

# A new role for vitamin D receptor activation in chronic kidney disease

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**Valdivielso JM, Cannata-Andía J, Coll B, Fernández E.** A new role for vitamin D receptor activation in chronic kidney disease. *Am J Physiol Renal Physiol* 297: F1502–F1509, 2009. First published July 22, 2009; doi:10.1152/ajprenal.00130.2009.—Vitamin D has proven to be much more than a simple “calcium hormone.” The fact that the vitamin D receptor has been found in cells not related to mineral metabolism supports that statement. The interest of nephrologists in vitamin D and its effects beyond mineral metabolism has increased over the last few years, evidencing the importance of this so-called “sunshine hormone.” In the present review, we highlight the most recent developments in the traditional use of vitamin D in chronic kidney disease (CKD) patients, namely, the control of secondary hyperparathyroidism (sHPT). Furthermore, we also explore the data available regarding the new possible therapeutic uses of vitamin D for the treatment of other complications present in CKD patients, such as vascular calcification, left ventricular hypertrophy, or proteinuria. Finally, some still scarce but very promising data regarding a possible role of vitamin D in kidney transplant patients also are reviewed. The available data point to a potential beneficial effect of vitamin D in CKD patients beyond the control of mineral metabolism.

VITAMIN D IS A STEROID HORMONE that has long been known for its important role in regulating body levels of calcium (Ca) and phosphorus (P) and in mineralization of bone. However, there is an increasing amount of data proving that vitamin D exerts its effects beyond kidney, intestine, and bone (Fig. 1). The active form of vitamin D (calcitriol) mediates its biological effects by binding to the vitamin D receptor (VDR), which then translocates to the nuclei of target cells (for review, see Ref. 47). The VDR is a ligand-activated transcription factor that, after activation, recruits cofactor molecules and binds to specific DNA binding sites to modify the expression of target genes. Ligand-mediated conformational changes of the VDR contribute to specific mechanisms in its signaling cascade. Thus the structural chemical modification of active vitamin D is a powerful tool in discovering new compounds that show selective activation of the VDR. Over the last years, a number of new VDR activators (VDRA), defined as compounds that can bind to VDR and induce its activation, have been synthesized and used in several diseases, including in patients with CKD. Their potential as new therapeutic agents has boosted this area of research. Moreover, new evidence suggests that VDR polymorphisms may influence the response to VDRA (125).

## Present Use of VDRA in Patients with CKD

One of the main complications in patients with CKD is the development of secondary hyperparathyroidism (sHPT). In the

past, the increase in parathyroid gland (PTG) size and parathyroid hormone (PTH) synthesis were attributed to a decrease in circulating Ca. As a result, patients with sHPT were treated with oral vitamin D metabolites to correct hypocalcemia. After discovering the presence of the VDR in PTGs and that calcitriol regulates parathyroid cell proliferation and PTH synthesis (88, 107, 110, 116), the treatment in CKD patients on dialysis shifted to intravenous injections of calcitriol. Furthermore, the fact that calcitriol levels decrease progressively as renal function declines (72) made it the treatment of choice as hormone replacement therapy. In addition, low levels of calcitriol in CKD are expected to have even lower biological effects, since the binding of activated VDR to the response elements in the DNA is compromised in uremia (89). However, the treatment with calcitriol was not successful in all cases, because the PTG frequently undergoes a nodular transformation that leads to a marked decline in VDR density (34).

Treatment with calcitriol has been routinely used with the aim to halt the PTG hyperplasia and hypertrophy and to reduce serum levels of PTH. The calcitriol-mediated regulation of sHPT would have its effect through two different mechanisms involving both the VDR and the Ca-sensing receptor (CaSR) (21). On the one hand, VDRA increases the currently reduced expression of VDR (21) in the PTG, favoring a reduction in PTH synthesis and gland growth. Although this mechanism will decrease PTH levels, it is in contrast to one of the main objectives of calcitriol, which is to raise Ca levels back to normal. This effect of calcitriol could make physiological sense if VDR-mediated effects on the PTG were to occur only when Ca levels are not low. Thus Carrillo-Lopez et al. (21) showed that increasing concentrations of Ca produced a dose-dependent increase in VDR mRNA. Furthermore, addition of

