Review

New Insights on the Role of Vitamin D in the Progression of Renal Damage

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Abstract

Several studies indicate a relationship between hypovitaminosis D, survival, vascular calcification and inflammation. In addition to its central role in the regulation of bone mineral metabolism, vitamin D also contributes to other systems, including the immune, cardiovascular and endocrine systems. Vitamin D analogs reduces proteinuria, in particular through suppression of the renin-angiotensin-aldosterone system (RAAS) and exerts anti-inflammatory and immunomodulatory effects. In particular vitamin D deficiency contribute to an inappropriately activated RAAS, as a mechanism for progression of chronic kidney disease (CKD) and/or cardiovascular disease. Human and sperimental models of CKD showed that vitamin D may interact with B and T lymphocytes and influence the phenotype and function of the antigen presenting cells and dendritic cells, promoting properties that favor the induction of tolerogenic T regulators rather than T effectory. Interstitial fibrosis may be prevented through vitamin D supplementation. Renal myofibroblast, an activated fibroblast with expression of a molecular hallmark α-smooth muscle actin (α-SMA), is generally considered the principal matrix-producing effector cells that are responsible for the excess production of extracellular matrix (ECM) components in the fibrotic tissues. It turns out that calcitriol effectively blocks myofibroblast activation from interstitial fibroblasts, as evidenced by suppression of TGF-β1-mediated α-SMA expression.

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Introduction

It is now well established that people with chronic kidney disease (CKD) have a higher risk of mortality and cardiovascular diseases compared with those without CKD. The rate of progression of CKD is quite variable, and patients who have a greater urine protein excretion rate have, in general, a faster decline in renal function.

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Proteinuria is a hallmark of kidney diseases, and a surrogate prognostic marker for progression of renal failure in patients with CKD [1-3]. A reduction in proteinuria invariably translates into a protection from renal function decline in patients with diabetic and nondiabetic renal disease with overt proteinuria [4]. Proteinuria is associated with increased of cardiovascular risk [5]. Ruggementi et al. demostred that measurable urinary albumin predicts cardiovascular risk among normoalbuminuric in patients with type 2 diabetes [6]. Reduction in proteinuria has been linked to improvement in both renal and cardiovascular outcomes [7, 8]. Therefore, strategies to reduce proteinuria – such as inhibition of the renin-angiotensin-aldosteron-system (RAAS) with angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) and blood pressure reduction - are currently the standard of care for CKD patients [1].

Most, if not all, pleiotropic actions of vitamin D and its analogues are mediated by the specific vitamin D receptor (VDR) [9]. Recent evidence suggests that, in addition to the traditional therapies, activators of the vitamin D receptor (VDRAs) have been shown to reduce proteinuria [10-13]. VDR is a ligand-dependent transcription factor that belongs to the steroid nuclear receptor gene family which [14], after activation, recruits cofactor molecules and binds to specific DNA-binding sites to modify the expression of target genes [15]. VDRAs have been in use for treatment of the secondary hyperparathyroidism (sHPT) of CKD since the 1990s, but in the last decade, non-calcaemic actions of VDRAs have received much attention. There is evidence that VDR is a modulator of glomerular injury. Animal studies have demonstrated possible reno-protective effects of VDRAs, with reduction in proteinuria and glomerulosclerosis [10, 16].

The first clinical study to report an effect of anti- proteinuric VDRA was in 2005 [13]. Agarwal et al, using data from three randomized controlled trials (RCTs), have compared paricalcitol and placebo for the treatment of SHPT. They reported a reduction in proteinuria dipstick - in 51% of treated patients compared to 25 % in the placebo group [17].

Three randomized, placebo-controlled studies have used paricalcitol 1–2 μg/d as add-on-treatment to stable RAAS-blockade with ACEi or ARBs. Alborzi et al. [18], conducted a pilot trial in 24 patients who were randomly allocated equally to 3 groups to receive 0, 1, or 2 microg of paricalcitol orally or placebo for 1 month. They reported a 46-48% reduction in 24 hour albuminuria with either dose, with an increase of 35% in the placebo-group. A concomitant decrease in inflammation was reported: high-sensitivity C-reactive protein levels were reduced after paricalcitol (20% reduction with 1 μg/d, and 30% reduction with 2 μg/d) compared to 50% increase with placebo.

