

Vitamin D prohormone in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease

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Abstract: Secondary hyperparathyroidism (sHPT) represents the adaptive and very often, finally, maladaptive response of the organism to control the disturbed homeostasis of calcium, phosphorus, and vitamin D metabolism caused by declining renal function in chronic kidney disease (CKD). sHPT leads to cardiovascular and extravascular calcifications and is directly linked to an increased risk of cardiovascular morbidity and mortality as well as excess all-cause mortality. Vitamin D plays an important role in the development of sHPT. CKD patients are characterized by a high prevalence of hypovitaminosis D. Supplementation with both vitamin D prohormones cholecalciferol and ergocalciferol enables the achievement and maintenance of a normal vitamin D status when given in adequate doses over an appropriate treatment period. In patients with earlier stages of CKD, sHPT is influenced by and can be successfully treated with vitamin D prohormone supplementation, whereas in patients with very late stages of CKD and those requiring dialysis, treatment with prohormones seems to be of limited efficacy. This review gives an overview of the pathogenesis of sHPT, summarizes vitamin D metabolism, and discusses the existing literature regarding the role of vitamin D prohormone in the treatment of sHPT in patients with CKD.

Keywords: cholecalciferol, CKD, CKD-MBD, dialysis, ergocalciferol, SHPT.

Pathogenesis of secondary hyperparathyroidism (sHPT) in chronic kidney disease (CKD)

sHPT represents the adaptive and very often, finally, maladaptive response of the organism to control the disturbed homeostasis of calcium, phosphorus, and vitamin D metabolism caused by declining renal function in CKD. These disturbances in mineral metabolism lead to vascular^{1,2} and valvular³ calcifications and are directly linked to an increased risk of cardiovascular morbidity and mortality as well as excess all-cause mortality.⁴ Apart from extra-skeletal side effects, sHPT also leads to profound alterations in bone metabolism, which become obvious in the different forms of renal osteodystrophy.⁵ This clinical syndrome encompassing mineral, bone, and cardiovascular abnormalities has been termed “CKD-related mineral and bone disorder” (CKD-MBD).⁶ sHPT generally develops in CKD stage 3 with an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m², and its prevalence increases as kidney function declines.^{7,8} Initially, it is characterized by normocalcemia with intermittent transient hypocalcemia, fasting normo- or hypophosphatemia, and reduced 1,25(OH)₂D₃ (calcitriol) concentration, together with increasing levels of fibroblast growth factor 23 (FGF23), a decrease in plasma soluble Klotho, and the development of renal osteodystrophy.^{8–11} These alterations result in increased secretion

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and synthesis of parathyroid hormone (PTH) and parathyroid cell hyperplasia (Figure 1).¹² The precise sequence of metabolic alterations in early CKD leading to sHPT still remains a matter of debate. Traditionally, retention of phosphorus with accompanying reduction in ionized calcium due to decreasing GFR was considered to be the primary event in the pathogenesis of sHPT. These transient metabolic changes would induce an increase in PTH, which would rapidly correct these alterations due to a decreased tubular reabsorption of phosphorus and increased tubular calcium reabsorption. A new steady state is reached at the expense of the development of hyperparathyroidism. This concept was originally described with the “trade-off hypothesis” by Slatopolsky et al.¹³ The discovery of phosphatonin FGF23 as a key player in the control of phosphorus metabolism changed and broadened the conceptual framework. This bone-derived protein decreases serum phosphorus concentration by reducing tubular phosphorus reabsorption independent of PTH. In contrast to PTH (which stimulates

tubular 1 α -hydroxylase activity), FGF23 decreases the synthesis of calcitriol in the kidney. To activate its membrane-bound receptors FGFR-1 and FGFR-3 on tubular cells, it requires the presence of its co-receptor Klotho.¹⁴ Clinical as well as animal model studies suggest that FGF23 levels increase earlier than PTH in CKD.^{9,15} More recent data found that vitamin D status critically determines the order of FGF23 or PTH elevation. Whereas in vitamin D-replete patients with CKD stage 3, FGF23 levels were elevated in a greater proportion of patients compared with PTH over all GFR strata, in vitamin D insufficient patients, the opposite pattern with an earlier increase in PTH was found.¹⁶ Reduced renal Klotho expression and synthesis might even precede the raise of FGF23.^{17,18} With progressive CKD renal Klotho expression and levels of soluble Klotho decrease.^{19,20} PTH increases FGF23 synthesis directly through the activation of its receptor PTH-R1 and the orphan nuclear receptor Nurr1 and indirectly through an increased calcitriol synthesis stimulating renal tubular 1 α -hydroxylase.^{21–23} In contrast,