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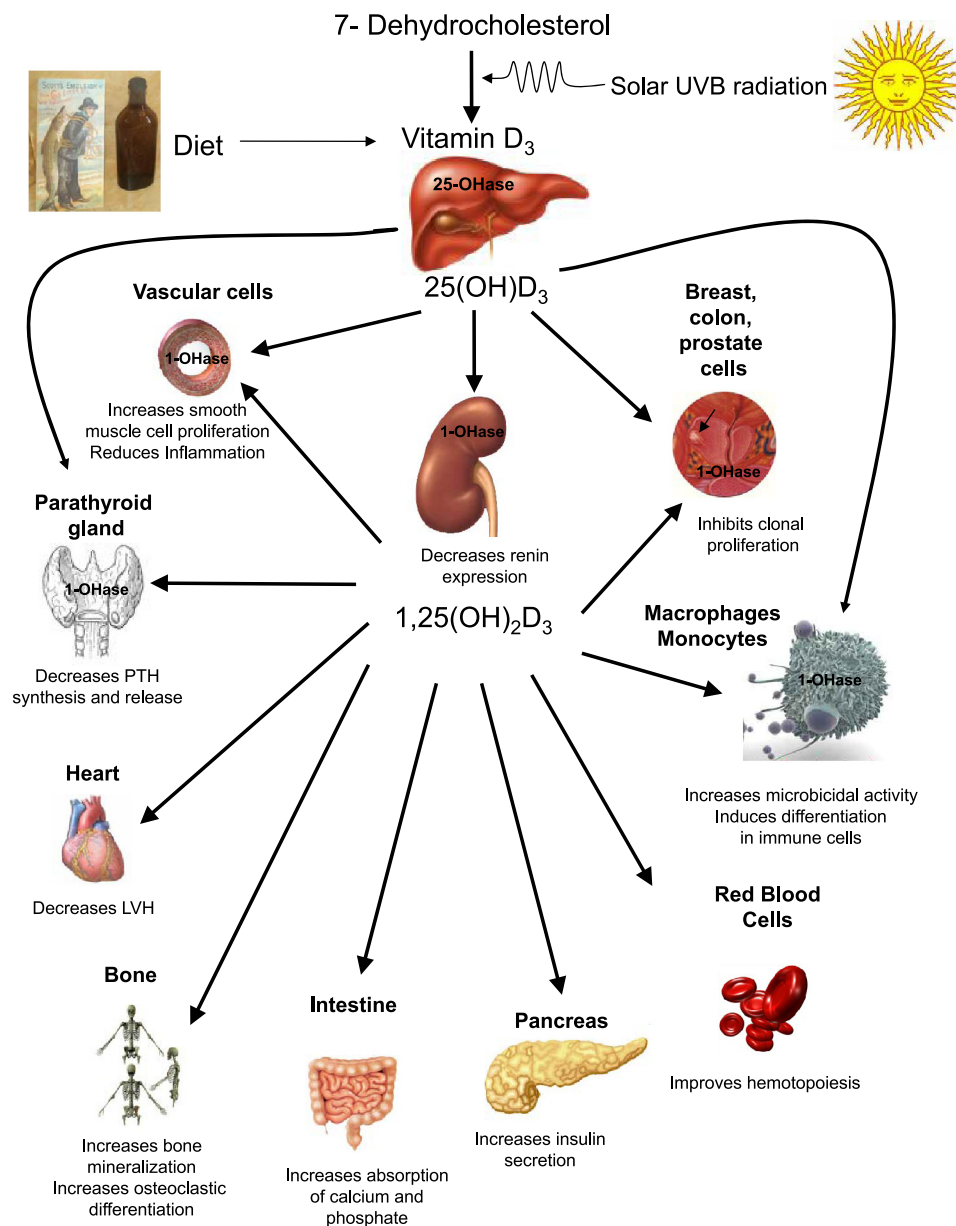


Fig. 1. Synthesis and target organs for vitamin D. Vitamin D<sub>3</sub> obtained from the diet or by photolytic conversion in the skin is hydroxylated in the liver into 25-hydroxyvitamin D<sub>3</sub> [25(OH)D<sub>3</sub>]. The formation of 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>] occurs mainly in the kidney, but extrarenal synthesis also has been described in vascular cells, parathyroid gland, macrophages, and some cancer cells. The presence of vitamin D receptor has been shown in many target cells regulating calcium and phosphorus absorption, cell proliferation, immune function, and other processes. OHase, hydroxylase; PTH, parathyroid hormone; LVH, left ventricular hypertrophy.

