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The Use of Vitamin D Metabolites and Analogs in the Treatment of Chronic Kidney Disease

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Abstract

CKD and ESRD are associated with abnormalities in bone and mineral metabolism collectively known as chronic kidney disease-bone mineral disorder (CKD-MBD). Patients with CKD and ESRD have skeletal abnormalities characterized by hyperparathyroidism, mixed uremic osteodystrophy, osteomalacia and adynamic bone disease. Such patients also frequently have enhanced vascular and ectopic calcification. Hyperparathyroidism and mixed uremic osteodystrophy are the commonest manifestations of CKD-MBD, and are due to phosphate retention, reduced concentrations of 1, 25 dihydroxyvitamin D and intestinal calcium absorption, and negative calcium balance. Treatment with 1-hydroxylated vitamin D analogs is useful in treating secondary hyperparathyroidism and mixed uremic osteodystrophy in CKD/ESRD.

The spectrum chronic kidney disease-mineral bone disorder (CKD-MBD)

Skeletal abnormalities in patients with chronic kidney disease (CKD)

Alterations in skeletal, cardiovascular, and neurological function occur in CKD and end-stage renal disease (ESRD). Abnormalities in bone and mineral metabolism result not only in changes in the skeleton but also alterations in vascular and soft tissue calcification, the entire syndrome being referred to as chronic kidney disease-mineral and bone disorder (CKD-MBD)¹. The role of abnormalities in the vitamin D endocrine system is most clearly defined in the pathogenesis of bone disease in CKD/ESRD^{2–4}. The salutary effects of vitamin D analogs are most apparent in the treatment of disorders of CKD/ESRD-associated bone disease, and are of unknown value in the treatment of vascular and soft tissue calcification. When assessed by bone histomorphometry and the rate of bone mineralization, renal osteodystrophy comprises several groups including secondary hyperparathyroidism of varying severity, mixed uremic osteodystrophy, osteomalacia, and adynamic bone disease^{1, 5–11}. Hyperparathyroidism is the most frequent type of renal osteodystrophy and is most responsive to therapy with vitamin D analogs. Although hyperparathyroidism is readily detectable by the time the glomerular filtration rate (GFR) reaches 40–50 mL/minute/1.73m² in both adults^{7, 11–13} and children^{14, 15}, histologic changes in bone in the form of abnormal

woven osteoid have been described when the GFR has declined to only 80 mL/minute/1.73m²¹². Phosphate retention^{7, 16–25}, a decline in concentrations of the active metabolite of vitamin-D, 1 α ,25 dihydroxyvitamin-D₃ (1 α ,25(OH)₂D)^{3, 4, 26–33} with an attendant decrease in intestinal calcium absorption^{34–37}, increased fibroblast growth factor 23 concentrations^{38–43}, and diminished acid excretion by the kidney^{44–46} occur when the GFR has decreased to 30–50 mL/min/1.73m², and contribute in inter-related ways to the pathogenesis of CKD-MBD. We will briefly review some aspects of vitamin D metabolism (see reviews by Christakos and Pike in this volume, as well as those in other journals^{47–64}) and describe abnormalities that are known to occur in the context of CKD/ESRD. We will subsequently discuss the value of various vitamin-D analogs in the treatment of CKD MBD.

The pathophysiology of the vitamin D endocrine system in CKD/ESRD

The major physiologic role of vitamin D, through the action of its active metabolite 1 α ,25(OH)₂D, is the maintenance of normal calcium and phosphorus balance^{65–68}. Many other biological effects of 1 α ,25(OH)₂D have been described such as the modulation of immune function^{69, 70}, muscle function^{51, 59, 71}, and cell growth and differentiation^{53, 72, 73} but are not relevant to the pathogenesis of CKD-MBD.