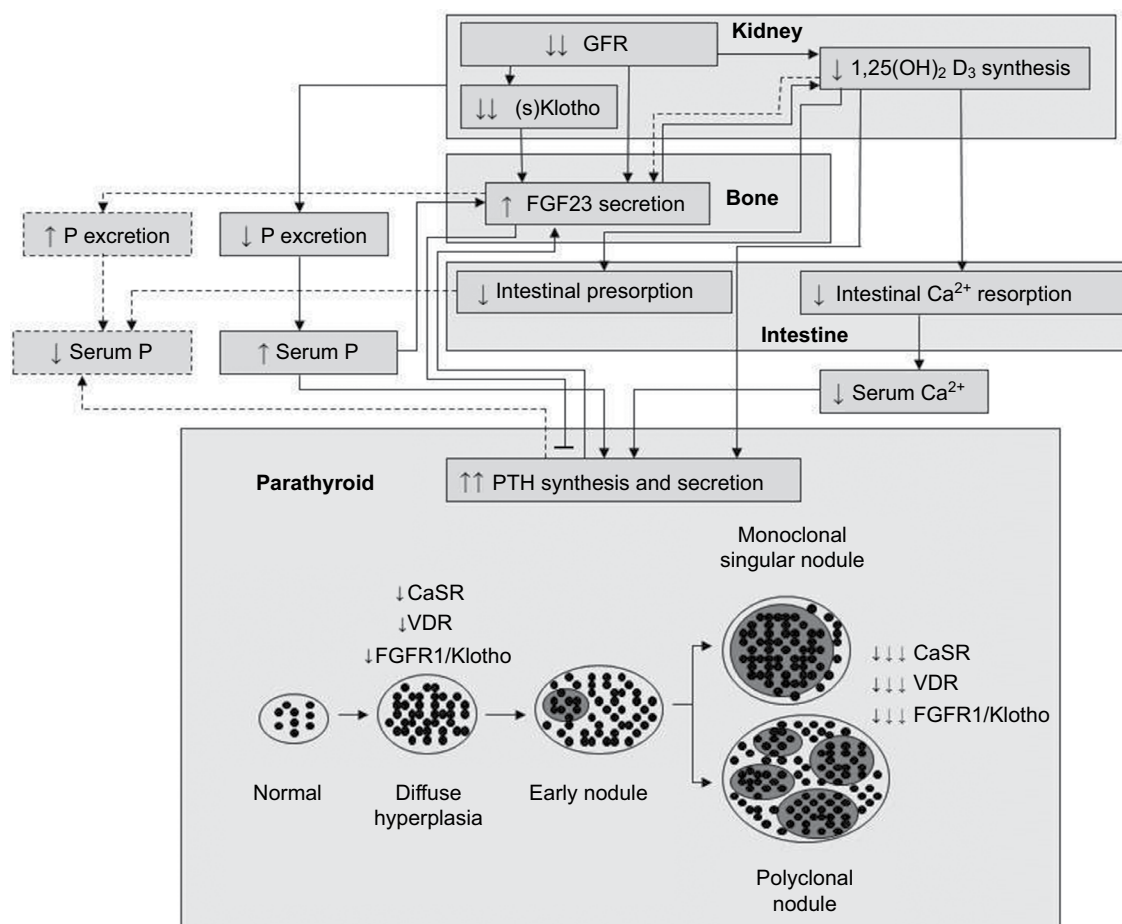


Figure 1 Pathogenesis of secondary hyperparathyroidism in chronic kidney disease.

Notes: Dashed lines indicate counter-regulatory pathways.

Abbreviations: CaSR, calcium-sensing receptor; FGF23, fibroblast growth factor 23; FGFR1, fibroblast growth factor receptor 1; GFR, glomerular filtration rate; VDR, vitamin D receptor; (s) Klotho, soluble Klotho; PTH, parathyroid hormone.

FGF23 inhibits PTH synthesis and secretion, although this effect is diminished in CKD due to a reduced expression of Klotho and FGFR-1 on parathyroid cells.^{24–26}

Vitamin D deficiency

Vitamin D plays a key role in the regulation of mineral and bone metabolism. Vitamin D deficiency is an important component in the pathogenesis of sHPT, which is defined as a reduced serum level of 25(OH)D and is common in the general population with significantly higher prevalence in patients with CKD.^{27,28} Compared to patients with normal renal function, impaired kidney function was associated with a 32% higher risk for vitamin D deficiency.²⁸ It develops early in the course of CKD and its prevalence increases with the progressive loss of renal function.²⁹ In a study conducted by LaClair et al, only 29% and 17% of patients with CKD stage 3 and 4, respectively, had sufficient vitamin D levels, defined as a serum 25(OH)D concentration >30 ng/mL.³⁰ In hemodialysis patients, 76%–94% were found to have 25(OH)D <30 ng/mL.^{31–35} A high prevalence of vitamin D deficiency of 87% was also observed in a large cohort of peritoneal dialysis patients.³⁶ Studies have shown that African-Americans have lower 25(OH)D levels compared with whites. The reasons for this finding seem to be multifactorial and are not completely clarified yet.³⁷

Vitamin D deficiency is associated with elevated PTH in the general population as well as in patients with CKD.^{30,32,38–40} Gonzalez et al found a significant negative correlation between vitamin D levels and intact PTH (iPTH) in patients with CKD stage 1–5.⁴⁰ These findings are consistent with those from a US cross-sectional study, which revealed an inverse relationship between 25(OH)D and iPTH levels in CKD 3 and 4.³⁰ In a prospective cohort study, 25(OH)D levels correlated better with iPTH in patients with CKD 1–5, than did 1,25(OH)₂D.²⁹ Even in end-stage renal disease, vitamin D deficiency is associated with high PTH.^{32,41}

To date, there is no consensus on optimal serum levels of 25(OH)D in the general population as well as in CKD.³⁸ Since, in non-CKD patients, 25(OH)D levels <30 ng/mL are associated with an increase in PTH concentrations, most experts define 25(OH)D concentrations from 20 to 29 ng/mL as vitamin D insufficiency and 25(OH)D <20 ng/mL as vitamin D deficiency.³⁸ However, compared to the general population, sHPT in CKD is more distinct and the pathogenesis is multifactorial, as described earlier. Therefore, whether optimal 25(OH)D levels for patients with CKD are the same as for the general population is a matter of debate. A recently published cross-sectional study conducted in

>14,200 patients with CKD stage 1–5 revealed an inverse relationship between 25(OH)D and iPTH in all five CKD stages.⁴² Interestingly, 25(OH)D levels >42–48 ng/mL did not result in further PTH reduction, suggesting a higher threshold for optimal 25(OH)D levels in CKD patients than in the general population.⁴²

Vitamin D terminology

Technically, vitamin D is not a vitamin, since it is not an essential dietary factor and is synthesized endogenously in the skin. However, vitamin D also meets the criteria of a vitamin, since humans can derive their vitamin D requirement through the diet.^{38,43} Vitamin D itself has no significant biological activity and has to be transformed into the active form 1,25(OH)₂D to exert significant physiological actions. The characteristics of 1,25(OH)₂D are those of a hormone, and consequently vitamin D could be considered a prohormone.⁴⁴ The effect of 1,25(OH)₂D depends on the adequate availability of 25(OH)D, which in turn depends on an appropriate vitamin D nutritional status. The terminology used to describe various forms of vitamin D is confusing and non-uniform. The nomenclature of the two major forms of vitamin D and their metabolites is presented in Table 1.