calcimimetics will further increase the VDR induction by calcitriol at a fixed Ca concentration (97). Additional support to this hypothesis came from experiments with mice lacking the VDR, the 1 $\alpha$ -hydroxylase protein, or both, in which normalization of Ca and P levels was enough to suppress PTH secretion (84), suggesting that the calcitriol system is ineffective in controlling PTH if Ca levels are low. On the other hand, VDRA increases the levels of CaSR (16) as well as serum Ca. Activation of CaSR will decrease PTH secretion through the PKC-AA pathway involving ERK1/2-MAP kinases, but, again, only if blood Ca levels are not low (56). Therefore, it appears that Ca (or calcimimetic agents) and VDRA combined efforts are more effective in reducing PTH secretion. Thus Ca not only inhibits PTH secretion but also increases VDR expression, which in turn facilitates the effect of calcitriol. In addition, calcitriol not only decreases PTH mRNA but also upregulates CaSR expression, making the parathyroid cell more receptive to the inhibition by Ca (21).

High P levels also are directly responsible for increasing PTH synthesis and release (3, 111). Hence, an additional indirect effect of calcitriol to decrease PTG hyperplasia would be through stimulating the synthesis of fibroblast growth factor 23 (98), which will stimulate phosphaturia and reduce plasma P levels (100). How P increases blood PTH levels is still unknown, but it could be through an indirect mechanism by decreasing VDR levels in the PTG (23, 27) and activating the transforming growth factor (TGF)- $\alpha$ -EGF receptor (EGFR) pathway. EGFR activation decreases VDR levels by increasing the synthesis of LIP (9), which is the truncated, dominant negative form of the transcription factor CCAAT/enhancer binding protein (C/EBP $\beta$ ) LAP. LAP binding to the C/EBP binding sites in the VDR gene promoter increases VDR gene expression (24). In the presence of EGFR activation, LIP levels are increased. Because LIP lacks the transactivation domain but binds to DNA with higher affinity than that of LAP, LAP heterodimerization with LIP results in inhibition of LAP func-

tion as a transcriptional activator of the VDR gene. Indeed, pharmacological inhibition of the EGFR signaling pathway, using EGFR-tyrosine kinase inhibitors (EGFR-TKI), blocked the decrease in VDR levels induced by high P concentrations and restored the response to VDRA treatment (26). Furthermore, treatment of experimental animals with EGFR-TKI induced a decrease in LIP levels and PTG growth and an increase in LAP/LIP ratio and VDR expression (5).

Throughout the years, one important disadvantage of using high doses of calcitriol in CKD patients was the risk of increasing extrasosseous calcifications from frequent episodes of hypercalcemia and hyperphosphatemia. This prompted the search for analogs that retained the effect of calcitriol on PTG while lacking the hypercalcemic and hyperphosphatemic effects. One of the most studied analogs has been paricalcitol [19-nor-1,25(OH)<sub>2</sub>D<sub>2</sub>], which in experimental studies has been shown to retain the capacity to inhibit sHPT while having less calcemic and phosphatemic effects (112). Dialysis patients treated with paricalcitol showed a faster decrease in PTH levels with fewer episodes of hypercalcemia and lower Ca × P product levels (115). The effects of calcitriol and paricalcitol on bone biology also are different. In vitro and in vivo, paricalcitol has been shown to be less effective than calcitriol in stimulating bone resorption and more effective in inducing bone formation (29, 79). These differences could be multifactorial, e.g., different affinity to VDR (113), different magnitude of the transactivation of several genes (15), secondary to differences in the conformational changes and corepressors or coactivators recruitment. In fact, it has been demonstrated that VDR bound to paricalcitol or 22-oxacalcitriol recruits different coactivators from those recruited by the same receptor when bound to calcitriol (51, 117).