The generation of vitamin D in the skin is impaired in uremia

The endogenous form of vitamin D, vitamin D₃ (cholecalciferol), is formed in the skin as a result of photolysis of the precursor sterol, 7-dehydrocholesterol (7-DHC)^{74–82} (Fig. 1). Ultraviolet light cleaves the B-ring of 7-DHC, giving rise to pre-vitamin D₃, which undergoes equilibration to vitamin D₃^{80–82}. Vitamin D₃, bound to vitamin D-binding protein (VDBP, or group specific component), to which it preferentially binds relative to its precursor, pre-vitamin D₃, exits the skin and enters the circulation⁸¹. In plants, a precursor sterol, ergosterol, is converted by photolysis to ergocalciferol or vitamin D₂^{83–85}. In mammals, vitamin D₂ and vitamin D₃ have similar metabolic transformations and equivalent bioactivities, and for purposes of this discussion the term vitamin D refers to both vitamin D₂ and vitamin D₃. The photolytic conversion of 7-DHC to vitamin D₃ is impaired in CKD/ESRD in humans⁸⁶. In uremic white subjects, plasma vitamin D was similar to that seen in normal white subjects but was not detectable in 70% of uremic black subjects studied. Following ultraviolet-B irradiation, the increase in plasma vitamin D was depressed in white dialysis patients when compared to healthy white subjects. 7-DHC content was similar in epidermis from site-matched skin of uremic and normal subjects. The precise reason for the impaired production of vitamin D₃ in the skin of uremic subjects is unknown although one might speculate that the accumulation of various pigments might play a role. Low serum concentrations of vitamin D contribute to a decrease in and circulating concentrations of 25-hydroxyvitamin D (25(OH)D).

25(OH)D concentrations are reduced in CKD/ESRD

Vitamin D is metabolized in the liver microsomes and mitochondria to 25-hydroxyvitamin D₃ (25(OH)D) by the vitamin D₃-25-hydroxylase^{87–98} (Fig 1). The vitamin D-25-hydroxylase is only partially inhibited by its product, and increasing amounts of administered vitamin D are associated with increases in 25(OH)D. 25(OH)D is the major

circulating vitamin D metabolite^{65, 78, 94, 99–101}, and measurements of its concentration are an excellent index of vitamin D nutritional status^{102–105}. In CKD, 25(OH)D concentrations are frequently diminished and increase upon the administration of vitamin D₃^{106–120}. The diminished concentrations of 25(OH)D may be related to a decrease in nutritional intake, a decrease in sun exposure, a reduction in the generation of vitamin D₃ from 7-DHC⁸⁶ or a loss of vitamin D binding protein in the proteinuric patients. Lower levels of 25(OH)D have been associated with increased risk of progression of renal disease and mortality^{116, 121}. 25(OH)D-1- α -hydroxylase enzyme activity is present in tissues other than the kidney^{122–124} and increased amounts of substrate may result in the generation of 1 α ,25(OH)₂D locally. Therefore, some have advocated the use of vitamin D supplementation in patients with CKD and ESRD. Before 1 α ,25(OH)₂D₃ was available for clinical use, 25(OH)D supplementation was used to suppress PTH levels in dialysis patients¹²⁵. A metaanalysis of observational and randomized controlled trials have shown that vitamin D supplementation results in a small reduction in PTH level in both CKD and dialysis patients¹¹³. In a recent randomized controlled trial of 105 dialysis patients comparing two different doses of ergocalciferol with placebo, ergocalciferol did not alter calcium, phosphorous, or PTH levels compared to placebo during a 12-week period¹²⁶. Given these results, the use of vitamin D supplementation in dialysis patients is not recommended. Vitamin D supplementation can be considered in patients with early stages of CKD where residual 25(OH)D 1- α -hydroxylase enzyme may still be present.

Reduced intestinal calcium absorption and serum 1 α ,25(OH)₂D is present in patients with CKD/ESRD

In CKD and ESRD there is a decrease in the intestinal calcium absorption with concomitant negative calcium balance^{34–37}. Reduced serum concentrations of 1 α ,25(OH)₂D^{3, 4, 26–33} are present. The central role of 1 α ,25(OH)₂D in maintaining calcium balance in CKD/ESRD is demonstrated by the observations that not only are 1 α ,25(OH)₂D concentrations reduced in CKD/ESRD but that 1 α ,25(OH)₂D readily increases intestinal calcium transport^{127, 128} and mobilizes calcium from bone¹²⁹ whereas pharmacological amounts of precursors such as vitamin D itself or intermediary metabolites such as 25(OH)D are required to elicit a biological response in anephric animals and patient^{27, 129, 130}. In the sections that follow we discuss how 1 α ,25(OH)₂D is synthesized, how the processes are regulated, and what perturbations occur in CKD/ESRD that inhibit the formation of 1 α ,25(OH)₂D.