Vitamin D sources

Vitamin D is a group of fat-soluble secosterols with several existing forms. The major compounds in humans are vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol).³⁸ Sunlight-induced synthesis of vitamin D₃ in the skin is the primary source of vitamin D in humans; ~90% of the requirement results from sunlight exposure.⁴⁵ Vitamin D can also be obtained from dietary sources. However, these sources are limited, since only a few foods (eg oily fish, fish liver oils) naturally contain vitamin D. Food sources of vitamin D₂, the plant-derived form of vitamin D, are very limited, and wild mushrooms are one of the significant sources. Further sources of dietary vitamin D are fortified foods and supplements.^{38,45} Both vitamin D₂ and D₃ are used in fortification and as dietary supplements. Although vitamin D₂ is the major compound used in the USA, vitamin D₃ is mainly used in Europe.⁴⁶

Vitamin D metabolism

The cutaneous synthesis of vitamin D₃ is a non-enzymatic process. The absorption of UVB radiation (290–315 nm) results in the conversion of 7-dehydrocholesterol to pre-vitamin D₃ followed by thermal isomerization to vitamin D₃.⁴⁵ Dietary vitamin D and endogenously synthesized vitamin D₃ enter the circulation. Vitamin D can be stored in and

Table I Vitamin D terminology

	Vitamin D ₂ and metabolites	Vitamin D ₃ and metabolites	Collective terminology
Prohormone (native vitamin)			
Abbreviation	D ₂	D ₃	D
Full term	Vitamin D ₂	Vitamin D ₃	Vitamin D
Synonym	Ergocalciferol	Cholecalciferol	
Prehormone (product of 1 st hydroxylation)			
Abbreviation	25(OH)D ₂	25(OH)D ₃	25(OH)D
Full term	25-Hydroxyvitamin D ₂	25-Hydroxyvitamin D ₃	25-Hydroxyvitamin D
Synonym	Ergocaldicol	Calcidiol	
Hormone (product of 2 nd hydroxylation)			
Abbreviation	1,25(OH) ₂ D ₂	1,25(OH) ₂ D ₃	1,25(OH) ₂ D
Full term	1,25-Dihydroxyvitamin D ₂	1,25-Dihydroxyvitamin D ₃	1,25-Dihydroxyvitamin D
Synonym	Ergocalcitriol	Calcitriol	

released from fat cells,³⁸ whereby vitamin D₃ is the major stored form of vitamin D in adipose tissue.⁴⁷ In the circulation vitamin D is bound to vitamin D-binding protein (DBP), the main transporting protein of vitamin D metabolites.⁴⁸ The process of activation of vitamin D involves two hydroxylation steps. The first step occurs primarily in liver, where native vitamin D undergoes hydroxylation of carbon 25 by cytochrome P450 enzymes, resulting in the formation of 25(OH)D. Several cytochrome P450 enzymes, including CYP2R1 and CYP27A1, have been shown to 25-hydroxylate vitamin D. However, CYP2R1 seems to be the key enzyme responsible for the formation of 25(OH)D.^{49,50} The 25-hydroxylation of vitamin D is not significantly regulated and depends on substrate availability. 25(OH)D is the major circulating form of vitamin D.⁴⁸ After its synthesis in liver, it is transported by DBP to kidneys. The DBP-25(OH)D complex is filtered by the glomerulus, followed by receptor-mediated re-uptake at the brush border of proximal renal tubular cells involving megalin and cubilin.^{51,52} There, 25(OH)D is then hydroxylated to 1,25(OH)₂D. This second hydroxylation is catalyzed by the enzyme 1 α -hydroxylase (also known as CYP27B1). In contrast to the hepatic 25-hydroxylases, the renal 1 α -hydroxylase is substrate-independent under normal conditions.⁴⁸ The production of 1,25(OH)₂D in kidneys is tightly regulated by several factors, including serum phosphorus, calcium, PTH, FGF23, and 1,25(OH)₂D itself.^{48,53} Low serum calcium, low serum phosphorus, and high PTH levels stimulate this enzyme, whereas FGF23 and 1,25(OH)₂D inhibit the expression.⁵³ The 1 α -hydroxylase gene is also expressed in several non-renal tissues. Extra-renally produced 1,25(OH)₂D primarily exerts local autocrine and paracrine effects.^{53,54} The regulation of this extra-renal 1 α -hydroxylase differs from that of the renal enzyme and is substrate-dependent.⁵³

Effects of 1,25(OH)₂D are mediated via binding to the vitamin D receptor (VDR) that is expressed in a large variety of human cells and regulates ~3% of the human genome.⁵⁵ 25(OH)D can also directly bind and activate the VDR. Although its affinity for the VDR is 100–200 times lower than that of 1,25(OH)₂D, it circulates at concentrations 1000-fold higher than serum 1,25(OH)₂D levels.⁵⁴

