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Potential role of active vitamin D in retarding the progression of chronic kidney disease

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Introduction

Delay up the progression of chronic kidney disease (CKD) is still an unsolved problem. The suppression of known ‘causes’ of progression by targeting high blood pressure as well as the renin–angiotensin system (RAS) has met with some success in REIN, RENAAL, IDNT, and other clinical trials [1–3]. However, although these therapies slow the progression of CKD, the residual risk of these patients for both renal and cardiovascular

end points remains high. Since the pathogenesis of renal progressive disease is multifactorial, a combined therapy strategy may be the way for the future to completely block renal disease progression. An interesting result of such a combined therapy strategy came from the COOPERATE trial [combining ACE-inhibition with angiotensin-II-receptor-blockade (ACEi/ARB)], targeting the same hormonal systems from different angles [4]. Other strategies target different pathophysiologically important systems at the same time, such as RAS and glycosaminoglycans [5], and RAS and endothelin [6]. Recent evidence supports the theory that active vitamin D and its analogues attenuate glomerular and tubular interstitial fibrosis. Could vitamin D become an additional therapeutic agent for CKD? The present review will focus primarily on the most recent advances in our understanding of the potential therapeutic roles of calcitriol and its analogues in the area of CKD.

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Vitamin D

Under normal conditions, humans acquire vitamin D either from the diet or from *de novo* synthesis in the skin as a result of direct sun exposure. Vitamin D₃ is initially hydroxylated in the liver by 25-hydroxylase to form 25-hydroxyvitamin D₃, with a subsequent hydroxylation in the kidney to form the active metabolite, 1 α -25-dihydroxyvitamin D₃, also known as calcitriol, which is eventually metabolized by 25-hydroxyvitamin D-24-hydroxylase (24-OHase). The binding of 1 α -25-dihydroxyvitamin D₃ or its analogues to the vitamin D receptor (VDR), a nuclear receptor, activates the VDR and leads to the recruitment of cofactors like the retinoid X receptor (RXR), resulting in the formation of the VDR–RXR–cofactor complex, which binds to the vitamin D response element (VDRE) in the promoter region of target genes to regulate gene transcription [7]. Several tissues have 25-hydroxyvitamin D 1 α -hydroxylase, which could convert 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D locally [8]. However, the serum level of 1,25 dihydroxyvitamin D is regulated by renal 25-hydroxyvitamin D 1 α -hydroxylase. In the recent Study to Evaluate Early Kidney Disease (SEEK), calcitriol deficiency (defined as serum levels <22 pg/ml) was found in 32% of CKD stage 3 and >60% of CKD stages 4 and 5 pre-dialysis patients [9]. The VDR has been

found in more than 30 tissues including the intestines, bone, kidney, parathyroid gland, pancreatic β -cells, monocytes, T-cells, keratinocytes and many cancer cells [10], suggesting that the vitamin D endocrine system may also be involved in regulating the immune systems, cellular growth, differentiation and apoptosis. The details of the effect of vitamin D in many different organs and diverse disease states have been described in several comprehensive reviews [11–15].

Current concepts for progressive renal function loss and the potential role of vitamin D

Renal fibrogenesis is a complex process in which many pathogenic pathways and mediators are implicated (Figure 1). Accordingly, an ideal therapy should have the potential to target multiple events along the pathogenic pathway to inhibit both glomerular and tubular interstitial fibrosis. Growing evidence supports a potential role for active vitamin D in ameliorating renal fibrosis and kidney dysfunction, in view of its targeted effects on multiple pathogenic pathways. The correlation between active vitamin D deficiency and the diseased kidney has been well established, and low serum levels of 1,25(OH)₂D₃ are often associated with decreased kidney function [16,17]. On one hand, decreased kidney mass and/or a reduced uptake of the precursor are likely to be the causes of vitamin D