In states of calcium demand, 25(OH)D is metabolized by the renal 25-hydroxyvitamin D-1 α -hydroxylase to the biologically active vitamin D metabolite, 1 α ,25(OH)₂D, in the kidney by parathyroid hormone-dependent processes^{60, 65, 78, 127, 128, 130–139} (Fig 2A). Increased concentrations of 1 α ,25(OH)₂D enhance the expression of genes required for the transport of calcium across the enterocyte^{140, 141} and in the distal convoluted tubule of the kidney. Calcium is absorbed by the intestine by passive paracellular and active transcellular mechanisms^{141–143}. Active Ca absorption is 1 α ,25(OH)₂D-dependent is transcellular and requires the expenditure of energy^{144, 145}. Several vitamin D dependent proteins, each with a specific function, play a role in the movement of calcium across the apical membrane, the enterocyte cytoplasm and the basal lateral membrane. These include the epithelial calcium or TRPV 5/6 channels (at the apical membrane), calbindin D_{9K} and D_{28K} (within the cell),

and the plasma membrane calcium pump (at the basal lateral membrane)¹⁴⁶. Deletions of *TrpV6* and *calbindin D_{9K}* genes are not associated with alterations in intestinal Ca transport *in vivo* in the basal state and following the administration of $1\alpha,25(\text{OH})_2\text{D}$ ^{147, 148}, although one report suggests that basal Ca transport is normal in *TrpV6* knockout mice but adaptations to a low Ca diet are impaired¹⁴⁹. Deletion of the *Pmca1* in the intestine is associated with reduced growth and bone mineralization, and a failure to up-regulate calcium absorption in response to $1\alpha,25(\text{OH})_2\text{D}_3$ thereby establishing the essential role of the pump in transcellular Ca transport¹⁵⁰. In states of calcium sufficiency, the $1\alpha,25(\text{OH})_2\text{D}$ synthesis is reduced, and the synthesis of $24R,25$ -dihydroxyvitamin D ($24R,25(\text{OH})_2\text{D}$)^{151–153}, a vitamin D metabolite of reduced but uncertain activity, is increased.

Serum phosphate concentrations also regulate the synthesis of $1\alpha,25(\text{OH})_2\text{D}$ by parathyroid hormone independent mechanisms¹⁵⁴. Thus, when serum phosphate concentrations are diminished and in states of phosphorous demand, $25(\text{OH})\text{D}$ is metabolized to $1\alpha,25(\text{OH})_2\text{D}$ and the synthesis of $24R,25(\text{OH})_2\text{D}$ is reduced^{64, 133, 154–164} (Fig 2B). The converse occurs in hyperphosphatemic states. A decrease in serum phosphate concentration is associated with an increase in ionized calcium, a decrease in PTH secretion, and a subsequent decrease in renal phosphate excretion. An increase in renal 25 -hydroxyvitamin D 1α -hydroxylase activity, increased $1\alpha,25(\text{OH})_2\text{D}$ synthesis, and increased phosphorus absorption in the intestine and reabsorption in the kidney occur. In the intestine and kidney, $1\alpha,25(\text{OH})_2\text{D}$ regulates the expression of the sodium-phosphate co-transporters IIB, and IIA and IIC, respectively, thereby regulating the efficiency of Pi absorption in enterocytes and proximal tubule cells^{146, 165–167}.

The bioactivity of vitamin D is dependent on the formation of $1\alpha,25(\text{OH})_2\text{D}$. Pharmacological amounts of precursors such as vitamin D itself or intermediary metabolites such as $25(\text{OH})\text{D}$ are required to elicit a biological response in anephric animals and patients^{27, 129, 130}. In such individuals, $1\alpha,25(\text{OH})_2\text{D}$ readily increases intestinal calcium transport^{127, 128} and mobilizes calcium from bone¹²⁹. The actions of $1\alpha,25(\text{OH})_2\text{D}_3$ require the presence of the vitamin D receptor, a steroid hormone receptor, that binds $1\alpha,25(\text{OH})_2\text{D}_3$ with high affinity and other vitamin D metabolites with lower affinities^{168–171}. Following binding of the ligand, $1\alpha,25(\text{OH})_2\text{D}_3$ to the VDR, a conformational change in the receptor is associated with the recruitment of other steroid hormone receptors such as the RXR α and various co-activator (or co-repressor) proteins to the transcription start side of $1\alpha,25(\text{OH})_2\text{D}_3$ regulated genes^{172–180} (see chapter 1). Several calcium regulating genes are induced or repressed in vitamin D-responsive target tissues such as the intestine, kidney, parathyroid gland and bone^{67, 71, 181–186}.