The enzyme 24-hydroxylase (CYP24A1) is responsible for the catabolism of 25(OH)D and 1,25(OH)₂D. Both the metabolites are 24-hydroxylated at carbon 24 by this enzyme, resulting in 24,25(OH)₂D and 1,24,25(OH)₃D, respectively. However, 1,25(OH)₂D is the preferred substrate relative to 25(OH)D. 1,24,25(OH)₃D has substantial affinity for the VDR and biological activity.^{48,53} 24-Hydroxylation is the first step in the catabolism of 25(OH)D and 1,25(OH)₂D, followed by oxidation and further hydroxylation ending in the production of the inactive metabolite calcitroic acid.^{48,53} The regulation of 24-hydroxylase in kidney is also tightly controlled in a reciprocal manner to that of 1 α -hydroxylase. It is induced by 1,25(OH)₂D, FGF23 and inhibited by PTH.^{48,53} By inactivating 25(OH)D and 1,25(OH)₂D, this enzyme regulates the concentration of circulating 1,25(OH)₂D in two ways: first, via decreasing the substrate availability of 25(OH)D and, second, via inactivation of 1,25(OH)₂D itself. In addition to its expression in kidney, 24-hydroxylase is present in all cells expressing VDR; however, its specific purpose in extra-renal tissues remains to be elucidated.⁴⁸

Impaired vitamin D metabolism in CKD

CKD affects all key steps of vitamin D metabolism, namely production, activation, and degradation of vitamin D and its metabolites. It is characterized by both low concentrations

of 25(OH)D and low levels of 1,25(OH)₂D.²⁸ There are various reasons for vitamin D deficiency in CKD, including reduced availability of vitamin D for 25-hydroxylation due to insufficient sun exposure,^{45,56} low dietary vitamin D intake,⁵⁷ impaired intestinal absorption,⁵⁸ impaired hepatic 25-hydroxylation,⁵⁹ loss of 25(OH)D-DBP in case of severe proteinuria,⁶⁰ reduced glomerular filtration of 25(OH)D-DBP as a consequence of low GFR,⁶¹ impaired re-uptake of 25(OH)D due to reduced renal megalin expression,⁶² and increased degradation of 25(OH)D induced by high FGF23 concentrations.⁶³

Low 25(OH)D levels have been assumed to be a calcitriol-independent risk factor of hyperparathyroidism based on observational data in hemodialysis patients with insufficient sun exposure⁴¹ and experimental data showing a direct inhibition of PTH production and secretion in bovine parathyroid cells with calcidiol.⁶⁴

Several mechanisms lead to reduced 1,25(OH)₂D levels in CKD. In contrast to patients without kidney disease, in those with CKD, the production of 1,25(OH)₂D is at least partially substrate-dependent as has been shown in hemodialysis patients with a significant increase in 1,25(OH)₂D₃ levels during a 4-week supplementation of calcidiol.⁶⁵ Furthermore, the reduction of functional renal mass is accompanied by a progressive loss of renal 1 α -hydroxylase and results in lower calcitriol production.⁶⁶ Moreover, FGF23 reduces 1,25(OH)₂D by down-regulating the renal 1 α -hydroxylase and enhancing the catabolism of 1,25(OH)₂D.⁶³ The effect of CKD on the regulation of the extra-renal 1 α -hydroxylase is unclear.⁶⁷ Supplementation with native vitamin D resulted in an increase in 1,25(OH)₂D levels even in anephric subjects, suggesting a compensatory activity of the extra-renal system in CKD.^{67,68}

sHPT treatment with vitamin D prohormone

From a pathophysiological aspect, avoidance of vitamin D deficiency early in the course of CKD to prevent or treat mild to moderate sHPT seems reasonable. With progressive CKD and loss of renal 1 α -hydroxylase (mainly in stage 5 and 5D), the importance of the supplementation with vitamin D prohormone for systemic effects declines. There have been several studies with varying designs, investigating the response of cholecalciferol or ergocalciferol treatment on 25(OH)D concentration and its effect on PTH levels in patients with CKD summarized in two meta-analyses.^{69,70} However, studies are heterogeneous and differ significantly in supplementation compound, dosing, duration of supplementation, and patient characteristics.

Differences between the two vitamin D prohormones vitamin D₂ and D₃

Vitamin D₂ and D₃ have long been considered equivalent in their clinical activity; however, the current body of literature strongly suggests the preference of vitamin D₃ over D₂. Several studies in humans have shown that vitamin D₃ is more effective than vitamin D₂ in raising and maintaining serum 25(OH)D concentrations.^{47,71–74} Daily administration of 4000 IU vitamin D₃ or D₂ for 2 weeks revealed an 1.7-fold increase in serum 25(OH)D levels with vitamin D₃.⁷¹ Armas et al showed that the administration of a single dose of 50,000 IU vitamin D₂ or D₃ produced similar initial increases in 25(OH)D serum concentrations in healthy men, indicating equivalent absorption. However, in the vitamin D₃ group, 25(OH)D levels continued to rise through day 14, whereas in the vitamin D₂ group, levels decreased again resulting in concentrations indifferent from baseline. The comparison of the area under the curve revealed a >3-fold higher potency for vitamin D₃.⁷² A meta-analysis including seven randomized controlled trials (RCTs) found that vitamin D₃ is more effective in raising serum 25(OH)D levels than vitamin D₂. Separate analyses comparing the dosage frequency (bolus vs daily administration) indicated that either administration resulted in higher 25(OH)D levels with vitamin D₃ compared with vitamin D₂.⁷³ The same holds true for patients with CKD and end-stage renal disease.^{75,76} An RCT comparing supplementation with vitamin D₂ and D₃ (50,000 IU weekly for 12 weeks) in patients with CKD stage 3–5 revealed a higher increase in 25(OH)D levels in the vitamin D₃ group.⁷⁶ Vitamin D₃ was also found to be more effective than vitamin D₂ in raising and providing adequate 25(OH)D levels over 3 months in hemodialysis patients using equal-unit monthly doses of 200,000 IU.⁷⁵

Several mechanisms contribute to the greater capacity of vitamin D₃ to increase and maintain 25(OH)D concentrations including higher affinity of vitamin D₃ and its metabolites to 25-hydroxylase and DBP and differences in 24-hydroxylation.^{46,77} Due to the differences in the bioequivalence of vitamin D₂ and D₃, this study has summarized prospective observational studies and RCTs, stratified by vitamin D compound and CKD stages.