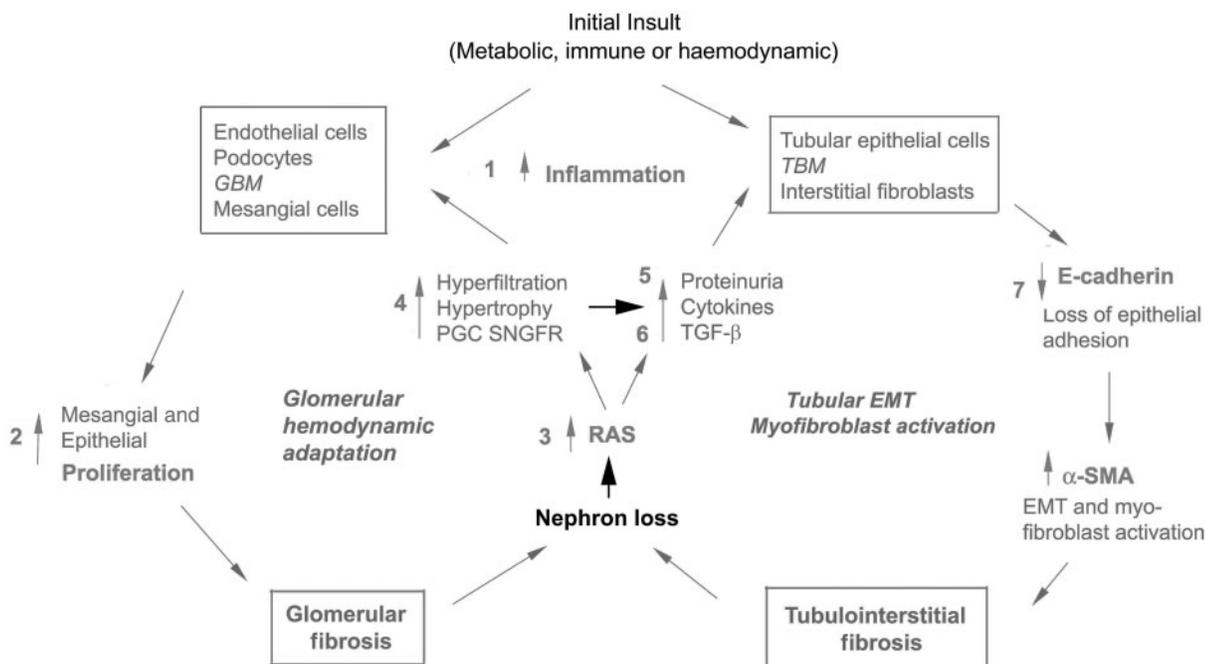


Fig. 1. Active vitamin D has been shown to inhibit multiple pathogenic pathways in renal fibrosis. Active vitamin D (1) has anti-inflammatory effects; (2) inhibits mesangial and podocyte proliferation; (3) down-regulates the renin–angiotensin system (RAS) by inhibiting renin production; (4) prevents glomerular hypertrophy as measured by glomerular volume in 5/6 subtotal nephrectomized rats; (5) decreases proteinuria in different animal models of CKD; (6) decreases fibrogenic cytokine production in the kidney by regulating Smad3 and TGF- β pathways; (7) has the potential to block the EMT and myofibroblast activation. RAS, renin–angiotensin system; PGC, glomerular capillary pressure; SNGFR, single-nephron glomerular filtration rate; α -SMA, α -smooth muscle actin; EMT, epithelial to mesenchymal transition.

deficiency because renal tubular cells are the active sites of calcitriol synthesis. On the other hand, since adequate local concentrations of active vitamin D may be required to maintain structural and functional integrity of renal parenchyma, lower vitamin D levels might be one of the causative factors that initiate and promotes the progression of CKD; this could then further impact on renal function loss, causing a vicious circle. The targets of vitamin D therapy in CKD identified thus far involve renal inflammation (such as T-cells and other immune cells), the RAS and glomerular (mesangial cells and podocytes) and tubulointerstitial (tubular epithelial cells and interstitial fibroblasts) fibrosis.

