Effect of nutritional vitamin D preparations on parathyroid hormone in patients with chronic kidney disease

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Introduction

Vitamin D deficiency is common and may be a risk factor for nearly all major diseases, including cancer, infections, autoimmune and cardiovascular disease [1]. Vitamin D (VitD) stores decline with age, during winter, after menopause and in chronic kidney disease (CKD) [2]. VitD supplementation is advocated for the treatment of musculoskeletal disorders, for prevention of fractures and secondary hyperparathyroidism [3].

Vitamin D metabolism

To appreciate the impact of VitD on parathyroid hormone (PTH), it may be useful to review VitD sources and metabolism. VitD synthesis involves the conversion of 7-dehydrocholesterol to $VitD_3$ (cholecalciferol) by ultraviolet B rays from sunlight. Dietary intake of VitD is usually limited. Only a few foods contain $VitD_3$, mostly fatty fish such as salmon and mackerel, fish oil, and to a lesser extent eggs. Enriched foods and supplements contain $VitD_3$ or $VitD_2$ (ergocalciferol), a steroid available from plant sources. Both $VitD_2$ and $VitD_3$ are stored in adipose tissue or converted to 25

hydroxy vitamin D [25(OH)D] or calcidiol in the liver. 25(OH)D circulates bound to VitD-binding protein and is metabolized to $1,25(OH)_2D$ (calcitriol), the most active form of VitD, through the action of 1a-hydroxylase. Although 1a hydroxylase is expressed predominantly in the kidney, it has also been detected in a variety of extrarenal tissues such as the vasculature, gastrointestinal tract, skin, mammary epithelial cells, osteoblasts and osteoclasts [4]. Calcitriol produced locally is considered to have autocrine and paracrine actions on cellular proliferation and differentiation, apoptosis, insulin and renin secretion, interleukin and bactericidal proteins [5]. Calcitriol synthesis may also be modulated by vitamin D receptors on the cell surface; downregulation of these receptors may play an important role in regulating vitamin D activation [6]. Increased levels of PTH and hypophosphatemia stimulate expression of 1 a-hydroxylase, while Fibroblast Growth Factor 23 (FGF23) -secreted by osteocytes in the bone matrix- inhibits the expression of the enzyme and thus calcitriol synthesis [7].

Persistent nutritional Vitamin D shortage leads to intestinal calcium malabsorption, resulting in hypocalcemia and PTH secretion, causing secondary hyperparathyroidism. Its deficiency has been described as the main pathogenetic mechanism for rickets in children, osteomalacia in adults and osteoporosis in the elderly [8]. Calcidiol [25(OH)D] also has activity in bone and intestine, but is only one percent as potent as calcitriol. 25(OH)D deficiency has been associated with increased falls, cancer risk, hypertension, fibromyalgia-like

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symptoms, rheumatologic disease, diabetes, depression and fractures [9]. In addition, low levels of 25(OH)D have been recently linked to the presence of metabolic syndrome and cardiovascular mortality [10].

Vitamin D and PTH in the general population

In the general population, most data suggest that oral administration of inactive VitD (ergocalciferol or cholecalciferol) leads to an increase in 25(OH)D and to a linear reduction in PTH [11]. Initially, it had been suggested that the reduction in PTH with VitD supplementation reaches a plateau level, after which PTH starts to increase. Several workers have tried to identify the 25(OH)D cutoff point for maximal suppression of PTH [11, 12]; however, uncertainty in the available data about the contribution of sunshine, diet and age makes it difficult to determine the VitD requirements to achieve this plateau. Therefore, the exact serum 25(OH)D cutoff threshold to define optimal VitD status remains controversial. Some consider VitD insufficiency present at levels of serum 25(OH)D below 20 ng/mL (50 nmol/L) or 30 ng/mL (75 nmol/L). Individuals with serum 25(OH)D values less than 20 ng/mL (50 nmol/L) are classified as VitD deficient [11, 13]. These ranges were accepted because in most studies when serum 25(OH)D levels fall below 30 ng/mL (75 nmol/L), PTH levels rise [3, 14, 15] and calcium absorption is suboptimal [16].

Chronic kidney disease

Correlations of hypovitaminosis D with increased mortality, glucose intolerance and bone fractures have been observed in patients with end stage renal disease receiving dialysis [17–19]. Generally, patients with CKD are predisposed to low calcitriol $(1,25(OH)_2D)$ levels due to the progressive lack of kidney mass to perform 1a-hydroxylation, increasing age, reduced sun exposure and immobilization [20, 21]. Uremia impairs the response to ultraviolet B rays [22] and, in animal models, reduces calcidiol synthesis secondary to PTH -mediated reduction in liver CYP450 isoforms [23]. Moreover, uremic plasma contains factors that inhibit nuclear uptake of calcitriol receptor and 1a -hydroxylase activity [24, 25].

The best indicator of VitD insufficiency is the serum level of 25(OH)D [26]. Blood levels of 25(OH)D reflect the total VitD derived from diet, sunlight exposure and adipose store [7]. Studies have reported varying prevalence rates of VitD deficiency in predialysis and dialysis patients ranging between 70 and 98% [23, 27] and 51 and 100% [28, 29], respectively. Patients with severe proteinuria have the lowest 25(OH)D levels (probably because of losses of protein-bound 25(OH)D) [30], while patients on PD have significantly lower levels of 25(OH)D compared to those on HD (probably because of increased 25(OH)D losses in the peritoneal effluent) [31].