Vitamin D prohormone supplementation in CKD stages 3–5

In light of the fact that vitamin D deficiency is highly prevalent in patients with CKD and is associated with sHPT as well

as with negative clinical outcomes in observational studies,^{29,32,33,78} current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on CKD-MBD published in 2009 (update awaited this year) suggest to measure 25(OH)D levels in patients with CKD stages 3–5D and to correct vitamin D deficiency and insufficiency by using treatment strategies for the general population. However, these guidelines provide neither a specific threshold for 25(OH)D levels to initiate vitamin D supplementation nor an optimal target value.⁷⁹

Regarding treatment of sHPT, KDIGO guidelines suggest that in CKD stages 3–5, patients with iPTH levels above the upper normal limit of the assay should be evaluated for vitamin D deficiency. It is suggested to correct vitamin D deficiency with the supplementation of native vitamin D. It is acknowledged that in CKD stages 3–5, optimal PTH levels are not known. In patients with CKD 5D, it is suggested to maintain iPTH levels in the range of 2–9 times the upper normal limit for the assay in use. No recommendations are made for native vitamin D in the treatment of sHPT in dialysis patients.⁷⁹

Current guidelines may be limited because they recommend treatment of sHPT as opposed to prevention. A recent trial reported that ergocalciferol prevented sHPT in children with CKD stage ≥ 2 .⁸⁰ As PTH levels remain relatively stable with eGFR values >60 mL/min/1.73 m², a longer supplementation phase and follow-up period might be necessary in the adult CKD population to see a preventive effect of vitamin D prohormone on the development of sHPT.

Available data indicate a more pronounced decrease in PTH in patients with earlier stages of CKD. Several studies reported a decline of PTH in CKD stage 3, but not in stage 4.⁷⁰ Other studies on vitamin D prohormone supplementation found variable results, some reporting a decrease in PTH levels across different stages of CKD^{76,81–86} and some reporting no effect.^{87–93} Tables 2 and 3 provide a detailed overview of published prospective studies investigating the effect of either cholecalciferol or ergocalciferol on PTH levels in patients with CKD stages 3–5.

The magnitude of response can vary considerably among individuals. One of the most important determinants of 25(OH)D response to a given vitamin D dose is body weight, as with increasing fat mass more vitamin D is stored in the fat tissue and not available for 25-hydroxylation.^{94,95} Indeed, obesity is associated with hypovitaminosis D in normal and impaired kidney function^{96,97} and negatively affects the response to supplementation.^{98,99}

Even high-dose and long-term supplementation of vitamin D prohormones is characterized by an excellent safety

profile. Throughout all studies, no increased risk of hypercalcemia or hyperphosphatemia, well known side-effects of active vitamin D compounds¹⁰⁰ limiting their use, was observed. In addition, high-dose ergocalciferol supplementation with 50,000 IU weekly over a short term of 6 weeks in patients with CKD 4–5 had no influence on FGF23 concentrations, as shown recently.⁹⁰

Aiming for the prevention and treatment of sHPT in vitamin D deficient or insufficient patients with CKD, the following approach is suggested: 1) evaluation for vitamin D deficiency or insufficiency measuring 25(OH)D levels; 2) cholecalciferol supplementation in case of a 25(OH)D level <30 ng/mL using a daily (3000–3900 IU or 2800–4000 IU, dependent on the available preparation, eg, 300 or 400 IU/drop) or weekly (20,000–30,000 IU) dosing regimen. These regimens may differ from one country to another due to the availability of pharmaceutical cholecalciferol dosages; 3) re-evaluation of 25(OH)D level, PTH, serum calcium, and phosphorus after 3 months. In case of vitamin D sufficiency, it is suggested to halve the cholecalciferol maintenance dose. Otherwise, it has been proposed to continue the initial dose under regular control with thrice-monthly re-evaluation. In the rare event of hypercalcemia or hyperphosphatemia, cholecalciferol supplementation should be temporarily stopped.

In summary, an improvement in sHPT by vitamin D supplementation has been demonstrated in many but not all studies of CKD patients. Several reasons could account for these discrepancies: differences in patient characteristics, different baseline PTH levels prior to supplementation, differences in vitamin D dosing and duration of supplementation, and finally achieved degree of vitamin D restoration. All these factors may contribute to the lack of congruent findings across studies.

Vitamin D prohormone supplementation in CKD stage 5D (dialysis patients)

Optimal ranges for 25(OH)D levels are not known in patients on hemodialysis. Observational studies have shown an association between low 25(OH)D levels and adverse clinical outcomes.^{32–34} Although data from clinical trials are missing to show a survival benefit after increasing 25(OH)D levels in insufficient or deficient hemodialysis patients, current guidelines suggest to replete 25(OH)D stores in these patients on grounds of low costs and relative and potential therapeutic impact.⁷⁹ The postulated suppression of PTH secretion with the supplementation of vitamin D may be found even in anuric or anephric patients on dialysis, as

Table 2 Cholecalciferol dosing regimes and associated changes in 25(OH)D and PTH in CKD stage 3–5

