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Primary hyperparathyroidism

Is vitamin D supplementation safe?

Background
Vitamin D deficiency is commonly seen in patients with primary hyperparathyroidism. However, there is a widespread reluctance to provide vitamin D supplementation to this group of patients.

Objective
This article examines the relationship between vitamin D deficiency and primary hyperparathyroidism and the effects of vitamin D supplementation.

Conclusion
Vitamin D deficiency exacerbates primary hyperparathyroidism and vice versa. With care, vitamin D supplementation can safely be given to selected patients with asymptomatic primary hyperparathyroidism and is suggested before deciding on medical or surgical management. Monitoring serum calcium concentration and urinary calcium excretion is recommended while achieving vitamin D repletion.

Keywords: vitamin D; primary hyperparathyroidism

In recent years vitamin D deficiency and supplementation have received considerable attention, not only in the context of bone health, but also with regard to overall physical and mental functioning.[1] One patient population targeted for vitamin D supplementation, older individuals at risk of osteoporosis, is also the population in which primary hyperparathyroidism (PHPT) is most prevalent. As vitamin D and parathyroid hormone (PTH) are both calciotropic hormones that increase serum calcium concentration, the question arises: is it safe to provide vitamin D supplementation in vitamin D deficient individuals with known primary hyperparathyroidism?

The role of vitamin D and parathyroid hormone in calcium metabolism

Vitamin D is a steroid prohormone produced in the skin in response to ultraviolet light. It is also present in variable amounts in the diet, as vitamin D_2 (ergocalciferol) from plants or vitamin D_3 (cholecalciferol) from animal derived foods. Vitamin D is converted to its active form by two-stage hydroxylation: 25-hydroxylation, predominantly in the liver, to give 25-hydroxyvitamin D (25-OHD), then 1α-hydroxylation, predominantly in the kidney and regulated by PTH, to give the active metabolite 1,25-dihydyroxyvitamin D. 25-hydroxyvitamin D is measured to determine adequacy of vitamin D stores, with concentrations of 25-OHD of less than 60 nmol/L typically reflecting vitamin D deficiency.[2,3] Below this concentration, secondary markers of vitamin D deficiency occur such as increases in PTH levels and urinary bone resorption markers. Deficiency cutoffs may vary according to the assays used by different laboratories.[3] Vitamin D supplementation has been shown to be safe in most ambulant subjects.[4]

Parathyroid hormone and vitamin D are involved in homeostatic mechanisms controlling serum calcium ion activity. In response to decreased serum calcium ion, feedback loops increase PTH secretion, thereby increasing renal resorption of calcium, mobilising calcium from bone, and stimulating renal 1α-hydroxylation of 25-OHD (with subsequent increased gastrointestinal absorption of calcium). The net effect is an increase in serum calcium ion activity, and subsequent reduced PTH secretion[5] (*Figure 1*).

Primary hyperparathyroidism

Primary hyperparathyroidism is due to inappropriate autonomous secretion of PTH – typically from solitary parathyroid adenomas – leading to hypercalcaemia.[5] Historically, PHPT was a rare condition characterised by marked skeletal disease, nephrolithiasis, nephrocalcinosis and skeletal and gastrointestinal syndromes. With increased biochemical testing, the presentation of PHPT has changed markedly. The diagnosis is often made on

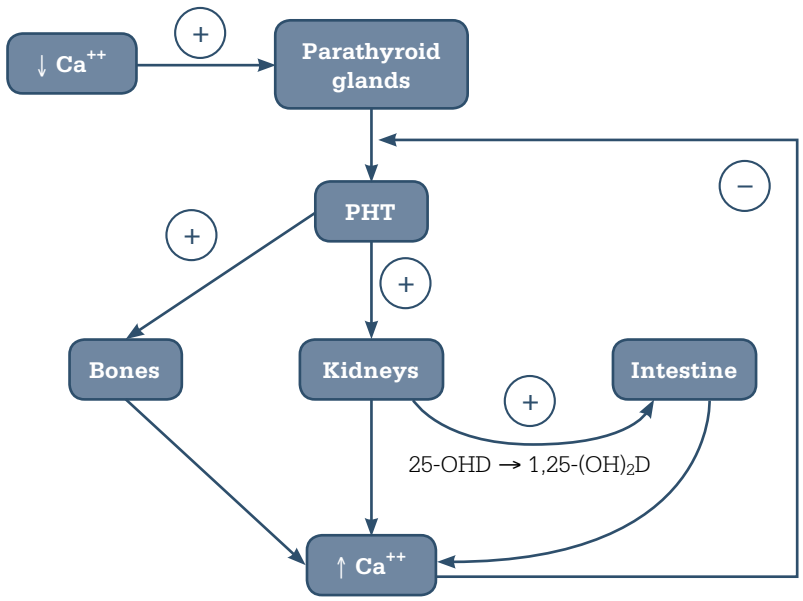

Figure 1. Normal calcium homeostasis showing the relationship between serum calcium activity (Ca^{++}), parathyroid hormone (PTH) and vitamin D
(25-OHD = 25-hydroxyvitamin D; 1,25-$(OH)_2$D = 1,25-dihydroxvitamin D)