Fishbane et al. [12] randomized 61 patients with estimated glomerular filtration rate of 15 to 90 mL/min/1.73 m(2) and protein excretion greater than 400 mg/24 h to 6 mounth of 1 μg/d paricalcitol or placebo. Half of these patients were diabetics and almost all in treatment with ACEi/ARBs (90.1%). Changes in protein excretion from baseline to last evaluation were +2.9% for controls and -17.6% for the paricalcitol group (P = 0.04)

In the VITAL-study performed by de Zeeuw et al. [19], 281 patients with type 2 diabetes, albuminuria and stable ACEi/ARB-therapy, were randomized to 1 or 2 μg/d paricalcitol or placebo for 24 weeks. Most had macroalbuminuria (72%). Results were reported as urinary albumin-to-creatinine ratio (UACR), but 24 hour urinary albumin was also available for a large subgroup (82%). Change in UACR was: –3% in the placebo group; –16% in the combined paricalcitol groups; –14% in the 1 μg paricalcitol group and –20% in the 2 μg paricalcitol group. There was a reduction also in 24 hour urinary albumin (10% and 34%).

Anti-proteinuric effects have been reported for the activated vitamin D hormone, calcitriol, as well. In an open-label study Szeto et al. [20], studied ten patients with IgA nephropathy and persistent proteinuria despite RAAS-blockade who received calcitriol, 0.5 microg, twice weekly for 12 weeks. After calcitriol treatment, there was a significant overall decrease in proteinuria with time by using a general linear model with repeated measures (P = 0.03). There was a progressive decrease in urine protein-creatinine ratio from 1.98 +/- 0.74 to 1.48 +/- 0.81 g/g (P = 0.007) during the first 6 weeks that persisted throughout the study period.

Table 1. Studies from experimental models of renal disease and on human subjects cited in each individual section of the review (RAAS, inflammation, fibrosis, podocytes)

	HUMAN STUDIES	EXPERIMENTAL MODELS
Vitamin D and Renin-Angiotensin-Aldosterone System (RAAS)	Burgess ED et al Am J Hypertens 1990 (32) Resnick LMet al Ann Intern Med, 1986 (33) Tomaschitz A et al. Clin Chim Acta, 2010 (34) Forman JP et al. Hypertension, 2010 (35) Park CW et al Am J Kidney Dis, 1999 (36)	Li YC, et al J Clin Invest, 2002 (37) Kong J, et al Kidney Int, 2008 (38) Yuan W, et al. J Biol Chem, 2007 (39) Freundlich M, et al., Kidney Int. 2008 (40) Fischer SS, et al. Am J Physiol Renal Physiol, 2010 (41)
Vitamin D and Inflammation	Zehnder D, et al. J Am Soc Nephrol, 2004 (49) Liu P. T., et al. Science, 2006 (53) Di Rosa M, et al., Cell Immunol. 2012 (54) Campbell GR, et al., PLoS Pathog. 2012 (55) Liu PT, et al., PLoS One. 2009 (56) Hewison M., et al., . J. Immunol. 2003 (59) Hewison M., et al., J. Steroid Biochem. Mol. Biol. 2007 (60) Zhang Y, et al., J Immunol. 2012 (61)	Mizobuchi M, et al. J Am Soc Nephrol, 2007 (22) Makibayashi K, et al. Am J Pathol, 2001 (25) Panichi V, et al. Kidney Int, 2001 (48) Tan X, et al. J Am Soc Nephrol, 2008 (51)
Vitamin D and Fibrosis		Tan X, et al., J Am Soc Nephrol 2005 (63) Zhang Z, et al., Proc Natl Acad Sci U S A. 2008 (64) Li Y, et al., Kidney Int 2005 (65) Zhang Y, et al., J Am Soc Nephrol. 2010 (66) Tan X, et al., Kidney Int. 2009 (67)
Vitamin D and Podocytes	Verouti SN, et al., Nephron Exp Nephrol. 2012 (79)	Tan X, et al., JASN 2006 (26) Kriz W, et al., Am Soc Nephrol 1998 (77) Wang Y, et al., J Am Soc Nephrol. 2012 (78) Kuhlmann A, et al., Am J Physiol Renal Physiol 2004 (27)

