfitt, Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications, J. Clin. Endocrinol. Metab. 86 (May (5)) (2001) 2328.
[23] B. Moosgaard, P. Vestergaard, L. Heickendorff, F. Melsen, P. Christiansen, L. Mosekilde, Plasma 25-hydroxyvitamin D and not 1,25-dihydroxyvitamin D is associated with parathyroid adenoma secretion in primary hyperparathyroidism: a cross-sectional study, Eur. J. Endocrinol. 155 (August (2)) (2006) 237–244.
[24] H. Raef, S. Ingemansson, S. Sobhi, A. Sultan, M. Ahmed, M. Chaudhry, The effect of vitamin D status on the severity of bone disease and on the other features of primary hyperparathyroidism (pHPT) in a vitamin D deficient region, J. Endocrinol. Invest. 27 (October (9)) (2004) 807–812.
[25] N. Ozbey, Y. Erbil, E. Ademoğlu, S. Ozarmağan, U. Barbaros, A. Bozbora, Correlations between vitamin D status and biochemical/clinical and pathological parameters in primary hyperparathyroidism, World J. Surg. 30 (March (3)) (2006) 321–326.

[26] E. Kebebew, O.Y. Duh, O.H. Clark, Tertiary hyperparathyroidism: histologic patterns of disease and results of parathyroidectomy, Arch. Surg. 139 (September (9)) (2004) 974–977.
[27] S.A. Rivkees, G. el-Hajj-Fuleihan, E.M. Brown, J.D. Crawford, Tertiary hyperparathyroidism during high phosphate therapy of familial hypophosphatemic rickets, J. Clin. Endocrinol. Metab. 75 (December (6)) (1992) 1514–1518.
[28] G. Akerström, C. Rudbeerg, L. Grimelius, R. Bergström, H. Johansson, S. Ljunghall, J. Rastad, Histologic parathyroid abnormalities in an autopsy series, Hum. Pathol. 17 (May (5)) (1986) 520–527.
[29] S. Yano, T. Sugimoto, T. Tsukamoto, K. Chihara, A. Kobayashi, S. Kitazawa, S. Maeda, R. Kitazawa, Decrease in vitamin D receptor and calcium-sensing receptor in highly proliferative parathyroid adenomas, Eur. J. Endocrinol. 148 (April (4)) (2003) 403–411.
[30] A.J. Brown, M. Zhong, J. Finch, C. Ritter, R. McCracken, J. Morrissey, E. Slatopolsky, Rat calcium-sensing receptor is regulated by vitamin D but not by calcium, Am. J. Physiol. 270 (March (3 Pt 2)) (1996) F454–F460.
[31] A. Arnold, T.M. Shattuck, S.M. Mallya, L.J. Krebs, J. Costa, J. Gallagher, Y. Wild, K. Saucier, Molecular pathogenesis of primary hyperparathyroidism, J. Bone Miner. Res. 17 (Suppl. 2) (2002) N30–N36.
[32] K. Lauter, A. Arnold, Analysis of CYP27B1, encoding 25-hydroxyvitamin D-1alpha-hydroxylase, as a candidate tumor suppressor gene in primary and severe secondary/tertiary hyperparathyroidism, J. Bone Miner. Res. 24 (January (1)) (2009) 102–104.
[33] E.H. Samander, A. Arnold, Mutational analysis of the vitamin D receptor does not support its candidacy as a tumor suppressor gene in parathyroid adenomas, J. Clin. Endocrinol. Metab. 91 (December (12)) (2006) 5019–5021.
[34] T. Carling, A. Kindmark, P. Hellman, E. Lundgren, S. Ljunghall, J. Rastad, G. Akerström, H. Melhus, Vitamin D receptor genotypes in primary hyperparathyroidism, Nat. Med. 1 (December (12)) (1995) 1309–1311.
[35] T. Kobayashi, T. Sugimoto, A. Kobayashi, K. Chihara, Vitamin D receptor genotype is associated with cortical bone loss in Japanese patients with primary hyperparathyroidism, Endocr. J. 45 (February (1)) (1998) 123–125.