biochemical criteria[5,6] in asymptomatic patients with mild hypercalcaemia on routine blood testing. Population screening in the context of bone health has led to the identification of a new clinical entity, normocalcaemic PHPT. These patients have persistently elevated PTH levels, despite normal serum calcium concentrations, when causes of secondary hyperparathyroidism have been excluded.[7,8] With this shift in presentation and early detection, PHPT is now the third most common endocrinopathy in developed countries, behind diabetes mellitus and thyroid pathologies. The incidence is approximately 0.01% in the general population[5] rising to 3% in selected populations such as postmenopausal women.[9]

The prevalence of vitamin D deficiency is higher in people with PHPT than the general population. Patients with PHPT and concomitant vitamin D deficiency have higher PTH concentrations, higher parathyroid adenoma weight,[10] and increased bone catabolism and turnover.[11,12] Despite this, there is reluctance to prescribe vitamin D supplementation in PHPT because of concerns of exacerbating hypercalcaemia and hypercalciuria.[12,13] This reluctance is reinforced in medical texts[14] and by prescribing resources such as the *Australian Medicines Handbook*,[15] which states that vitamin D is contraindicated in hypercalcaemia, with no reference to aetiology.

Vitamin D deficiency in primary hyperparathyroidism: cause or effect?

In PHPT, PTH stimulated renal 1α-hydroxylase activity is increased, leading to uncontrolled 1α-hydroxylation of vitamin D (*Figure 1, Table 1*). This is thought to account for the severity of vitamin D deficiency in those with PHPT, through consumption of substrate and increased catabolism of 25-OHD in response to elevated levels of 1,25-dihydroxyvitamin D.[16] Conversely, in vitamin D deficiency, intestinal absorption of calcium is impaired and compensatory secondary hyperparathyroidism ensues (*Table 1*). In chronic vitamin D deficiency this secondary hyperparathyroidism is a possible contributor to the subsequent development of parathyroid autonomy and adenoma growth.[16,17] Although the aetiological relationships between PHPT and vitamin D deficiency remain speculative, it is clear that PHPT can contribute to vitamin D deficiency, and vice versa, suggesting that the treatment of vitamin D deficiency is indicated in PHPT.[18]

Vitamin D supplementation in primary hyperparathyroidism

Studies addressing the effects of vitamin D supplementation on serum calcium and other parameters in patients with PHPT and coexistent vitamin D deficiency were identified by serial searches of PubMed using the search terms 'vitamin D' and 'primary' in combination with 'parathyroid', 'hyperparathyroid' and/or 'hyperparathyroidism', with no limits set. Abstracts and papers were then examined to identify studies in which the effects of vitamin D supplementation were reported as primary or secondary outcomes. The reference lists of review papers were also examined. Six studies were identified (*Table 2*).

Table 1. Physiological and biochemical effects of primary hyperparathyroidism and vitamin D deficiency

Pathology	Primary events	Physiological effects	Biochemical effects
Primary hyperparathyroidism	↑ PTH	↑ renal Ca^{++} resorption ↑ mobilisation of Ca^{++} from bone ↑ catabolism of 25-OHD	↑ PTH ↑ Ca^{++} ↓ 25-OHD
Vitamin D deficiency	↓ 25-OH D	↓ Ca^{++} absorption from gut ↑ PTH secretion (secondary hyperparathyroidism)	↑ PTH Normal or ↓ Ca^{++} ↓ 25-OHD
Primary hyperparathyroidism and vitamin D deficiency	↑ PTH and ↓ 25-OHD	↑ renal Ca^{++} resorption ↑ mobilisation of Ca^{++} from bone ↑ catabolism of 25-OHD ↓ Ca^{++} absorption from gut ↑ PTH secretion (secondary hyperparathyroidism)	↑↑ PTH Normal or ↑ Ca^{++} ↓↓ 25-OHD

In 2000, Kantorovich et al[19] published a study of the effects on bone mineral density of simultaneous vitamin D repletion and calcium supplementation in 15 subjects with low vitamin D levels and elevated PTH levels. They also assessed the effects of the supplementation regimen on serum calcium and urinary calcium excretion and of the five subjects with true PHPT, all tolerated vitamin D repletion without worsening hypercalcaemia, but three developed hypercalciuria.

Subsequently, a series of studies specifically aimed at investigating the effects and safety of vitamin D repletion in PHPT were published.[13,20–22] Although the supplementation regimens differed markedly across the studies, among the 189 subjects examined in the three studies using nonhydroxylated vitamin D supplements,[13,20,21] no cases of hypercalcaemia and only three cases of hypercalciuria were recorded. In addition, a 25% reduction in PTH levels on vitamin D repletion was recorded by Grey et al,[13] and Isidro and Ruano,[22] who used a 25-hydroxylated vitamin D formulation, did note a small but statistically significant increase in mean urinary calcium excretion, although no urolithiasis was reported.