Similar results were reported in a RCT by Liu et al. [21]. 50 patients with IgA nephropathy received 2 doses (0.5 μg) of calcitriol per week or no treatment for 48 weeks . There was a changes in urinary protein excretion of +21% in the control group and -19% in the calcitriol-treated group [17].

The mechanism involved in the protective and anti-proteinuric effects of vitamin D are not well known. Multiple mechanisms are likely involved (table 1) such us, primarily suppression of RASS- system, reduced inflammatory response with inhibition of neutrophile and monocyte cell accumulation and reduction in chemoattractants [22, 23], anti-proliferative effects [22, 24-27] and reduced podocyte-damage with restoration of the glomerular filtration barrier [25, 28-30]. All the mechanisms may explain the link that have been established between low levels of vitamin D and mortality, especially in patients with chronic kidney disease [31].

Vitamin D and Renin-Angiotensin-Aldosterone System (RAAS)

Several lines of evidence support the impact of vitamin D on RAAS activity at the clinical, pathophysiological, and molecular level. The RAAS is a regulatory cascade that plays an essential role in the regulation of blood pressure, electrolyte, and volume homeostasis. The rate-limiting component of this cascade is renin, a protease synthesized and secreted predominantly by the juxtaglomerular apparatus in the nephron.

The main function of renin is to cleave angiotensin (Ang) I from angiotensinogen. The decapeptide Ang I is then converted to the octapeptide Ang II by the angiotensin converting enzyme. Ang II is the central effector of the RAS, which exerts diverse actions in multiple organs, including the brain, heart, kidney, adrenal glands, and peripheral vasculature,

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to regulate the blood pressure and electrolyte and extracellular volume balance [31, 32]. Inappropriate stimulation of the RAS has been associated with hypertension, heart attack, and stroke.

The mechanism underlying the relationship between vitamin D and blood pressure and/or plasma renin activity is unclear. The first clinical studies suggesting an inverse relationship between calcitriol and renin levels were published two decades ago [33, 34] and were recently confirmed in a large cohort study of CKD patients [35]. Forman J. et al. have examined the relation between plasma 25-hydroxyvitamin D and elements of the RAS in 184 normotensive individuals in high sodium balance; these included circulating levels of plasma renin activity and Ang II, and the renal plasma flow response to infused Ang II, which is an indirect measure of the intrinsic RAS activity in the kidney. Compared to individuals with sufficient 25-hydroxyvitamin D levels (≥ 30 ng/mL), those with insufficiency (15 - 29.9 ng/mL) and deficiency (<15 ng/mL) had higher circulating Ang II levels (p-trend = 0.03). Moreover, those with vitamin D deficiency had significantly blunted renal plasma flow responses to infused Ang II (mean decrease of 115 mL/min/1.732 in renal plasma flow vs. 145 ml/min/1.73m2 among those with sufficient vitamin D levels; p-value = 0.009). Although plasma renin activity was higher among individuals with insufficient levels of vitamin D, the result was not statistically significant. These data suggest that low plasma 25-hydroxyvitamin D levels may result in upregulation of the RAS in otherwise healthy humans [36].