Retention of phosphate and reductions in renal mass are responsible for reduced $1\alpha,25(\text{OH})_2\text{D}$ synthesis

As glomerular filtration rate declines (usually less 50 ml/min/SA) hyperphosphatemia develops which is accompanied by hypocalcemia, secondary hyperparathyroidism, a reduction in $1\alpha,25(\text{OH})_2\text{D}$ concentrations and an elevation in fibroblast growth factor 23 (FGF23) levels. The retention of phosphate with decreasing GFR^{21, 25, 187–193} and a reduction in the number of tubular cells^{2, 4, 26, 106, 194, 195} in which the synthesis of $1\alpha,$

25(OH)₂D occurs are major determinants in evolution of low serum 1α,25(OH)₂D concentrations (Fig. 3). Decreased phosphate excretion and increased serum phosphate concentrations enhance the production of the phosphaturic factor, FGF23^{43, 196}, which inhibits the production of 1α,25(OH)₂D^{197, 198}. Hyperparathyroidism occurs as a result of reduced concentrations of 1α,25(OH)₂D and the attendant negative calcium balance from reduced intestinal calcium absorption, and as a result of loss of inhibition of PTH synthesis associated with the low serum concentrations of 1α,25(OH)₂D and decreased parathyroid gland VDR concentrations^{199–209}.

Vitamin D analogs in the treatment of hyperparathyroidism in CKD/ESRD

A combined approach aimed at reducing serum phosphate concentrations, improving the negative calcium balance and inhibiting parathyroid hormone secretion is required for the effective treatment of hyperparathyroidism in the context of CKD/ESRD. We favor a stepwise approach of first reducing serum phosphate concentrations with the use of phosphate binders such as sevelamer, calcium salts (e.g. calcium acetate, calcium carbonate), lanthanum carbonate, or various iron preparations (ferric citrate, sucroferric oxyhydride), correcting the negative calcium balance with the use of various 1α-hydroxylated vitamin-D analogs, and finally using calcium sensing receptor agonists such as cinacalcet. In the section that follows we will describe the use of various vitamin-D analogs in the treatment of CKD MBD in the context of CKD/ESRD. The structures of various compounds used in this regard are shown in Figure 4.

Calcitriol (1α,25(OH)₂D₃)

It is the naturally occurring, active form of vitamin D that is available for use in CKD/ESRD patients. Its primary use is to suppress the PTH gland. An unwanted side effect is increase in calcium and phosphorous levels through its action on the intestine. Both oral and intravenous formulations have been used. Multiple small clinical trials have compared the efficacy of oral vs. intravenous calcitriol in patients with ESRD^{210–215}. A majority of the studies have shown that oral calcitriol is as effective as intravenous calcitriol in reducing PTH concentrations with similar rates of hypercalcemia and hyperphosphatemia. In the most recent meta-analysis of 9 RCT similar findings were noted²¹⁶. Based on the available data either intravenous or oral formulations are reasonable choices when treating ESRD patients with secondary hyperparathyroidism. The intravenous formulation is more commonly used in the United States whereas the oral formulation is more frequently used in other countries. The intravenous formulation is more expensive but does ensure adherence. These issues need to be taken into account when deciding on what route to choose.

Paricalcitol (1,25(OH)₂-19-nor-D₂)

This vitamin D₂ analog lacks the axis cyclic methylene group on the A ring of the sterol. It was the first analog to be approved for use in patients with CKD. In animal models it is shown to cause equivalent suppression of PTH relative to calcitriol but with less hypercalcemia and hyperphosphatemia²¹⁷. In uremic rat models, paricalcitol has shown to improve the bone histology²¹⁸. In placebo-controlled trials of paricalcitol in dialysis patients, 68% of patients treated with paricalcitol achieved 30% reduction in PTH as

opposed to 8% in control subjects, and there were few hypercalcemic events recorded in the patients treated with the drug²¹⁹. Paricalcitol also resulted in a reduction in the bone turnover marker, alkaline phosphatase²¹⁹. In another placebo-controlled trial, paricalcitol resulted in hypercalcemia mainly in patients who had significant reduction in their PTH concentrations, often with levels less than 100 pg/ml²²⁰. In a double blind randomized study comparing calcitriol to paricalcitol in dialysis patients, those treated with paricalcitol had lower PTH levels at the end of the study and achieved target PTH levels faster with fewer episodes of hypercalcemia and lower calcium phosphorous byproducts compared to those treated with calcitriol²²¹. In a large retrospective cohort study of dialysis patients, those treated with paricalcitol were shown to have a survival advantage compared to those treated with calcitriol²²². In adjusted models, survival was 16% (95% confidence interval 10–21%) lower in paricalcitol group compared to calcitriol group. The percentage rise in serum calcium and phosphorous was also lower in those who received paricalcitol compared to calcitriol. This survival advantage, however, has not been evaluated in any randomized controlled trials, and the results of this retrospective study should be interpreted with caution.