A study by Velayoudom-Cephise et al[23] examined the effects of PHPT on bone metabolism and bone mineral density. A subset of the PHPT subjects, who were also vitamin D deficient, was given conservative (ultimately inadequate) vitamin D supplementation. This corresponded to a nonsignificant rise in the mean 25-OHD concentration, but interestingly, a 49% decrease in mean PTH concentrations and a significant decrease in serum calcium levels.

All of the patients in the listed studies were asymptomatic and had serum calcium concentrations <3.0 mmol/L. Despite the heterogeneity of the supplementation regimens, it appears vitamin D supplementation can be safely instituted in selected patients with asymptomatic PHPT and vitamin D deficiency. This is reflected in a consensus statement issued following the Third International Workshop on Asymptomatic Primary Hyperparathyroidism in May 2008. This group recommended that 25-OHD be measured in all subjects with PHPT, and that 'vitamin D deficiency should be treated before making any medical or surgical management decisions'.[18] This need for vitamin D supplementation also applies to subjects with suspected normocalcaemic PHPT, in whom the diagnosis cannot be made unless the patient is vitamin D replete.[7,18]

Table 2. Studies addressing the effects of vitamin D supplementation in subjects with primary hyperparathyroidism

Study	No.	Inclusion criteria	Supplementation regimen	Outcomes
Kantorovich et al (2000)[18]	5	25-OHD <25 nmol/L	1000 mg elemental calcium daily and 50 000 units vitamin D_2 twice weekly for 5 weeks	No significant change in serum calcium Hypercalciuria in three subjects
Grey et al (2005)[13]	21	Serum calcium <3.0 mmol/L 25-OHD <50 nmol/L	50 000 units vitamin D_3 weekly for 4 weeks then monthly for 12 months	No significant change in serum calcium Hypercalciuria in three subjects at 6 months, persisting in two at 12 months: no consequent urolithiasis recorded 25% decrease in PTH
Grubbs et al (2008)[20]	112	25-OHD <75 nmol/L	Vitamin D_2, median dose 400 000 units (range 24 000–1 500 000 units) over 3–210 days (median 28 days)	No significant change in serum calcium
Tucci (2009)[21]	56	Serum calcium 2.63–3.0 mmol/L 25-OHD <60 nmol/L	50 000 units vitamin D_2 weekly for 8 weeks, then maintenance doses ranging from 800 units daily to 100 000 units monthly. Final measures after 34 weeks of supplementation	No significant change in serum calcium or urine calcium excretion
Isidro and Ruano (2009)[22]	27	25-OHD <50 nmol/L	480–960 units 25-OHD daily for 12 months	No significant change in serum calcium Significant increase in mean urinary calcium excretion
Velayoudom-Cephise et al (2011)[23]	22	25-OHD <75 nmol/L	800–1200 units vitamin D_2 daily for 3–6 months then 100 000 units vitamin D_3 monthly Final measures after 6 months of supplementation	Significant decrease in serum calcium Nonsignificant increase in mean urinary calcium excretion 49% decrease in mean PTH

25-OHD = 25-hydroxyvitamin D; vitamin D_2 = ergocalciferol; vitamin D_3 = cholecalciferol

As the cases of hypercalciuria noted in the studies were typically identified 6 months after commencing vitamin D supplementation, and in some persisted to 12 months (*Table 2*), measurement of serum calcium concentrations and urine calcium excretion at these time points, at the least, is advised. The varied supplementation regimens used in the examined studies precludes making recommendations regarding vitamin D dosing regimens. However, recent studies have shown little difference in achieving vitamin D repletion between regimens involving large loading doses and those using daily oral supplementation,[24,25] and that adequate long term maintenance dosing is required to prevent recurrence of vitamin D deficiency.[1,2]

Conclusion

Vitamin D deficiency is common in patients with PHPT and those with vitamin D deficiency tend to have more severe disease. Although the evidence is limited, it appears vitamin D supplementation can be safely commenced in selected patients with asymptomatic PHPT, mild hypercalcaemia and concomitant vitamin D deficiency. This supplementation should be part of the early management of PHPT. However, as there are no large published studies on vitamin D repletion in PHPT, and those studies recorded here have involved limited follow up, monitoring of serum calcium concentrations and urinary calcium excretion should be performed while achieving vitamin D repletion and as part of long term monitoring.

Key points

- Vitamin D deficiency is common in patients with PHPT and vitamin D levels should be checked in this patient group.
- Although studies are limited, there is evidence that vitamin D supplementation can be safely instituted in patients with asymptomatic PHPT when serum calcium is <3.0 mmol/L.
- It is reasonable to aim for low normal vitamin D levels (as per local laboratory definitions).
- Serum calcium levels and urinary calcium excretion should be measured at least 6 and 12 months after commencing supplementation.

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