Furthermore intervention with calcitriol decreases plasma renin and Ang II levels in hemodialysis patients with secondary hyperparathyroidism [37]. Several mechanistic studies confirming negative regulation of the renin gene by calcitriol have been published by the group of Li et al., who showed that renin expression and plasma angiotensin II production were increased severalfold in vitamin D receptor-null (VDR-null) mice, leading to hypertension, cardiac hypertrophy, and increased water intake. In wild-type mice, whereas 1,25-dihydroxyvitamin-D(3) injection led to renin suppression [38]. The negative regulation of renin by calcitriol seems independent of calcium and parathyroid hormone (PTH) [39]. On a molecular level, calcitriol binds to the VDR and subsequently blocks formation of the Cyclic adenosine monophosphate-response element-binding protein (CRECREB- CBP) complexes in the promoter region of the renin gene, reducing its level of expression [40]. Together, the associations found in clinical studies and the supporting mechanistic studies make it plausible that vitamin D deficiency could indeed contribute to an inappropriately activated RAAS, as a mechanism for progression of CKD and/or cardiovascular disease. This may well be relevant for therapeutic purposes [41].

Studies on suppression of renin-angiotensin gene expression in the kidney by paricalcitol were also conducted. Freundlich M et al. studied rats with the remnant kidney model of chronic renal failure (5/6 nephrectomy) to which have been given two different doses of paricalcitol thrice weekly for 8 weeks. Paricalcitol was found to decrease angiotensinogen, renin, renin receptor, and vascular endothelial growth factor mRNA levels in the remnant kidney by 30-50 percent compared to untreated animals. Similarly, the protein expression of renin, renin receptor, the Ang type 1 receptor, and vascular endothelial growth factor were all significantly decreased. Glomerular and tubulointerstitial damage, hypertension, proteinuria, and the deterioration of renal function resulting from renal ablation were all similarly and significantly improved with both treatment doses [42].

Interactions between vitamin D and other system RAAS components have been studied as well. Aldosterone binds mineralocorticoid receptor, which belongs to the same superfamily of nuclear receptors as the VDR. Therefore, cross talk between these receptors and their agonists could potentially exist. Fisher et al, observed that plasma concentration of 1,25-dihydroxyvitamin-D(3), were significantly higher in mice that are genetically deficient for klotho, a membrane protein participating in the inhibitory effect of Fibroblast Growth Factor-23 (FGF23) on the formation of 1,25-dihydroxyvitamin-D(3). Excessive levels of calcitriol were associated with hyperaldosteronism, which is similarly reversed by a vitamin D-deficient diet [43]. These findings suggest a possible interaction between vitamin D and aldosterone synthesis, it is uncertain whether hyperaldosteronism is a direct consequence

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of hypervitaminosis D. Data from in vitro studies do not support positive regulation of aldosterone synthesis by vitamin D, as calcitriol affects the production of hormones and expression of crucial steroidogenic enzymes in human adrenocortical cell [41, 44].

Vitamin D and Inflammation

Vitamin D has been shown to have potent anti-inflammatory effects and consequently, has been considered for adjunctive therapy in the treatment of numerous chronic diseases including asthma, rheumatoid arthritis, multiple sclerosis, diabetes mellitus type 1, psoriasis, chronic inflammatory bowel diseases and prostate cancer [45-47]. A variety of pro- and anti-inflammatory effects for vitamin D have previously been reported [48, 49]. Several lines of evidence have suggested a potential anti-inflammatory activity of vitaminD in CKD [23, 26]. In animal models of primary glomerular diseases, administration of vitamin D reduces glomerular infiltration of inflammatory cells [23, 50]. Consistently, a decreased inflammation is associated with higher serum vitamin D level in patients with CKD [51].

Vitamin D modulates the immune system by determining direct regulatory effects on the functions of B and T lymphocytes and influencing the phenotype and function of the antigen presenting cells and dendritic cells, promoting properties that favor the induction of tolerogenic T regulators rather than T effectory [52]. This adjustment is mediated by the action of vitamin D on nuclear transcription factors, such as Nuclear Factor of Activated T-cells and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) or direct interaction with vitamin D response element (VDRE) in the promoter regions of the genes of cytokines. Tan et al. demonstrated that paricalcitol displays a potent anti inflammatory activity by effectively inhibiting T lymphocyte and macrophage infiltration and proinflammatory cytokines Regulated on Activation Normal T cell Expressed and Secreted (RANTES) and TNF-kB expression in a mouse model of obstructive nephropathy. Paricalcitol induces VDR binding to the p65 subunit of NF-kB and prevents it from interacting with cis-acting DNA element, thereby sequestering its ability to transactivate the transcription of its targeted genes. Paricalcitol inhibits RANTES expression that is localized almost exclusively in renal tubules after injury, suggesting that tubular epithelial cells are likely the primary target of vitamin D in eliciting its anti-inflammatory action.