Study, year	Type of study	N	Cholecalciferol dose (cumulative dose)	Treatment period	Baseline 25(OH)D (ng/mL)	EOS 25(OH)D (ng/mL)	25(OH)D change (ng/mL)	Baseline PTH (pg/mL)	PTH change (pg/mL)
Chandra et al, 2008 ⁸⁷	RCT	12 CKD 3, 8 CKD 4	50,000 IU weekly (600,000 IU)	12 weeks	17.3	49.4	32.1	289	Decrease (–88, $p=0.07$)
Dogan et al, 2008 ⁸²	RCT	40 CKD 3–4	Placebo	4 weeks	18.6	19.5	0.9	291	No change (–21, ns)
			300,000 IU once		8.5	17.8	9.3	368	Decrease (–89, $p<0.001$)
Oksa et al, 2008 ⁸⁵	RCT	25 CKD 2, 45 CKD 3, 17 CKD 4	Placebo	48 weeks	6.8	7.2	0.4	273	Increase (+15, $p<0.04$)
			5,000 IU weekly (240,000 IU)		15	28	13	63	Decrease (–15, $p<0.001$)
Moe et al, 2010 ⁹²	RCT	28 CKD 3, 19 CKD 4	20,000 IU weekly (960,000 IU)	12 weeks	16	37	21	50	Decrease (–10, $p<0.001$)
			4000 IU daily for 1 month, followed by 2000 IU daily		14.0	37.2	23.2	109	No change (–12, ns)
			Doxercalciferol 1 µg daily		15.1	14.0	–1.1	106	Decrease (–26, $p=0.01$; between group comparison, ns)
Marckmann et al, 2012 ⁸⁴	RCT	25 CKD 1–5	40,000 IU weekly (320,000 IU)	8 weeks	15.8		51.1	79	Decrease (–29, $p<0.001$ between groups)
			Placebo		11.5		–2.8	120	Increase (+41)
Alvarez et al, 2012 ¹⁰⁴	RCT	21 CKD 2, 25 CKD 3–4	50,000 IU weekly for 12 weeks, followed by every other week for 40 weeks (1,600,000 IU)	52 weeks	26.7	40.3	13.6	89	Decrease at 12 weeks (–19, $p=0.01$), no change after 52 weeks (–14, ns)
			Placebo		32.1	31.2	–0.9	78	No change after 12 and 52 weeks
Garcia-Lopes et al, 2012 ⁹⁹	Prospective cohort	45 CKD 3–4	50,000 IU weekly, after 12 weeks 50,000 IU monthly if 25(OH)D ≥ 30 ng/mL, otherwise continued weekly	24 weeks	11.2	38.1	26.9	136	No change after 24 weeks (+2, ns), decrease after 12 weeks (–18, $p<0.01$)
			1,000 IU daily (180,000 IU)		19.2	52.3	33.1	94	Decrease (–16, $p=0.02$)
Kim et al, 2014 ⁸³	Prospective cohort	68 CKD 3–5	10,000 IU weekly (480,000 IU)	48 weeks	12.3	22.4	10.1	135	Decrease (–17, $p<0.05$)
Cupisti et al, 2015 ⁸¹	Prospective cohort	100 CKD 2–4	50,000 IU cholecalciferol weekly (600,000 IU)	12 weeks	20.9	45.0	24.1	77	Decrease (–15, $p=0.02$ for group difference)
Wermore et al, 2016 ⁷⁶	RCT	44 CKD 3–5	50,000 IU ergocalciferol weekly (600,000 IU)		20.5	30.7	10.2	149	No change (+2)

Notes: Only prospective studies with a minimum sample size of 20 patients were included.**Abbreviations:** CKD, chronic kidney disease; EOS, end of study; PTH, parathyroid hormone; RCT, randomized controlled trial; ns, not significant.

Table 3 Ergocalciferol dosing regimes and associated changes in 25(OH)D and PTH in CKD stage 3–5

Study, year	Type of study	N	Ergocalciferol dose (cumulative dose)	Treatment period	Baseline 25(OH)D (ng/mL)	EOS 25(OH)D (ng/mL)	25(OH)D change (ng/mL)	Baseline PTH (pg/mL)	PTH change (pg/mL)
DeVille et al, 2006 ⁸⁸	Prospective cohort	26 CKD 3, 51 CKD 4, 8 CKD 5	If 25(OH)D <16 ng/mL: 50,000 IU twice weekly for 8 weeks, followed by 800 IU/day If 25(OH)D 16–30 ng/mL: 50,000 IU monthly for 2 months, followed by 800 IU/day If 25(OH)D >30 ng/mL: 800 IU daily	90 days	17	42	25	176	Decrease (–27, $p<0.05$; significant only in CKD 4)
Zisman et al, 2007 ⁸⁶	Prospective cohort	24 CKD 3, 28 CKD 4	If 25(OH)D <15 ng/mL: 50,000 IU weekly for 4 weeks, followed by 50,000 monthly for 3 months, followed by 1200 IU/daily If 25(OH)D 15–25 ng/mL: 50,000 IU weekly for 4 weeks, followed by 1,200 IU daily If 25(OH)D >25 ng/mL: 1200–2000 IU daily	Mean 7.4 months (CKD 3)	20.3 (CKD 3)	31.6 (CKD 3)	11.3	154	Decrease (–24, $p=0.04$)
Kovesdy et al, 2012 ⁹¹	RCT	80 CKD 3–4	50,000 IU weekly to monthly 1 µg paricalcitol daily	Mean 6.8 months (CKD 4) 16 weeks	18.8 (CKD 4) 17.2	35.4 (CKD 4) 29	16.6 11.8	165 175	Decrease (–25, ns) No change (–9, ns)
Gravesen et al, 2013 ⁹⁰	Randomized	43 CKD 4–5	50,000 IU weekly	6 weeks	25.1	51.6	26.5	180	Decrease (–49, $p<0.001$; $p=0.009$ for between-group comparison) No change (–12, ns)
Dreyer et al, 2014 ⁸⁹	RCT	22 CKD 3, 16 CKD 4	50,000 IU weekly for 4 weeks followed by 50,000 IU monthly for 5 months (450,000 IU) Placebo	Control 24 weeks	23.8 ~14*	24.2 ~35*	0.4 21	168 103	No change (+11, ns) No change (–6, ns)
Thimachai et al, 2015 ¹⁰⁵	RCT	68 CKD 3–4	Double dose of KDOQI regimen	8 weeks	~10* 21	~10* 33.4	0 12.4	119 91	No change (+17, ns) Decrease (–15, $p=0.02$)
Susantitaphong et al, 2017 ⁹³	RCT	68 CKD 3–4	KDOQI regimen: 50,000 IU weekly if 25(OH)D <5 ng/mL; 50,000 IU weekly for 4 weeks followed by 50,000 IU monthly if 25(OH)D 5–15 ng/mL; 50,000 IU monthly if 25(OH)D 16–30 ng/mL 40,000 IU weekly + placebo (480,000 IU) 40,000 IU weekly + calcitriol 0.5 µg 2 times per week (480,000 IU)	12 weeks	20.8	23.4	2.6	97	No change (+4, ns)
					15.9	30.6	14.7	85	No change (+1, ns)
					19.3	33.4	14.1	89	Decrease (–15, $p=0.04$)