The search for new vitamin D analogs is of great interest, and it is an open field for research. The high plasticity of the VDR signaling mechanism allows for VDR from different tissues to behave differently despite being activated by the same VDRA. For instance, the renal VDR is upregulated by calcitriol and downregulated by Ca, whereas duodenal VDR is not (44). Similarly, different VDRA acting on the same cell type or tissue can produce different effects (19, 67). Therefore, chemical modifications of the calcitriol molecule can result in selective VDRA with a high degree of cell-tissue specificity. Two new compounds, 2-methylene-19-nor-(20S)-1 $\alpha$ -hydroxy-bishomopregnacalciferol (2Mbisp) and its 20R isomer (2Mbisp-20R) have been shown to be highly specific for lowering PTH, with almost no effect on Ca and P, whether released from bone or absorbed from the gut (91, 114). In addition, other compounds, such as 2-methylene-19-nor-(20S)-1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub> (2MD) and 2 $\alpha$ -methyl-19-nor-(20S)-1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub> (2AMD) have a preference for bone, where they act to increase osteoclastogenesis and bone formation (41, 55, 99, 103, 104, 108).

#### *Potential New Uses of VDRA on Renal Patients*

So far, VDRA have been used mainly by nephrologists to treat sHPT. However, there is new evidence suggesting that VDRA have more far-reaching consequences in CKD patients. One of the first reports on this subject was by Teng et al. (119), who showed improved survival in patients treated with paricalcitol compared with those treated with calcitriol. The findings that VDRA supplementation is associated with better

survival (54, 70, 76, 80, 105, 120, 121, 129) and that elevated Ca and P levels are associated with a higher risk of mortality in dialysis patients (10–12) support the hypothesis that the less calcemic and phosphatemic VDRA may be advantageous for CKD patients.

An emerging effective approach to VDR activation is through the enhancement of local synthesis of calcitriol from intracellular calcidiol in many target cells such as endothelial cells, monocytes, and vascular smooth muscle cells. Correcting the calcidiol deficiency, therefore, may be an important mechanism for improving vascular stiffness, hypertension, and inflammation. Most of the epidemiological studies linking vitamin D deficiency with many conditions such as cancer and cardiovascular disease use blood levels of calcidiol as an indicator of the nutritional status of vitamin D. The challenges to effectively correct vitamin D deficiency in CKD and the benefits of exclusive correction of vitamin D deficiency without correcting calcitriol deficiency in renal patients are beyond the scope of this review, although several excellent reviews are available (52, 135). High doses of VDRA may reduce the availability of calcidiol in target cells through the induction of 24-hydroxylase, which degrades calcitriol, calcidiol, and other VDRA. However, VDRA in CKD is probably important for normalizing calcidiol uptake into cells, which appears to be a VDR-dependent mechanism (35).

#### *Role of VDRA in the Heart and in Blood Pressure*

Cardiovascular disease is the leading cause of death among patients with CKD (124), with left ventricular hypertrophy (LVH) being a strong, independent risk factor (7, 30, 31, 36, 109). There is a growing body of evidence linking VDRA and improvement in left ventricular function in both humans and experimental animals. For instance, animals lacking the VDR show cardiovascular abnormalities, such as hypertension and LVH (131). Cardiomyocytes isolated from VDR knockout mice develop contractile abnormalities, with accelerated contraction and relaxation rates (123). Moreover, vitamin D is able to modulate contractility of cardiomyocytes in vitro by changing the distribution of the myosin chains (81) and by modulating Ca entry into cardiac muscle cells (127). Vitamin D also modulates the growth (81), hypertrophy (130), collagen deposition (92), and differentiation (82) of cardiomyocytes, pointing to a direct role for VDRA in cardiac physiology.

Vitamin D deficiency has been associated with poor cardiovascular outcomes in healthy (25, 37, 128) and CKD populations (129). Thus in vivo administration of vitamin D to experimental animals or patients has been shown to improve cardiac function. For example, hypertensive rats treated with paricalcitol showed a prevention of LVH and LV dysfunction in association with lower levels of brain natriuretic peptide and atrial natriuretic factor (13). In another experimental model of LVH, the Cp/+ rat model, VDRA therapy revealed similar results (69). In patients, the use of VDRA has been associated with improvements in left ventricular function (74, 75) and reductions in LVH (8, 57, 63, 87).