A schematic of the proposed pathophysiology of renal fibrosis along with the referenced data cataloguing potential effects of vitamin D on the progression of CKD are summarized in Figure 1.

Experimental evidence for a role of active vitamin D in CKD

Effect on renal compensation and RAS

Several studies have examined the effect of vitamin D on renal compensatory growth after subtotal nephrectomy (SNX) in animal models. Schwarz *et al.* [18] first examined the effect of 1,25(OH)₂D₃ on glomerulosclerosis in SNX rats. Administration of 1,25(OH)₂D₃ at 3 ng/100 g/day for 8 or 16 weeks significantly decreased both glomerular volume and albuminuria, compared with the untreated controls. Likewise, Hirata *et al.* [19] examined the effect of the vitamin D analogue, 22-oxa-calcitriol (OCT), in the same model, and found that OCT treatment significantly suppressed urinary albumin excretion, inhibited glomerular hypertrophy and glomerulosclerosis in the SNX rats at 8 weeks.

Li *et al.* [20] recently explored the mechanism underlying the relationship between vitamin D and the RAS using genetically modified animal models. They noted that plasma angiotensin II levels were markedly elevated in VDR knockout (KO) mice and 1- α hydroxylase KO mice, while angiotensinogen expression in the liver was not different from wild-type (WT) mice, indicating that plasma angiotensin II elevation was likely to be due to increased renin activity. The size of left ventricular cardiomyocyte in VDR KO mice was markedly increased compared with WT controls [21]. Further studies demonstrated that WT mice, when rendered vitamin D deficient, also had increased renin production, whereas 1,25(OH)₂D₃ treatment of normal mice resulted in renin suppression. By using As4.1 cells (a renin-expressing cell line isolated from a mouse renal tumour) *in vitro*, they also demonstrated that the effect of 1,25(OH)₂D₃ on renin regulation was independent of serum calcium and parathyroid hormone (PTH) levels [20]. Therefore, vitamin D serves as a negative endocrine regulator of the RAS, directly and independently suppressing renin

gene expression. This offers a potential mechanistic insight into the role of vitamin D on cardiorenal protection and homeostasis. These studies also provide a molecular basis to explore the potential of vitamin D analogues as therapeutic renin inhibitors to modulate the RAS and prevent glomerular haemodynamic adaptation [21].

Effects on podocytes and mesangial cells

Earlier studies have demonstrated the presence of the VDR in cultured human mesangial cells [22]. Numerous approaches showed the specific binding of 1,25(OH)₂D₃ to human mesangial cells. Two groups have provided clear evidence for the functional effects of 1,25(OH)₂D₃ on mesangial cells [23,24], by demonstrating the beneficial action of 1,25(OH)₂D₃ and OCT in regulating mesangial proliferation *in vivo*. In the anti-thy-1 glomerulonephritis model, both OCT and 1,25(OH)₂D₃ not only inhibited mesangial cell proliferation, as evidenced by a decreased proliferating cell nuclear antigen (PCNA) expression, but also decreased the degree of glomerulosclerosis and albuminuria, as well as the expression of type I and type IV collagen and α -SMA.

Alteration of mesangial cells has traditionally been considered the major process in the development of glomerular injury. However, more recently, podocytes have been recognized as key cells in the evolution of proteinuria, especially in diabetic nephropathy. Recent reports indicate that 1,25(OH)₂D₃ decreases podocyte loss and inhibits podocyte hypertrophy in the SNX rats [25]. Sprague–Dawley rats were either sham-operated or underwent subtotal nephrectomy, and then received either solvent vehicle or 1,25(OH)₂D₃ for up to 16 weeks. Mean podocyte volume was significantly higher in the SNX rats, compared with both the sham and 1,25(OH)₂D₃-treated SNX groups. These findings indicate that hypertrophy of podocytes could be prevented by treatment with 1,25(OH)₂D₃. Electron microscopic investigation has also shown that the glomerular ultrastructure was largely preserved when SNX rats were treated with 1,25(OH)₂D₃. Decreased expression of desmin, PCNA and an increased p27 were found in the 1,25(OH)₂D₃-treated SNX group, compared with the solvent controls, suggesting less podocyte injury and less activation of the cyclin cascade. This study clearly identifies the podocyte as a potentially important target for renal protective actions of vitamin D.