Notes: Only prospective studies with a minimum sample size of 20 patients were included.

Abbreviations: CKD, chronic kidney disease; EOS, end of study; PTH, parathyroid hormone; RCT, randomized controlled trial; ns, not significant; KDOQI, Kidney Disease Outcomes Quality Initiative.

Table 4 Cholecalciferol dosing regimes and associated changes in 25(OH)D and PTH in dialysis (CKD 5D) patients

Study, year	Type of study	N	Cholecalciferol dose (cumulative dose)	Treatment period	Baseline 25(OH)D (ng/mL)	EOS 25(OH)D (ng/mL)	25(OH)D change (ng/mL)	Baseline PTH (pg/mL)	PTH change (pg/mL)
Tokmak et al, 2008 ¹⁰⁶	Prospective cohort	64 HD	20,000 IU weekly (720,000 IU)	36 weeks	6.7	31.8	25.1	211	No change (-5, ns)
Jean et al, 2009 ¹⁰²	Prospective cohort	107 HD	100,000 IU monthly (1,500,000 IU)	60 weeks	12.8	42.4	29.6	294	Decrease (-104, p<0.05)
Matias et al, 2010 ¹⁰³	Prospective cohort	158 HD	50,000 IU weekly if 25(OH)D <15 ng/mL (1,200,000 IU, 34%) 10,000 IU weekly if 25(OH)D 16–30 ng/mL (240,000 IU, 46%) 2700 IU thrice per week if 25(OH)D >30 ng/mL (194,400 IU, 20%)	24 weeks	22.3	42	19.7	233	Decrease (-25, p<0.001)
Armas et al, 2012 ¹⁰⁷	RCT	42 HD	10,333 IU weekly po (154,995 IU)	15 weeks	13.3		23.6	174	No change (-25.7, ns)
Marckmann et al, 2012 ⁸⁴	RCT	27 HD	Placebo 40,000 IU weekly (320,000 IU)	8 weeks	15.2 8.3		0.5 46	126 170	No change (-8.3, ns) No change (-3, ns)
Wasse et al, 2012 ¹⁰⁸	RCT	52 HD	Placebo 200,000 IU weekly (600,000 IU)	3 weeks	14.4 14.3	52.4	-4.2 38.1	224 722	No change (-12, ns) No change (-48, ns)
Delanaye et al, 2013 ¹⁰⁹	RCT	30 HD	Placebo 25,000 IU every 2 weeks (600,000 IU)	48 weeks	19.0 12	18.4 34	-0.6 22	624 312	No change (-23, ns) Decrease (-115, p=0.02 between groups)
Hewitt et al, 2013 ¹¹⁰	RCT	60 HD	Placebo 50,000 IU weekly for 8 weeks, then monthly for 16 weeks (600,000 IU)	24 weeks	12 18	17 35	5 17	240 335	Increase (+80) No change
Li et al, 2014 ¹¹¹	RCT	96 HD	Placebo 50,000 IU weekly for 6 weeks, then if 25(OH)D >35ng/mL ↓ 10,000 IU weekly, otherwise continued	52 weeks	16 13.5	16 40.9	0 27.4	222 465	No change No change (+91, ns between groups)
Massart et al, 2014 ¹¹²	RCT	55 HD	Placebo 25,000 IU weekly for 13 weeks, afterwards individualized	39 weeks (13 weeks RCT, 26 weeks open-label)	13.0 17.1	15.8 35.2 (week 13)	2.8 18.1	434 414	No change (+203) No change (~-40, ns between groups)
Mose et al, 2014 ¹¹³	RCT	43 HD, 7 PD	Placebo 3,000 IU daily (504,000 IU)	24 weeks	18.4 11.2	16.4 (week 13) 33.7	-2.0 22.5	427 127	No change (~+50) No change (+37, ns between groups)
Dusilova-Sulkova et al, 2015 ¹¹⁴	Prospective cohort	68 HD	Placebo 5,000 IU weekly (75,000 IU) in n=34	15 weeks	11.2 7.4	12 27.5	0.8 20.1	170 205	No change (-48) Decrease (-34, p=0.05)
Zitt et al, 2015 ¹⁰¹	Prospective cohort	44 HD, 12 PD	10 µg paricalcitol + 5,000 IU weekly (75,000 IU) in n=34 100 IU per kg body weight weekly; mean weekly dose 7603 IU (200,000 IU)	26 weeks	7.3	27.1	19.8	364	Decrease (-44, p=0.01)
					9.9	26.1	16.2	362	Decrease (-65, p=0.001)

Notes: Only prospective studies with a minimum sample size of 20 patients were included.