It has been known for sometime that there is an association between vitamin D levels and blood pressure (BP) in humans. Low blood levels of calcidiol in blood have been linked to higher levels of BP in normotensive subjects (53, 60, 65, 102) as well as in hypertensive patients (45, 73). Furthermore, two

recent studies demonstrated that individuals with lower levels of calcidiol are at a higher risk of developing hypertension (32, 128). The rationale behind this may be related to the effect of vitamin D on the renin-angiotensin system. For example, VDR-null mice have elevated renin expression and plasma angiotensin II production (64) in addition to increased aldosterone levels. In wild-type mice, inhibition of calcitriol synthesis also led to an increase in renin expression, whereas calcitriol injection led to the suppression of renin expression via a VDR-mediated mechanism and independently of Ca metabolism. Although the mechanism is not clearly explained, it may be related to inhibiting the cyclic AMP response element in the renin gene promoter (132). Studies with the VDRA paricalcitol have shown an advantage over calcitriol, because it can provide additional renin suppression while being less calcemic at doses used to achieve the same PTH control clinically (33).

### *Role of VDRA in the Vasculature*

In addition to having a direct effect on the heart, the presence of VDR on the vascular wall suggests that some of the beneficial effects of VDRA in the cardiovascular system may be mediated by effects on the vasculature. We previously demonstrated that vitamin D has an effect on rat vascular smooth muscle cells and that this effect can vary among the different analogs (17, 18, 20). In rats treated with hypercalcemic and hyperphosphatemic doses of both compounds, paricalcitol showed almost no vascular calcification, whereas calcitriol induced massive aortic calcifications (19). Calcification was independent of the serum Ca and P levels and was associated with an increase in pulse pressure. In addition, *in vitro* data confirmed that the differential effects on calcification are directly related to differential activation of receptor activator of NF- $\kappa$ B ligand (RANK-L) (19), since RANK-L increases vascular smooth muscle cell calcification by increasing bone morphogenetic protein 4 expression (86). Studies by Mizobuchi et al. (77) validated these results with lower doses of both compounds, showing that paricalcitol did not increase pulse wave velocity, core binding factor- $\alpha$ , or osteocalcin gene expression in rat aortic tissue compared with calcitriol or doxercalciferol. We and others have also demonstrated that, contrary to other cell types, calcitriol increases rat vascular smooth muscle cell proliferation (59) by a VEGF-dependent mechanism (20). The increase in VEGF production is due to stimulation of the VEGF transcription through its binding to the vitamin D responsive element in the VEGF promoter (18).

The role of calcitriol within the vasculature could be dual, with low and high doses being equally deleterious. This has been recently demonstrated by Shroff et al. (106) in pediatric dialysis patients in which both low and high calcitriol levels were associated with increases in vascular calcification. It has been widely described how high levels of calcitriol can induce vascular calcification. However, low levels of calcitriol may induce vascular calcification through different mechanisms. In addition, high PTH levels, which are often associated with low calcitriol levels, may induce vascular calcification by stimulating high bone turnover (106).

*Role of VDRA in inflammation and fibrosis.* Another beneficial effect of VDRA in CKD patients can be related to its ability to decrease vascular inflammation. Low vitamin D levels are associated with higher CRP levels, which decrease

after VDRA administration (122). High C-reactive protein (CRP) levels are predictors of cardiovascular disease (90), and treatments aimed to decrease CRP may have a positive impact on cardiovascular health. In patients with end-stage renal disease, calcidiol and calcitriol levels are inversely correlated with atherosclerosis and endothelial dysfunction (66). Furthermore, VDRA downregulate LPS-induced immune activation of endothelial cells (28) and inhibit TNF- $\alpha$ -induced adhesion molecules expression in cultured endothelial cells (71). Mice lacking VDRs show lower platelet aggregation and higher fibrin formation in the liver and kidney after LPS administration (2), suggesting an important role for VDRA on endothelial dysfunction.

VDRA administration also has beneficial effects on several types of experimental inflammatory models of glomerulonephritis, such as nephrotoxic serum nephritis (43), Heymann nephritis (13), and anti-Thy-1 (68, 85). This effect also was observed in noninflammatory models of renal damage such as in subtotaly nephrectomized (SNX) rats (46, 61, 101). Administration of calcitriol to SNX rats reduced glomerular hypertrophy, mitigated podocyte loss and hypertrophy, and improved glomerular basement membrane thickening. Furthermore, calcitriol administration blunts the decrease in glomerular VDR content and the increase in VEGF, collagen IV, and nitrotyrosine score that is increased in glomeruli from SNX rats. In addition, calcitriol inhibits the increase in glomerular ET-1 expression as well as the decrease in glomerular endothelial nitric oxide synthase expression. Renal interstitial pathology also showed improvement with VDRA treatment as shown by a decrease in tubular dilatation and atrophy together with a decrease in macrophage infiltration and fibrosis.