In this regard, tubular expression and secretion of RANTES is a critical step that sets in motion toward the peritubular infiltration of inflammatory cells. As shown by chemotaxis assay, RANTES is a major chemotactic component in the supernatants of tubular cells after TNF-kB stimulation [53].

It has been shown that vitamin D can directly induce the production of important antimicrobial peptides, cathelicidin and human b defensin 4 in human monocytes/macrophages and epithelial cells [54, 55]. Vitamin D, also enhances the response of the innate immune system through activation of toll-like receptor (TLR) [55].

Di Rosa M et al. found that 1,25-dihydroxyvitamin-D(3) influences macrophages chemotaxis and differently modulates the expression of Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and TLRs in the two different stages of monocytes/macrophage maturation [56]. Campbell GR et al. report that TLR8 activation in human macrophages induces the expression of the human cathelicidin microbial peptide (CAMP), the VDR and cytochrome P450, family 27, subfamily B, polypeptide 1 (CYP27b1), which 1α-hydroxylates the inactive form of vitamin D, 25-hydroxycholecalciferol, into its biologically active metabolite. Moreover, they demonstrate using RNA interference, chemical inhibitors and vitamin D deficient media that TLR8 agonists inhibit Human Immunodeficiency Virus through a vitamin D and CAMP dependent autophagic mechanism [57].

Liu PT et al, have reported that TLR activation of monocytes triggers induction of the defensin beta 4 gene (DEFB4), requiring convergence of the IL-1beta and VDR pathways. TLR2/1 activation triggered IL-1beta activity, involving the upregulation of both IL-1beta and IL-1 receptor, and downregulation of the IL-1 receptor antagonist. TLR2/1L induction of IL-1beta was required for upregulation of DEFB4, but not cathelicidin, whereas VDR activation

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was required for expression of both antimicrobial genes. The differential requirements for induction of DEFB4 and cathelicidin were reflected by differences in their respective promoter regions; the DEFB4 promoter had one VDRE and two NF-kB sites, whereas the cathelicidin promoter had three VDREs and no NF-kB sites. Transfection of NF-kB into primary monocytes synergized with 1,25-dihydroxyvitamin-D(3) in the induction of DEFB4 expression. Knockdown of either DEFB4 or cathelicidin in primary monocytes resulted in the loss of TLR2/1-mediated antimicrobial activity against intracellular mycobacteria [58].

A study has found that human monocytes are capable of responding to treatment with two different forms of vitamin D: 1,25-dihydroxyvitamin-D(3) and 25-hydroxyvitamin-D. 25-hydroxyvitamin-D is converted into a functionally active form, 1,25-dihydroxyvitamin-D(3) , by the enzyme 25-hydroxyvitaminD3-1a-hydroxylase (CYP27b1), a process that primarily occurs in the kidneys [59, 60]. However, it has been shown that monocytes, macrophages, and dendritic cells also express CYP27b1 [55, 61]. Therefore1,25-dihydroxyvitamin-D(3), can be produced locally and exert immunomodulatory effects [62]. Zhang et al. have demonstrated that 15 ng/ml 25-hydroxyvitamin-D [a concentration amount considered in this vitamin D deficiency study] did not suppress Lipopolysaccharide (LPS)-induced cytokine (IL-6 and TNF-α) production in human monocytes. They found that 25-hydroxyvitamin-D at 30 ng/ml (a level considered to be sufficient in humans) significantly inhibited cytokine production induced by LPS, in vitro [63].