In general, in patients with CKD, an inverse correlation between plasma 25(OH)D and PTH has been noted. Extensive published evidence [22, 23, 26, 27, 32–35] demonstrates a modest decrease in PTH levels after calcidiol supplementation that does not, however, correct the PTH levels to normal. VitD supplementation is not accompanied by an increased risk of hypercalcemia and hyperphosphatemia.

Data are conflicting in terms of PTH reduction after VitD repletion in various CKD stages. Initial studies [36–38] found that, as renal insufficiency progresses, vitamin D_2 supplementation led to less reduction in serum PTH. Patients with CKD stage 3 benefited more from VitD supplements, than those with CKD stage 4 and those on maintenance hemodialysis (HD). Ergocalciferol administration had a favorable impact on PTH decline only if there was an increase in 25(OH)D levels. An increase in serum 25(OH)D level greater than 5 ng/mL (>12.5 nmol/L) was associated with significant likelihood of a greater than 30% decrease in intact PTH [32].

Contrary to the previous studies, a recent meta-analysis [27] found that the significant decline in PTH levels after VitD supplementation was more pronounced in dialysis patients and in transplant recipients compared to predialysis CKD patients. This meta-analysis included patients with all stages of CKD (predialysis, on HD, on peritoneal dialysis and after renal transplantation) enrolled in observational and randomized control studies from 1996 to 2009; outcomes were most obvious in the 17 observational studies included in the meta-analysis pool, whereas in the randomized control studies the results were not as prominent. In the observational studies, a mean increase of 24 ng/mL (60 nmol/L) in VitD level was associated with a decrease in PTH of

41 pg/mL (4.34 pmol/L) in predialysis CKD patients and 59 pg/mL (6.25 pmol/L) among HD patients, respectively [27].

The complementary role of VitD preparations to standard of care (calcitriol or its analogs, cinacalcet and surgical parathyroidectomy) for secondary hyperparathyroidism in CKD has also been assessed. Patients on maintenance HD treated simultaneously with VitD supplements in addition to the usual standard of care for secondary hyperparathyroidism have been followed up for 6 years. In these patients, the degree of hyperparathyroidism and the need for calcitriol analogs, cinacalcet and surgical parathyroidectomy were decreased drastically [32].

Given the fact that excess of calcitriol accelerates uremic vascular calcification [39], the use of lower doses of calcitriol in combination with calcidiol or the use of more selective VDR activators may result in cardiovascular disease prevention. To the same direction may lead the emergence of proteins inhibiting vascular mineralization. Osteoprotegerin -by binding several proinflammatory and promineralizing agents in circulation- and Fetuin-A -by antagonizing the action of growth factor and by promoting the phagocytosis of apoptotic bodies- are worth mentioning calcification inhibitors. Matrix GLa protein, despite the strong background from genetics, did not demonstrate association with calcium phosphate balance or vascular calcification in CKD patients [40].

Mechanism of PTH decrease with VitD supplementations

The mechanism through which VitD administration decreases elevated PTH levels remains to be clarified. PTH reduction could be attributed to either increased downstream calcitriol production, due to renal or extrarenal 1a hydroxylation of 25(OH)D, or/and to 25(OH)D actions independent of calcitriol generation [33, 34]. Indeed, in vitro models [41] have shown that 25(OH)D can directly activate the VitD receptor in the parathyroid gland without calcitriol involvement. Similarly, potential 25(OH)D actions could be seen indirectly among HD population. As noted previously, these patients benefited most from nutritional VitD preparations, although they might have a further calcitriol decline enhanced by the elevated FGF 23 [42, 43]; it takes at least 6 months of VitD supplementation to increase calcitriol levels in HD patients [44].

The positive correlation between serum 25(OH)D and $1,25(OH)_2D$ levels was documented only in VitD insufficient CKD patients, but not in persons with normal renal function [30, 45]. 25(OH)D probably exhibits biologic actions affecting patients with CKD differently compared with normal individuals [46].

The Kidney Disease Improving Global Outcome Initiative (KDIGO) recommends monitoring the serum 25(OH)D in stage 3–4 CKD and the treatment of patients with elevated PTH and 25(OH)D level less than 30 ng/mL (75 nmol/L) with oral VitD preparation [47, 48]. Cholecalciferol therapy leads to upregulation of VitD response genes in monocytes of patients on maintenance HD, indicating that oral VitD preparations have a biologic effect on circulating monocytes and associated inflammatory markers in HD patients [33, 36, 49].

Unresolved controversies surrounding 25(OH)D administration in patients with CKD

We do not have well-designed randomized clinical trials or large epidemiologic studies that examine fully the responses of PTH to oral VitD administration in CKD patients. Furthermore, no optimal 25(OH)D level has been established [7]. The available studies applied various VitD repletion approaches (relating to dose, duration, and route of administration and monitoring of 25(OH)D and targeted dissimilar ranges of serum 25(OH)D levels. The two forms of nutritional VitD (D_2, D_3) were regarded as equal and interchangeable [50], while recent literature suggests that $VitD_3$ (cholecalciferol) is more potent than $VitD_2$ (ergocalciferol) at lowering PTH levels [51–53]. Considering the advantages of various VitD analogs, such as low cost, minor risks for hypercalcemia and hyperphosphatemia, and survival benefit on HD population [54], it will be of interest to explore their usefulness, especially to determine whether concurrent use of 25(OH)D with $1,25(OH)_2D$ or calcimimetics will provide better outcomes.

Conclusion

VitD deficiency is common among CKD patients, and many authors have assessed the benefits of calcidiol repletion in those patients. We reviewed the potential effect of oral vitamin D preparations on secondary

hyperparathyroidism in CKD patients. The correction of VitD status might be a novel pharmacological approach to further optimize existing therapies in CKD patients with secondary hyperparathyroidism.

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