Doxercalciferol (1 α -(OH)D₂)

1 α -(OH)D₂ is converted to the active form, 1 α ,25(OH)₂D₂ through the action of 25-hydroxylase in the liver. Clinical studies of doxercalciferol have shown it to be effective in suppressing PTH levels but have also shown a modest rise in serum calcium and phosphorous levels^{223, 224}. An intravenous preparation of doxercalciferol is available, and the drug was found to be effective in suppressing PTH with lower rates of hypercalcemia and hyperphosphatemia than 1 α -(OH)D₂²²⁵. In a small clinical study comparing the dosing of doxercalciferol to paricalcitol, dosing doxercalciferol at 60% of the dose of paricalcitol results in similar reduction in PTH level²²⁶. In another study comparing doxercalciferol to paricalcitol, doxercalciferol was found to produce a similar reduction in PTH levels and was associated with higher rates of hyperphosphatemia or the Ca X P product²²⁷.

Alfacalcidol (1 α -(OH)D₃)

1 α -(OH)D₃ is converted to the active form, 1 α ,25(OH)₂D₃, in the liver. A study comparing alfacalcidol to calcitriol showed that at doses 1.5 to 2 times that of calcitriol, alfacalcidol is equally effective in suppressing PTH with a similar rate of hypercalcemia and hyperphosphatemia²²⁸. In a randomized cross over trial comparing alfacalcidol to paricalcitol in ESRD patients, alfacalcidol was shown to be as effective in suppressing PTH levels with similar rates of hypercalcemia and hyperphosphatemia as paricalcitol²²⁹.

Maxacalcitol (22-oxa-1,25(OH)D₃)

The structure of maxacalcitol is similar to calcitriol except for the presence of an oxygen between C21 and C23. Maxacalcitol has been shown to result in less hypercalcemia in animal models, but this has not translated into clinical trials²³⁰. In humans maxacalcitol has been shown to be effective in suppressing PTH levels^{231–233}, but in a study of 124 dialysis patients treated with maxacalcitol, 41 experienced hypercalcemia²³². There is a dose-dependent relationship between the dose of maxacalcitol and risk of hypercalcemia²³¹.

Intravenous maxacalcitol is not superior to oral calcitriol²³⁴ in as much as decrements in PTH concentrations and the rate of hypercalcemia are similar²³⁴.

Falecalcitriol (1,25(OH)₂-26,27-F₆-D₃)

It is a newer analog and is currently only available in Japan. In animal studies it is suggested to be highly potent in inhibiting PTH²³⁵. In clinical trials comparing falecalcitriol to alfacalcidol, falecalcitriol has been shown to be more effective than alfacalcidol in reducing PTH with similar rates of hypercalcemia²³⁶.

A comparison of the various drugs available for the treatment of hyperparathyroidism in CKD/ESRD is shown in Table 1.

Other effects of vitamin D and its analogs

Hypertension and left ventricular hypertrophy

Vitamin D deficiency has been suggested to play a role in both development of cardiac hypertrophy and hypertension. Indeed vitamin D receptor knock out mice have been shown to develop both hypertension and left ventricular hypertrophy (LVH) suggesting that vitamin D may directly affect the myocardium²³⁷. Vitamin D may contribute to development of hypertension and LVH through inhibition of renin. Vitamin D receptor null mice are shown to have higher expression of renin and angiotensin II associated with both hypertension and LVH²³⁸. Similarly, hypertensive rats treated with vitamin D analogs have less cardiac hypertrophy than rats treated with vehicle^{239,240}. In small clinical trials of dialysis patients, treatment with calcitriol has been shown to attenuate LVH^{241, 242}. In a large randomized placebo-control trial of 227 patients with CKD with mild to moderate LVH, treatment with paricalcitol at a dose of 2 µg/day for 48 weeks did not result in any improvement in left ventricular mass index²⁴³.