It is well known that glomerular haemodynamic changes, podocyte abnormality and mesangial activation are associated with proteinuria. The beneficial effect of active vitamin D on glomerular structures is consistent with the results of proteinuria reductions in several animal models [18,19,23,24] and in humans [26]. By reducing proteinuria, vitamin D may attenuate protein-dependent interstitial inflammation in nephropathies [27]. In addition, vitamin D has direct anti-inflammatory properties.

Effect on renal inflammation

Chronic inflammation, characterized by infiltration of inflammatory cells into the glomeruli and tubulointerstitium, is regarded as one of the key pathogenic mechanisms in the development and progression of CKD [28]. Clinical studies also reveal that the decline in renal function in patients with CKD often correlates closely to the extent of inflammation.

Inflammatory cells contribute to tissue damage in many ways. For example, the production of pro-fibrotic cytokines such as transforming growth factor- β (TGF- β), which in turn induces the matrix-producing myofibroblast activation and tubular epithelial to mesenchymal transition (EMT), thereby promoting the fibrogenic process. In addition, inflammatory cells can elicit their effects by producing radical oxygen species and by releasing pro-inflammatory cytokines, which modulate the response of renal residential cells to injurious stimuli. Vitamin D has long been known to possess immunomodulatory properties that are mediated through the VDR, which is present in most cell types of the immune system, in particular, the antigen presenting cells such as macrophages, dendritic cells and both CD4+ and CD8+ T-cells [29,30].

Transcription factor nuclear factor- κ B (NF- κ B) plays a crucial role in acute and chronic inflammation by regulating the gene expression of cytokines, chemokines, adhesion molecules and growth factors [31]. Before the era of ACEi/ARB therapy, steroids were widely used for patients with glomerulonephritis and inflammatory tubular interstitial nephritis. The major effect of steroids on immune suppression occurs by down-regulation of NF- κ B. Similarly, several different studies have illustrated an inhibitory effect of vitamin D on NF- κ B signalling. In normal human lymphocytes, 1,25(OH) $_2$ D $_3$ decreased the levels of NF- κ B protein, whereas 25(OH)D or 24,25(OH) $_2$ D were ineffective [32]. Studies by Xing *et al.* [33] revealed that treatment of dendritic cells with a combination of steroids and active vitamin D analogue resulted in significant, additive inhibition of pro-inflammatory cytokines, chemokines and NF- κ B components. Those findings suggest that the use of steroids in the presence of 1,25(OH) $_2$ D $_3$ may affect different pathways of immune regulation as compared with steroids alone.

Tumour necrosis factor- α (TNF- α) also stimulates the production of chemotactic factors by resident cells. Macrophages, as well as intrinsic kidney cells, are the primary source of TNF- α . *In vivo*, calcitriol induces a dose-dependent inhibition of TNF- α production in both healthy volunteers and haemodialysis (HD) patients [34]. Furthermore, in addition to the inhibitory effects on dendritic cells and macrophages, 1,25(OH) $_2$ D $_3$ has a direct effect on naïve CD4+ T-cells to enhance the development of Th2 cells, which down-regulates the immune response [35]. As summarized by Mathieu and Adorini [36], vitamin D can elicit a number of regulatory activities in the immune system.