[36] S. Corbetta, L. Vicentini, S. Ferrero, A. Lania, G. Mantovani, D. Cordella, P. Beck-Peccoz, A. Spada, Activity and function of the nuclear factor kappaB pathway in human parathyroid tumors, Endocr. Relat. Cancer 12 (December (4)) (2005) 929–937.
[37] X. Tan, X. Wen, Y. Liu., Paricalcitol inhibits renal inflammation by promoting vitamin D receptor-mediated sequestration of NF-kappaB signaling, J. Am. Soc. Nephrol. 19 (September (9)) (2008) 1741–1752.
[38] B. Moosgaard, S.E. Christensen, P. Vestergaard, L. Heickendorff, P. Christiansen, L. Mosekilde, Vitamin D metabolites and skeletal consequences in primary hyperparathyroidism, Clin. Endocrinol. (Oxf.) 68 (May (5)) (2008) 707–715.
[39] Y. Inoue, H. Kaji, I. Hisa, T. Tobimatsu, J. Naito, M.F. Iu, T. Sugimoto, K. Chihara, Vitamin D status affects osteopenia in postmenopausal patients with primary hyperparathyroidism, Endocr. J. 55 (March (1)) (2008) 57–65.
[40] E. Nordenström, J. Westerdahl, B. Lindergård, P. Lindblom, A. Bergenfelz, Multifactorial risk profile for bone fractures in primary hyperparathyroidism, World J. Surg. 26 (December (12)) (2002) 1463–1467.
[41] H. Yamashita, S. Noguchi, S. Uchino, S. Watanabe, E. Koike, T. Murakami, T. Fujihira, Y. Koga, T. Masatsugu, H. Yamashita, Vitamin D status in Japanese patients with hyperparathyroidism: seasonal changes and effect on clinical presentation, World J. Surg. 26 (August (8)) (2002) 937–941.
[42] V. Carnevale, G. Manfredi, E. Romagnoli, S. De Geronimo, F. Paglia, J. Pepe, A. Scillitani, E. D'Erasmo, S. Minisola, Vitamin D status in female patients with primary hyperparathyroidism: does it play a role in skeletal damage? Clin. Endocrinol. (Oxf.) 60 (January (1)) (2004) 81–86.
[43] P.V. Pradeep, A. Mishra, G. Agarwal, A. Agarwal, A.K. Verma, S.K. Mishra, Long-term outcome after parathyroidectomy in patients with advanced primary hyperparathyroidism and associated vitamin D deficiency, World J. Surg. 32 (May (5)) (2008) 829–835.
[44] B.R. Untch, M.E. Barfield, M. Dar, D. Dixit, G.S. Leight Jr., J.A. Olson Jr., Impact of 25-hydroxyvitamin D deficiency on perioperative parathyroid hormone kinetics and results in patients with primary hyperparathyroidism, Surgery 142 (December (6)) (2007) 1022–1026.
[45] Z.A. Stewart, A. Blackford, H. Somervell, K. Friedman, E. Garrett-Mayer, A.P. Dackiw, M.A. Zeiger, 25-Hydroxyvitamin D deficiency is a risk factor for symptoms of postoperative hypocalcemia and secondary hyperparathyroidism after minimally invasive parathyroidectomy, Surgery 138 (December (6)) (2005) 1018–1025 (discussion 1025-6).
[46] V. Kantorovitch, M.A. Gacad, L.L. Seeger, J.S. Adams, Bone mineral density increases with vitamin D repletion in patients with coexistent vitamin D insufficiency and primary hyperparathyroidism, J. Clin. Endocrinol. Metab. 85 (October (10)) (2000) 3541–3543.
[47] A. Grey, J. Lucas, A. Horne, G. Gamble, J.S. Davidson, I.R. Reid., Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency, J. Clin. Endocrinol. Metab. 90 (April (4)) (2005) 2122–2126.
[48] E.G. Grubbs, S. Rafeeq, C. Jimenez, L. Feng, J.E. Lee, D.B. Evans, N.D. Perrier, Preoperative vitamin D replacement therapy in primary hyperparathyroidism: safe and beneficial? Surgery 144 (December (6)) (2008) 852–858 (discussion 858-9).
[49] J.R. Tucci, Vitamin D therapy in patients with primary hyperparathyroidism and hypovitaminosis D, Eur. J. Endocrinol. 161 (July (1)) (2009) 189–193.