These data support the hypothesis that to achieve optimal anti-inflammatory effects by vitamin D, it is important to maintain serum vitamin D levels at 30 ng/ml in the physiologic range [54, 64].

Vitamin D and Fibrosis

Interstitial fibrosis together with tubular athrotrophy is a hallmark of chronic renal failure and strongly correlates with deterioration of renal function, regardless of the underlying disease.

Renal fibrosis is a common downstream event leading to renal failure; thus, understanding the development of renal fibrosis has important implications for therapeutic intervention of kidney disease. In animal models as well as in clinical trials involving patients with chronic renal insufficiency, active vitamin D has proven to have beneficial effects, resulting in substantial attenuation of renal fibrosis and kidney dysfunction. However, relatively little is known about the potential role of vitamin D in interstitial fibrosis, a lesion that is widely accepted as the common pathway of CKD that leads to end-stage renal failure.

Tan X. et al. evaluated the efficacy of active vitamin D in mouse model with nephropathy induced by unilateral ureteral obstruction, a widely used, aggressive interstitial fibrosis model characterized by rapid tubular atrophy and interstitial expansion and matrix deposition. The activation of vitamin D receptor, through the use of paricalcitol, significantly reduced the fibrotic lesions in obstructed kidney in a dose-dependent fashion, as demonstrated by a reduced interstitial volume and decreased deposition of interstitial matrix components [65]. Paricalcitol substantially inhibited renal mRNA expression of fibronectin, type I and type III collagen, and fibrogenic TGF-β1, while preserved E-cadherin and VDR expression in the obstructed kidney [65].

In an other study, Zhang Z et al, demonstrated that combination therapy with an AT1 receptor blocker (losartan) and a vitamin D analog (paricalcitol) markedly ameliorated renal injury in the streptozotocin-induced diabetes model. The combined treatment suppressed the induction of fibronection, TGF-beta, and monocyte chemotactic protein-1and reversed the decline of slit diaphragm proteins nephrin, Nephrin-like molecules-1, ZO-1, and alpha-actinin-4 preventing renal injury in diabetic nephropathy [66].

In view of its therapeutic effectiveness in renal interstitial fibrosis, Tan X et al. examined the extracellular direct effect of active vitamin D on myofibroblast activation, one of the key events that lead to matrix over-production and deposition. Renal myofibroblast, an activated fibroblast with expression of a molecular hallmark α-smooth muscle actin (α-SMA), is

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generally considered as the principal matrix-producing effector cells that are responsible for the increase of extracellular matrix (ECM) components in the fibrotic tissues. It turns out that calcitriol effectively blocks myofibroblast activation from interstitial fibroblasts, as evidenced by suppression of TGF-β1-mediated α-SMA expression [67]. Meanwhile, active vitamin D also inhibits type I collagen and thrombospondein-1 expression in cultured renal interstitial fibroblasto [67]. It is interesting that paricalcitol almost completely suppressed renal induction of Snail, a critical transcription factor that is implicated in epithelial to mesenchymal transition programming.

To address the role of the VDR in renal fibrogenesis, Zhang Y. et al. underwent VDR-null mice to unilateral ureteral obstruction for 7 days. Compared with wild-type mice, VDR-null mice developed more severe renal damage in the obstructed kidney, with marked tubular atrophy and interstitial fibrosis. Significant induction of extracellular matrix proteins (fibronectin and collagen I), profibrogenic and proinflammatory factors (TGF-b, connective tissue growth factor, and monocyte chemoattractant protein 1), and epithelial-to-mesenchymal transition were present together with morphologic lesions. Because VDR ablation activates the renin-angiotensin system and leads to accumulation of AngII in the kidney, they assessed whether elevated Ang II in the VDR-null kidney promotes injury. Treatment with the Ang1 antagonist losartan eliminated the difference in obstruction-induced interstitial fibrosis between wild-type and VDR-null mice, suggesting that AngII contributes to the enhanced renal fibrosis observed in obstructed VDR-null kidneys [68] .