Numerous studies have evaluated the anti-inflammatory potential of vitamin D in animal models of CKD. Lemire and associates studied the effect of 1,25(OH) $_2$ D $_3$ on lupus nephropathy in MRL/I mice [37]. Calcitriol treatment reduced proteinuria, and a reduction in serum titres of anti-ssDNA antibody was observed at 18 weeks. The therapeutic effect of 1,25(OH) $_2$ D $_3$ on Heymann nephritis was also investigated in Lewis rats. At a dose of 0.5 mcg/kg every other day during the first 13 days following active immunization, calcitriol significantly reduced proteinuria and the magnitude of this reduction was comparable with that treated with cyclosporine A [38]. The association between serum 1,25(OH) $_2$ D $_3$ levels and local inflammation in renal biopsy tissue was also analysed by Zehnder *et al.* [39] in 186 patients with kidney disease. Renal MCP-1 mRNA, urinary MCP-1 and infiltrating tissue macrophages were found to be inversely correlated with serum 1,25(OH) $_2$ D $_3$ levels. Similarly, treatment with calcitriol almost completely abrogated the glomerular infiltration of neutrophils in the anti-thy-1 model [23].

In addition to its ability to induce tolerogenesis in dendritic cells, calcitriol enhances macrophage anti-bacterial, anti-viral and anti-tumoural properties. However, in human studies, active vitamin D analogues failed to show significant effects on the regulation of several cytokines including IL-2, IL-6, TNF- α and interferon- γ , but showed a tendency toward improving delayed hypersensitivity reactions in dialysis patients [40]. The net overall effect of active vitamin D on cytokine production remains to be determined in the context of higher levels of inflammatory cytokines, decreased VDR and interference of 1,25(OH) $_2$ D $_3$ actions by uraemic toxins in CKD patients.

Vitamin D and tubular interstitial fibrosis

Unlike glomerular fibrosis, until recently, much less was known about the effect of vitamin D on tubular interstitial fibrosis (TIF). The proximal tubular epithelial cell is the site of endogenous synthesis of 1,25(OH) $_2$ D $_3$. The 24 hydroxylase is an important enzyme, that metabolizes 1,25(OH) $_2$ D $_3$ to the less active 24,25(OH) $_2$ Vitamin D $_3$. The balance between 1, α hydroxylase and 24 hydroxylase may be one of the major determinants in maintaining plasma levels of 1,25(OH) $_2$ D $_3$, at least in the early stages of CKD. The initial compensatory changes following kidney damage (as noted in the 5/6 nephrectomy model) was down-regulation of 24 hydroxylase in order to maintain 1,25(OH) $_2$ D $_3$ levels [41]. The VDR is present in these tubular epithelial cells, and regulates functions in these cells well beyond calcium homeostasis. The VDR, in the presence of hypocalcaemia, is normally down-regulated in CKD and in active vitamin D deficiency. Studies show that 1,25(OH) $_2$ D $_3$ significantly enhances renal VDR and VDR mRNA expression both *in vivo* or *in vitro* [42]. The 1,25(OH) $_2$ D $_3$ -mediated increase in renal VDR was the result of the activation of gene

expression and stabilization of the VDR. Another change during the early stages following kidney injury is the down-regulation of megalin in the renal tubular cells. Lower megalin levels affect endocytosis, which lead to decreased $25(\text{OH})\text{D}_3$ reabsorption as well as increased proteinuria [43]. If $1,\alpha$ hydroxylase and VDR levels are preserved, $25(\text{OH})\text{D}_3$ administration may be sufficient to maintain the high levels of $1,25(\text{OH})_2\text{D}_3$ production that are required for a cell specific function. Most probably, endogenously generated calcitriol could overcome the dramatic decline of megalin expression [41], and thereby prevent the onset of protein loss or the impaired $25(\text{OH})\text{D}_3$ uptake necessary for calcitriol synthesis. In this context, the use of active vitamin D might play a role in retarding the progression of renal disease. Notably, the vitamin D used to evaluate the effects on renal protection in all published studies was either active vitamin D (calcitriol) or one of its analogues.