[50] M.L. Isidro, B. Ruano, Biochemical effects of calcifediol supplementation in mild, asymptomatic, hyperparathyroidism with concomitant vitamin D deficiency, Endocrine 36 (October (2)) (2009) 305–310.
[51] P. Lips., Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications, Endocr. Rev. 22 (August (4)) (2001) 477–501.
[52] M.C. Chapuy, P. Preziosi, M. Maamer, S. Arnaud, P. Galan, S. Hercberg, P.J. Meunier, Prevalence of vitamin D insufficiency in an adult normal population, Osteoporos Int. 7 (1997) 439–443.
[53] R. Heaney, Vitamin D: how much do we need and how much is too much? Osteoporos Int. 11 (2000) 553–555.
[54] S. Nussbaum, R. Zahradnik, J. Lavigne, G. Brennan, K. Nozawa-Ung, L. Kim, H.T. Keutmann, C. Wang, J.T. Potts, G. Segre, Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia, Clin. Chem. 33 (1987) 1364–1367.
[55] E. Blind, H. Schmidt-Gayk, S. Scharla, D. Flentje, S. Fischer, U. Göhring, W. Hitzler, Two-site assay of intact parathyroid hormone in the investigation of primary hyperparathyroidism and other disorders of calcium metabolism compared with a mid-region assay, J. Clin. Endocrinol. Metab. 67 (1988) 353–360.
[56] D. Endres, R. Villanueva, C. Sharp Jr., F. Singer, Immunochemiluminometric and immunoradiometric determinations of intact and total immunoreactive parathyrin: performance in the differential diagnosis of hypercalcemia and hypoparathyroidism, Clin. Chem. 37 (1991) 162–168.
[57] W. Ratcliffe, D. Heath, M. Ryan, S. Jones, Performance and diagnostic application of a two-site immunometric assay for parathyrin in serum, Clin. Chem. 35 (1989) 1957–1961.
[58] P. Gao, S. Scheibel, P. D'Amour, M. John, S. Rao, H. Schmidt-Gayk, T. Cantor, Development of a novel immunoradiometric assay exclusively for biologically active whole parathyroid hormone 1–84: implication for improvement of accurate assessment of parathyroid function, J. Bone Miner. Res. 16 (2001) 605–614.
[59] J.C. Souberbielle, C. Cormier, C. Kindermans, P. Gao, T. Cantor, F. Forette, E.E. Baulieu, Vitamin D status and redefining serum parathyroid hormone reference range, J. Clin. Endocrinol. Metab. 86 (2001) 3086–3090.
[60] J.C. Souberbielle, V. Fayol, C. Sault, E. Lawson-Body, A. Kahan, C. Cormier, Assay-specific decision limits for two new automated parathyroid hormone and 25-hydroxyvitamin D assays, Clin. Chem. 51 (2005) 395–400.
[61] J.C. Souberbielle, E. Lawson-Body, B. Hammadi, E. Sarfati, A. Kahan, C. Cormier, The use in clinical practice of parathyroid hormone normative values established in vitamin D-sufficient subjects, J. Clin. Endocrinol. Metab. 88 (2003) 3501–3504.
[62] J.F. Aloia, M. Feuerman, J.K. Yeh., Reference range for serum parathyroid hormone, Endocr. Pract. 12 (2006) 137–144.
[63] R. Vieth, Y. Ladak, P.G. Walfish, Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D, J. Clin. Endocrinol. Metab. 88 (2003) 185–191.
[64] J.F. Aloia, S.A. Talwar, S. Pollack, M. Feuerman, J.K. Yeh., Optimal vitamin D status and serum parathyroid hormone concentrations in African American women, Am. J. Clin. Nutr. 84 (2006) 602–609.
[65] N.H. Bell, A. Greene, S. Epstein, M.J. Oexmann, S. Shaw, J. Shary, Evidence for alteration of the vitamin D-endocrine system in blacks, J. Clin. Invest. 6 (1985) 470–473.
[66] R. Lepage, S. Whittom, S. Bertrand, G. Bahsali, P. D'Amour, Superiority of dynamic over static reference intervals for intac, midmolecule, and C-terminal parathyrin in evaluating calcemic disorders, Clin. Chem. 38 (1992) 2129–2135.