In another study Tan X et al. have compared the individual renal protective efficacy of paricalcitol and trandolapril (an ACEi) in obstructive nephropathy, and examined any potential additive effects of their combination on attenuating renal fibrosis and inflammation. Mice underwent unilateral ureteral obstruction and were treated individually with paricalcitol or trandolapril or their combination. Compared to vehicle-treated controls, monotherapy with paricalcitol or trandolapril inhibited the expression and accumulation of fibronectin and type I and type III collagen, suppressed alpha-smooth muscle actin, vimentin, and Snail-1 expression, and reduced total collagen content in the obstructed kidney. Combination therapy led to a more profound inhibition of all parameters. Monotherapy also suppressed renal RANTES (regulated on activation, normal T cell expressed and secreted) and TNF-alpha expression and inhibited renal infiltration of T cells and macrophages, whereas the combination had additive effects. Renin expression was induced in the fibrotic kidney and was augmented by trandolapril. Paricalcitol blocked renin induction in the absence or presence of trandolapril.

These findings are consistent with the notion that active vitamin D is also effective in preventing renal interstitial lesions. Paricalcitol has renal protective effects, in reducing interstitial fibrosis and inflammation. Combination therapy, paricalcitol and inhibition of the RAAS, may have additive efficacy in lowering progression of renal disease [69] .

Vitamin D and Podocytes

There has been increasing recognition of an important role of podocytes in the progression of renal disease [70] It has recently become clear that initial glomerular injury affects the podocyte as an important target cell for progression [71], e.g., in diabetic nephropathy [72, 73], fawn hooded rats [74], or subtotally nephrectomized (SNX) rats [75]. This is illustrated by clinical observations of podocyte loss in patients with progressive renal diseases, e.g., type 2 [76] or type 1 diabetes [77], and patients with lupus nephritis and focal segmental glomerulosclerosis [78]. There is also abundant experimental evidence that the progression of renal injury is associated with progressive podocyte loss [71, 73].

Some studies have identified podocytes as another target of active vitamin D [27, 79]. Podocyte possesses VDR, and administration of active vitamin D markedly protects podocytes from injury in both immune and non-immune mesangial proliferative glomerulonephritis rat models. Wang Y. et al. investigate this question used the 2.5 kb podocin promoter to target Flag-tagged human vitamin D receptor (hVDR) to podocytes in DBA/2J mice, a

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widely used inbred strain. After the induction of diabetes with streptozotocin, transgenic mice had less albuminuria than wild-type controls. In transgenic mice, a low dose of the vitamin D analog doxercalciferol prevented albuminuria, markedly attenuated podocyte loss and apoptosis, and reduced glomerular fibrosis, but it had little effect on the progression of diabetic nephropathy in wild-type mice. Moreover, reconstitution of VDR-null mice with the hVDR transgene in podocytes rescued VDR-null mice from severe diabetes-related renal damage. In culture, 1,25-dihydroxyvitamin D suppressed high-glucose induced apoptosis of podocytes by blocking p38- and ERK-mediated proapoptotic pathways [80].

In an other study Kuhlmann A et al. have investigated glomerular structure and cellular composition in SNX rats treated with non-pharmacological doses of 1,25-dihydroxyvitamin-D(3). Male Sprague-Dawley rats were sham operated (sham) or underwent SNX under general anesthesia and received either solvent or 1,25-dihydroxyvitamin-D(3) (3 ng.100 g body wt(-1).day(-1) sc). The main finding obtained was a significantly higher number of podocytes in SNX+1,25-dihydroxyvitamin-D(3) (88 +/- 9) and sham (98 +/- 17) compared with SNX+solvent rats (81 +/- 8.7). In parallel, the increase in podocyte volume in SNX+solvent rats was abrogated by treatment with 1,25-dihydroxyvitamin-D(3), and immunohistochemistry revealed less expression of desmin, Proliferating cell nuclear antigen , and p27, suggesting less podocyte injury and activation of the cyclin cascade. This study identifies the podocyte as an important target cell for the renoprotective action of 1,25-dihydroxyvitamin-D(3). This notion is suggested by less evidence of podocyte injury, decreased podocytes loss, and abrogation of podocyte hypertrophy, findings that may also explain less pronounced albuminuria and glomerulosclerosis [28].