Weinreich *et al.* [44] reported that $1,25(\text{OH})_2\text{D}_3$ and another vitamin D analogue, KH 1060, inhibited proximal tubular epithelial cell proliferation in a dose-dependent manner. Diminished local production of $1,25(\text{OH})_2\text{D}_3$ by tubular epithelial cells in CKD may facilitate interstitial fibrosis as a result of decreased inhibitory control of $1,25(\text{OH})_2\text{D}_3$ on renal cell proliferation. Direct evidence for vitamin D inhibition of interstitial fibrogenesis was recently obtained in cultured interstitial fibroblasts. We found that $1,25(\text{OH})_2\text{D}_3$ suppressed the myofibroblast activation from interstitial fibroblast [45], a critical event in generating α -SMA-positive, matrix-producing effector cells in diseased kidney. Myofibroblast activation was initiated by incubation with TGF- β 1, and treatment of rat renal interstitial fibroblasts (NRK-49F) with $1,25(\text{OH})_2\text{D}_3$ suppressed TGF- β 1 induced α -SMA expression in a dose-dependent manner. Similarly, $1,25(\text{OH})_2\text{D}_3$ suppressed type I collagen and thrombospondin-1 expression triggered by TGF- β 1. These results establish the anti-fibrotic activities of active vitamin D, through its counteraction of the pro-fibrotic TGF- β 1.

The mechanism underlying vitamin D's ability to inhibit myofibroblast activation was further investigated. It turns out that $1,25(\text{OH})_2\text{D}_3$ -induced anti-fibrotic hepatocyte growth factor (HGF) mRNA expression and protein secretion in renal interstitial fibroblasts [45]. There is a putative VDRE in the regulatory region of the HGF gene [46]; and $1,25(\text{OH})_2\text{D}_3$ indeed stimulated HGF gene promoter activity and induced the binding of the VDR to the VDRE in the HGF promoter region. Furthermore, $1,25(\text{OH})_2\text{D}_3$ was capable of stimulating HGF receptor phosphorylation in renal fibroblasts, and HGF-neutralizing antibody largely abolished $1,25(\text{OH})_2\text{D}_3$ -mediated suppression of myofibroblast activation. These studies provide a significant, mechanistic insight into understanding the potential beneficial role of active vitamin D against renal fibrosis. Moreover, the connection between active vitamin D and HGF provides additional clues on the

potentially broader effect of $1,25(\text{OH})_2\text{D}_3$ on kidney cells. In essence, any beneficial properties of HGF in kidney fibrosis can be potentially shared by $1,25(\text{OH})_2\text{D}_3$. Although the anti-fibrotic effect of $1,25(\text{OH})_2\text{D}_3$ is only illustrated in interstitial fibroblasts, it could have a wide range of actions on all kidney cells, because the HGF receptor, c-met, is expressed in all kidney cells tested to date [45].

In addition to its effect on the HGF expression, active vitamin D also antagonizes pro-fibrotic TGF- β 1 in tubular epithelial cells, leading to the inhibition of tubular EMT, a key event in the pathogenesis of TIF. We recently showed that paricalcitol was able to preserve tubular epithelial E-cadherin after TGF- β 1 treatment [52], suggesting a critical role of active vitamin D in the maintenance of mature epithelial cell phenotypes. It remains unclear how vitamin D blocks TGF- β 1 action in tubular epithelial cells, but one possibility is that the VDR can directly interact with Smads, the intracellular mediators that transduce TGF- β 1 signals. Although previous studies showed that the interaction between VDR and Smad3 results in stimulation of Smad3-mediated gene transcription [47], similar interactions may repress TGF- β 1/Smad actions in tubular epithelial cells. In addition, activation of VDR may inhibit TGF- β 1 expression, as vitamin D-treated rats had a significant reduction in bioactive renal TGF- β 1 [48].