Abbreviations: CKD, chronic kidney disease; EOS, end of study; PTH, parathyroid hormone; RCT, randomized controlled trial; HD, hemodialysis; PD, peritoneal dialysis; ns, not significant.

1 α -hydroxylase is present in parathyroid tissue.⁶⁸ There are no convincing data regarding the choice of vitamin D product or the administration route. Altogether, oral repletion seems to be more favorable compared with the intramuscular route in hemodialysis patients. Different dosing regimens in controlled and uncontrolled prospective studies have been used for both the vitamin D prohormones. Apart from fixed doses, also a body-weight-adapted dosing regimen has been recently shown to be safe and effective.¹⁰¹ Due to these methodological differences, the change of 25(OH)D levels and concurrent changes in PTH levels varied significantly. A detailed overview of published prospective studies investigating the effect of either cholecalciferol or ergocalciferol on PTH levels in dialysis patients is presented in Tables 4 and 5.

Although no significant changes were found in most studies, as shown in a very recent meta-analysis covering seven RCTs published during the last 5 years,⁶⁹ two earlier prospective studies with larger sample size and a long treatment period found a significant PTH reduction in patients with mild to moderate sHPT.^{102,103} Interestingly, in both the studies also 1,25(OH)₂D₃ increased significantly. Although in the study by Jean et al¹⁰² no patient received active vitamin D treatment, 44% of patients were treated with paricalcitol at baseline in the study by Matias et al.¹⁰³ In the latter one, higher 1,25(OH)₂D₃ levels were only found in patients without concurrent paricalcitol. In other studies, despite an increase in 1,25(OH)₂D₃ during the supplementation with cholecalciferol, PTH levels did not change. Obviously, the calcitriol levels, albeit higher but still far below the normal range, cannot sufficiently control sHPT. Pharmacological doses are necessary for that purpose as given with active vitamin D therapy. Nevertheless, cholecalciferol supplementation with very high doses (100,000 IU monthly) over a long period of 15 months without active vitamin D resulted in almost normal 1,25(OH)₂D₃ levels and may have thereby caused an impressive PTH reduction.¹⁰² Because of the significant increase in 1,25(OH)₂D seen with the supplementation of the prohormone even in dialysis-dependent patients, one might hypothesize whether a dual therapy with an active vitamin D (calcitriol, alfacalcidol, or analogs) and a vitamin D prohormone could help to reduce the dose of the active compound. By this means, such an approach could help to attenuate its toxicity and potentially lower the risk of vascular calcification with a lower hypercalcemic and hyperphosphatemic burden. On the other hand, metabolic interactions between both compounds might become important in this situation, as the active vitamin D compound may downregulate 1,25(OH)₂D production and the prohormone activate the catabolism of 1,25(OH)₂D via the activation of 24-hydroxylase.

Table 5 Ergocalciferol dosing regimens and associated changes in 25(OH)D and PTH in in dialysis (CKD 5D) patients

Study, year	Type of Study	N	Ergocalciferol dose (cumulative dose)	Treatment period	Baseline 25(OH)D (ng/mL)	EOS 25(OH)D (ng/mL)	25(OH)D change (ng/mL)	Baseline PTH (pg/mL)	PTH change (pg/mL)
Shirazian et al, 2013 ¹¹⁵	RCT	50 HD	50,000 IU weekly (600,000 IU) Placebo	12 weeks	19.7	38.7	19.0	288	No change (+17, ns)
Bhan et al, 2015 ¹¹⁶	RCT	105 HD	50,000 IU weekly (600,000 IU) 50,000 IU monthly (150,000 IU) Placebo	12 weeks	15.3	16.7 ~48.5* ~38*	1.4	313 265 253	No change (-1, ns) No change No change
Miskulin et al, 2016 ¹¹⁷	RCT	276 HD	50,000 weekly if 25(OH)D \leq 15 ng/mL (1,200,000 IU) or 50,000 weekly for 12 weeks followed by 50,000 IU monthly if 25(OH)D 16-30 ng/mL (750,000 IU) Placebo	24 weeks	22.3 21.7 16.0	~28*	23.2	249 425	No change No change (+58, ns)
					16.9	17.5	0.6	439	No change (-24, ns)

Notes: Only prospective studies with a minimum sample size of 20 patients were included. *Data extracted from figure.

Abbreviations: CKD, chronic kidney disease; EOS, end of study; PTH, parathyroid hormone; RCT, randomized controlled trial; HD, hemodialysis; PD, peritoneal dialysis; ns, not significant.

The efficacy of vitamin D prohormone supplementation on bone-related outcomes (such as fractures and bone pain) in CKD has not been established in high-quality studies. But such evidence is absent for all forms of vitamin D therapy. Given the available evidence by RCTs, supplementation with vitamin D prohormone has no consistent effect on PTH in patients on dialysis.

Conclusion

Vitamin D plays an important role in the development of sHPT in patients with declining renal function. These patients are characterized by a high prevalence of vitamin D insufficiency and deficiency. Supplementation with both vitamin D prohormones enables the achievement and maintenance of a normal vitamin D status when given in adequate doses over an appropriate treatment period. Although sHPT is influenced and can be successfully treated in patients with earlier stages of CKD, vitamin D prohormone supplementation seems to be of limited efficacy in patients with very late stages of CKD and those requiring dialysis. Despite all available evidence, there is still a need for high-quality RCTs determining the effect of vitamin D supplementation on sHPT with emphasis on 1) adequate supplementation protocols enabling a high proportion of patients to reach target levels, 2) identifying the target range for 25(OH)D level in CKD, 3) evaluating the role of a sequential compared with a combined treatment with prohormone and active compounds, and 4) collecting detailed data about 1,25(OH)₂D and FGF23 and clinically relevant side effects.

Disclosure

The authors report no conflicts of interest in this work.

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