Renal podocytes form the main filtration barrier possessing a unique phenotype maintained by proteins including podocalyxin and nephrin, the expression of which is suppressed in pathological conditions. Verouti SN et al. used immortalized human podocytes (human glomerular epithelial cells, HGEC) to assess podocalyxin and nephrin expression after treatment with 1,25-dihydroxyvitamin D3 and its analogue paricalcitol. The involvement of VDR was investigated by silencing with hVDR-siRNA and ChIP analysis. Their results showed that HGEC exhibit high glucose-mediated downregulation of podocalyxin and nephrin, loss of which has been linked with loss of the permselective renal barrier and proteinuria. Calcitriol and paricalcitol reversed high glucose-induced decrease of nephrin and significantly enhanced podocalyxin expression in podocytes cultured in high glucose. HGEC express VDR and retinoid X receptor (RXR). In the presence of calcitriol and paricalcitol, VDR expression was upregulated and VDR colocalized with RXR in the nucleus. VDR knockdown abolished the protective action of calcitriol and paricalcitol on podocalyxin expression indicating that podocalyxin activation of expression is partly mediated by VDR. Furthermore, VDR specifically regulates podocalyxin expression by bounding to a site upstream of the podocalyxin promoter [81].

In conclusion, taken together, these data provide strong evidence that vitamin D/VDR signaling in podocytes plays a critical role in the protection of the kidney from diabetic injury. Vitamin D and its analogues maintain and, furthermore, re-activate the expression of specialized components of podocytes including podocalyxin, hence they provide protection against loss of the permselective renal barrier, with molecular mechanisms elucidated herein.

Conclusion

Recent data from in vivo and in vitro experiments as well as clinical trials suggest that active vitamin D and/or its analogous are renoprotective, resulting in an attenuation of proteinuria, inflammation, glomerulosclerosis and interstitial fibrosis and an improvement of kidney functions (figure 1). Dependent on the etiologies of the CKD models, diverse actions of active vitamin D may account for its beneficial effects in vivo, which include the regulation of RAS system, antiinflammation, podocyte protection, HGF induction and preservation

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of tubular epithelium via blocking EMT. Pharmacologic supplementation of active vitamin D may be a rational strategy to halt the vicious cycle between its deficiency and decline in kidney function in CKD patients.

In this regard, active vitamin D may hold promise as a new addition to our anti-proteinuric armamentarium.

Conflict of Interests

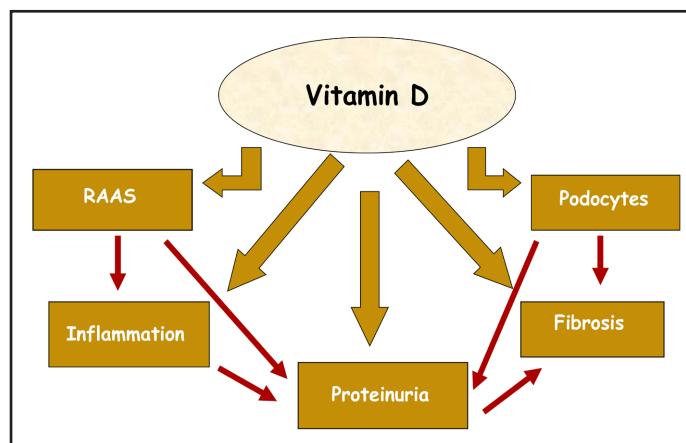The authors declare that they do not have any conflicts.

Fig. 1. Complex interactions between Vitamin D and Kidney. (thick line indicates direct interaction; thin lines indicates mediated-interaction). RAAS = Renin Angiotensin-Aldosteron System.

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