Albuminuria

In multiple animal models, vitamin D and its analogs have been shown to reduce albuminuria^{244–248}. Similar results have been shown in human clinical trials. Patients with CKD treated with paricalcitol had lower urinary protein or 24 hour albumin excretion rates compared to placebo^{249, 250}. In a larger RCT involving patients with type 2 diabetes those treated with paricalcitol had lower urinary albumin to creatinine ratios compared to placebo-treated subjects, but they also had a lower eGFR²⁵¹. Whether the reduction in urinary albumin is a true reduction or reflection of hemodynamic changes remains unclear. Similarly whether this reduction translates to better renal outcome long-term is also to be seen. More recent studies however, have failed to show a benefit in albuminuria in patients treated with doxercalciferol²⁵².

Mortality

Low 25(OH)D levels have been associated with increased mortality in patients with CKD and ESRD similar to the general population^{116, 253–256}. Similarly, lower vitamin D levels are associated with increased rate of progression to ESRD¹¹⁶. Many observational studies have suggested that use of active vitamin D in CKD and dialysis patients improves

survival^{257–263}. These studies are all confounded by the fact that patients who do not receive vitamin D or who had lower vitamin D levels might have been sicker with attendant higher mortality. This type of bias is not accounted for in standard regression models. Tentori F *et al.* re-evaluated the data from participants in the DOPPS study to evaluate the association between vitamin D and mortality²⁶⁴. Indeed, patients who were prescribed vitamin D had fewer comorbidities; when adjusted for confounding variables, vitamin D administration was no longer associated with improved mortality²⁶⁴. The lack of mortality benefit with use of vitamin D or its analog was also shown in a large meta-analysis of 76 trials²⁶⁵. Not only did the administration of vitamin D or its analogs not result in mortality benefit, but 1 α , 25(OH)₂D₃ administration was associated with higher rate of hypercalcemia and hyperphosphatemia and had a variable effect on reducing PTH levels²⁶⁵. It should be noted that in the various trials included in the meta-analysis²⁶⁵, the degree of suppression of PTH was variable and there were methodological differences in the measurement of PTH.

In conclusion, 1-hydroxylated vitamin D analogs are effective in the treatment of secondary hyperparathyroidism in the context of CKD/ESRD. Further studies are required to assess their benefits in the treatment of heart disease and albuminuria.

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Key points

- Secondary hyperparathyroidism and mixed-uremic osteodystrophy are common in chronic kidney disease (CKD) and end-stage renal disease (ESRD).
- Reduced concentrations of 1,25-dihydroxyvitamin D, intestinal malabsorption of calcium, and negative calcium balance contribute to secondary hyperparathyroidism in these conditions.
- A stepwise approach of reducing serum phosphate concentrations with the use of phosphate binders such as sevelamer, calcium salts (e.g. calcium acetate, calcium carbonate), lanthanum carbonate, or various iron preparations (ferric citrate, sucroferric oxyhydride); correcting negative calcium balance with 1 α -hydroxylated vitamin-D analogs; and using calcium sensing receptor agonists such as cinacalcet is generally effective in correcting secondary hyperparathyroidism in CKD and ESRD.
- Treatment with 1-hydroxylated vitamin D metabolites or analogs such as calcitriol, alphacalcidol, doxercalciferol, paricalcitol, maxacalcitol and falecalcitriol are effective in the treatment of secondary hyperparathyroidism seen in CKD and ESRD.

Figure 1.
The metabolism of vitamin D

Figure 2.**A.** Adaptations in response to a decrease in serum calcium concentrations.**B.** Adaptations in response to decrease in serum phosphate concentrations.

Figure 3.
Pathogenesis of secondary hyperparathyroidism in CKD/ESRD

Figure 4.
Structures of vitamin D analogs used in the treatment of CKD MBD

Table 1

Drugs available for the treatment of secondary hyperparathyroidism in CKD/ESRD

Drug	Brand Name	Available in US	Oral or IV	Starting doses	Effect on calcium *	Effect on phosphorous *
Calcitriol	Rocaltrol/Calcijex	Yes	Both	1–2 µg IV thrice weekly	NA	NA
Paricalcitol	Zemplar	Yes	Both	2–4 µg IV thrice weekly	Less hypercalcemia	Less hyperphosphatemia
Alfacalcidol	One-Alpha (Canada)	No	Both		Similar to calcitriol	Similar to calcitriol
Doxercalciferol	Hectorol	Yes	Both	2–4 µg IV thrice weekly	Similar to calcitriol	Similar to calcitriol
Maxacalcitol	Oxarol (Japan)	No	IV		Similar to calcitriol	Similar to calcitriol
Falecalcitriol	Homel (Japan)	No	Oral		Similar to calcitriol	Similar to calcitriol

* compared to calcitriol