A NEW ROLE FOR VITAMIN D RECEPTOR ACTIVATION IN CHRONIC KIDNEY DISEASE

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Abstract

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 are also reviewed. The available data point to a potential beneficial effect of vitamin D in CKD patients beyond the control of mineral metabolism.

Introduction

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 which, 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 (VDRAs) defined as compounds which can bind to VDR and induce its activation, have been synthesized and used in several diseases including patients with CKD. Their potential as new therapeutic agents has boosted this area of research. Moreoever, new evidence suggests that VDR polymorphisms may influence the response to VDRAs.(125).

Present Use of VDRAs in patients with CKD

One of the main complications in patients with CKD is the development of 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 which 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. While 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 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-α-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 are also 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 TGFa-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 C/EBPbeta (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 function as a transcriptional activator of the VDR gene. Indeed, pharmacological inhibition of the EGFR signalling 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 ration and VDR expression (5).

Throughout the years, one important disadvantage of using high doses of calcitriol in CKD patients was the risk of increasing extraosseous calcifications from frequent episodes of hypercalcemia and hyperphosphatemia. This prompted the search for analogues which 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- $1,25(OH)_2D_2$), which in experimental studies has 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 x P product levels (115). The effects of calcitriol and paricalcitol on bone biology are also 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 OCT recruits different coactivators from those recruited by the same receptor when bound to calcitriol (51; 117).

The search for new vitamin D analogues is of great interest, and it is an open field for research. The high plasticity of the VDR signalling 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 VDRAs 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 VDRAs with a high degree of cell-tissue specificity. Two new compounds, 2-methylene-19-nor-(20S)-1a-hydroxy-bishomopregnacalciferol (2MbisP) and 2-methylene-19-nor-1a-hydroxy-bishomopregnacalciferol (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)-1a,25(OH)2D3 (2MD) and 2a-methyl-19-nor-(20S)-1a,25(OH)2D3 (2AMD) have a preference for bone where they act to increase ostoclastogenesis and bone formation (41; 55; 99; 103; 104; 108).

Potential new uses of VDRA on renal patients

So far, VDRAs have been mainly used by nephrologists to treat sHPT. However, there is new evidence suggesting that VDRAs have more far-reaching consequences in CKD patients. One of the first papers on this subject was by Teng et al (119) who showed improved survival in patients treated with paricalcitol compared to those treated with calcitriol. The finding 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 VDRAs 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 like 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, though several excellent reviews are available (52; 135). High doses of VDRAs may reduce the availability of calcidiol in

targets cells through the induction of 24-hydroxylase which degrades calcitriol, calcidiol, and other VDRAs. 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 on the heart and 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 VDRAs and improvement in left ventricular function both in humans and in experimental animals. For instance, animals lacking the VDR show cardiovascular abnormalities, like 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 to 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 in 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 papers demonstrate 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 independent of Ca metabolism. While 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 varies 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 is directly related to differential activation of RANK-L (19), since RANK-L increases VSMC calcification by increasing BMP4 expression (86). Studies by Mizobuchi et al validated these results with lower doses of both compounds (77), showing that paricalcitol did not increase pulse wave velocity (PWV), CBFalpha nor osteocalcin gene expression in rat aortic tissue compared to 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 in pediatric dialysis patients (106) 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 on inflammation and fibrosis

Another beneficial effect of VDRAs 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 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 ESRD, calcidiol and calcitriol levels are inversely correlated with atherosclerosis and endothelial dysfunction (66). Furthermore, VDRAs downregulate LPS-induced immune activation of EC (28) and inhibit TNF alpha induced adhesion molecules expression in cultured EC (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, like nephrotoxic (43), Heyman nephritis (13) and anti-Thy-1 (68; 85). This effect was also observed in non-inflammatory models of renal damage such as in SNX rats (46; 61; 101). Administration of calcitriol to SNX rats reduced glomerular hypertrophy, mitigated podocyte loss and hypertrophy and improved, GBM 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 ET1 expression as well as the decrease in glomerular eNOS 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 TGFbeta and its

type 1 receptor, and restored VDR abundance (118). In vitro, paricalcitol suppresses snail activation (a key step in EMT) and blocks TGFbeta-mediated EMT (118). The physiological relevance of paricalctiol-induced renal perivascular fibrosis is unclear though it may be related to a decrease of the endogenous calcitriol synthesis (96).

Role of VDRA on 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 by a semi-quantitative dipstick method) decreased after 23 weeks (1), independently of GFR, blood pressure or ACE inhibitor. It has also been shown that calcitriol decreases the glomerulosclerosis index (101) and the albumin excretion (61) in rats with SNX, 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 ATI receptors and the local production of AII 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 AII, 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 TGFbeta 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 AII receptor blocker plus a VDRA may be a good therapeutic option.

Role of VDRA on transplantation

VDRA therapy also shows promise in kidney transplantation. Since the main obstacle to successful kidney transplantation is the need of a 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 co-morbidities.

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 β (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) . VDRAs also decrease TGFβ1 expression (6), interstitial fibrosis, glomerular sclerosis (50), vascular intimal hyperplasia (4; 93) and SMAD 2 expression, while increasing SMAD 7 and MMP-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

While 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.

Figure legends

Figure 1: Synthesis and target organs for Vitamin D. Vitamin D_3 obtained from the diet or by photolytic conversion in the skin is hydroxylated in the liver into 25 hydroxyvitaminD_3. The formation of 1,25 dihydroxyvitamin D3 occurs mainly in the kidney, but extrarenal synthesis has been also described in vascular cells, PTG, macrophages and some cancer cells. The presence of VDR has been shown in many targets cells regulating Ca and P absorption, cell proliferation, immune function, etc.

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Diet

7- Dehydrocholesterol

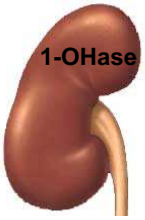
Solar UVB radiation

Vitamin D_3

$25(OH)D_3$

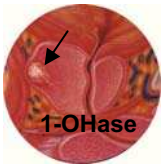
Vascular cells

Increases smooth muscle cell proliferation
Reduces Inflammation



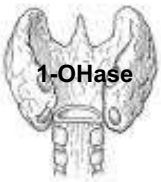
Decreases renin expression

Breast, colon, prostate cells



Inhibits clonal proliferation

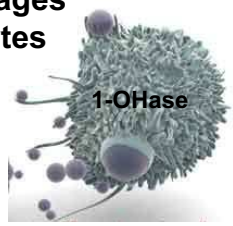
Parathyroid gland



Decreases PTH synthesis and release

$1,25(OH)_2D_3$

Macrophages Monocytes



Increases microbicidal activity
Induces differentiation in immune cells

Heart

Decreases LVH

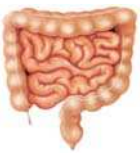
Red Blood Cells

Improves hemotopoiesis

Bone

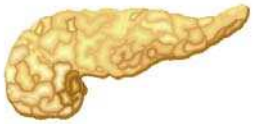
Increases bone mineralization
Increases osteoclastic differentiation

Intestine



Increases absorption of calcium and phosphate

Pancreas



Increases insulin secretion

Figure 1