Additional studies suggest that paricalcitol can inhibit epithelial-to-mesenchymal transition (EMT) that may be responsible for renal fibrosis. For example, paricalcitol administration decreased interstitial matrix components, suppressed TGF- $\beta$  and its type 1 receptor, and restored VDR abundance (118). *In vitro*, paricalcitol suppresses snail activation (a key step in EMT) and blocks TGF- $\beta$ -mediated EMT (118). The physiological relevance of paricalcitol-induced renal perivascular fibrosis is unclear, although it may be related to a decrease of the endogenous calcitriol synthesis (96).

### *Role of VDRA in Proteinuria*

It is now widely accepted that proteinuria is a good prognostic marker in the progression of CKD. Thus new strategies aimed to reduce proteinuria could have a positive impact in the nephrological community. In CKD patients treated with paricalcitol, proteinuria (measured using a semiquantitative dipstick method) decreased after 23 wk (1), independently of glomerular filtration rate, blood pressure, or angiotensin-converting enzyme (ACE) inhibitor. It also has been shown that calcitriol decreases the glomerulosclerosis index (101) and albumin excretion (61) in SNX rats and that mice lacking the VDR are more susceptible to hyperglycemia-induced renal injury (133), which may be related to podocyte loss (61). Since podocytes express both ACE and type I ANG II receptors and the local production of ANG II may be responsible for the renal injury, calcitriol-mediated inhibition of renin expression may have a role in mitigating renal damage (64).

In addition to ANG II, renin may have direct effects to increase proteinuria in CKD, acting through the (pro)rennin receptor (48). Interestingly, the combination of enalapril and paricalcitol showed a larger decrease in renal glomerulosclerosis in experimental CKD, possibly by decreasing TGF- $\beta$  expression and macrophage infiltration (ED1 positive) (78). Combined therapy with losartan and paricalcitol completely reduced proteinuria in a model of experimental diabetic nephropathy (134), suggesting that combination of an ACE inhibitor or an ANG II receptor blocker plus a VDRA may be a good therapeutic option.

#### Role of VDRA in Transplantation

VDRA therapy also shows promise in kidney transplantation. Since the main obstacle to successful kidney transplantation is the need for life-long immunosuppressive therapy, which increases the risk for infection, malignancy graft loss, and cardiovascular and bone disease, VDRA therapy is expected to have beneficial effects at many levels of comorbidities.

Retrospective analyses of kidney transplant recipients receiving oral calcitriol, compared with an untreated control group, demonstrated improved graft function and superior graft survival after 3 years of follow-up (83). In experimental studies, VDRA treatment improves survival of heart grafts (49, 62) as well as survival of kidney (94), liver (95), and pancreatic islet grafts (38). Furthermore, its effects are additive to those of cyclosporine/tacrolimus (14, 22, 94), corticosteroids (58), mycophenolate (38, 126), and interferon- $\beta$  (42). The beneficial effects may be related to the modulation of dendritic cell/T cell interaction (40), the generation of tolerogenic dendritic cells, and the promotion of regulatory T cells (38, 39). VDRA also decrease TGF- $\beta$ 1 expression (6), interstitial fibrosis, glomerular sclerosis (50), vascular intimal hyperplasia (4, 93), and SMAD2 expression while increasing SMAD7 and matrix metalloproteinase-2 expression (50). Thus VDRA activation can have a positive impact in allograft survival by modulating the inflammatory response to inhibit graft rejection and reduce fibrosis.

#### Conclusions

Although the older literature supports a role for VDRA in the prevention and treatment of bone disease in dialysis patients, new information suggests a potential role for preventing cardiovascular dysfunction and reducing proteinuria and fibrosis in CKD. Furthermore, promising data have been obtained showing a beneficial effect of VDRA on allograft survival on kidney transplantation. Further prospective randomized trials are needed to address whether the use of VDRA will indeed decrease mortality in CKD patients.

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#### DISCLOSURES

No conflicts of interest are declared by the authors.

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