Another potential mechanism for the role of active vitamin D against TGF- β 1 is that active vitamin D preserves tubular epithelial phenotypes by inhibiting β -catenin signalling, a critical signal pathway downstream to TGF- β 1/integrin-linked kinase, which mediates tubular EMT [49,50]. It has been reported that the ligand-activated VDR competes with T-cell transcription factor (TCF)-4 for β -catenin binding. Accordingly, vitamin D repressed β -catenin/TCF-4 transcriptional activity in colon carcinoma cells [51]. Regardless of the mechanisms, the observation that vitamin D blocks TGF- β 1-mediated tubular EMT, together with its ability to inhibit myofibroblast activation, suggests that active vitamin D may be capable of suppressing renal interstitial fibrogenesis in the pathologic conditions.

Finally, the beneficial effect of $1,25(\text{OH})_2\text{D}_3$ on renal TIF was also confirmed in animal models of CKD induced by unilateral ureteral obstruction (UUO). We have demonstrated that mice injected with paricalcitol for 7 days developed significantly less fibrotic lesions after obstructive injury when compared with vehicle control. Paricalcitol significantly attenuated the expression of α -SMA, fibronectin, collagen I and collagen III, while it largely restored the expression of E-cadherin and VDR [52]. To prove that the renal protective effects of $1,25(\text{OH})_2\text{D}_3$ are independent of PTH, Schwarz *et al.* [18] examined parathyroidectomized SNX rats with or without $1,25(\text{OH})_2\text{D}_3$ treatment. In animals treated with $1,25(\text{OH})_2\text{D}_3$, the number of PCNA-positive cells was significantly less in tubules, thereby decoupling the renal protective effects of vitamin D from changes in PTH levels.

Vitamin D deficiency and the progression of CKD

Without an initial insult, 1,25(OH)₂D₃ deficiency alone may not cause kidney damage. However, subjects with vitamin D deficiency may be vulnerable to kidney injury, which, in turn, could accelerate the progression of renal disease [53,54]. Aihara *et al.* [54] studied the possibility that activation of the VDR down-regulates thrombotic stimuli. When an intravenous injection of LPS at a dose of 5 mg/kg was administered to VDR KO and WT mice, although all mice survived the treatment, immunohistochemical analysis revealed that VDR KO mice exhibited an increased fibrin deposition in the glomeruli and peritubular capillaries of the kidney compared with WT mice. Li *et al.* [55] studied the gene expression profile in the kidney of VDR KO mice by using three independent DNA microarrays and noted alterations in the profile that covered multiple functional categories including signal transduction, transcriptional regulation, cell adhesion, metabolism, immune response and other functions. These findings strongly support the notion that active vitamin D is an endocrine hormone with multiple functions.

Clinical evidence

The current clinical indication for calcitriol or its analogues is the treatment of renal osteodystrophy or secondary hyperparathyroidism (SHPT) associated with CKD. In the past, there have been concerns that vitamin D might be 'nephrotoxic', based on two reports published in the 1970s [56,57]. There is no doubt that high doses of vitamin D and resultant hypercalcaemia and hypercalciuria may lead to decreased GFR; for many years, the fear of accelerating the decline in renal function limited the use of active vitamin D or its analogues in early CKD. However, recent studies, including several prospective randomized trials, have shown beneficial effects of moderate doses of active vitamin D on bone health and decrease PTH levels without adverse consequence to renal function in patients with mild to moderate CKD [58–61]. Interestingly, a retrospective analysis of 76 renal transplant patients with chronic allograft nephropathy found that treatment with calcitriol was associated with a significant improvement of graft survival at 3 years compared with the group that was not treated with calcitriol [62]. However, there are no prospective trials that have studied the possible renoprotective effect of active vitamin D on renal outcome using appropriate hard end points. Proteinuria is not only an unequivocal sign of kidney disease, but it also contributes to progression of CKD and serves as a significant marker for future cardiovascular (CV) events [63,64]. In this context, Agarwal *et al.* [26] have recently reported some interesting findings. They found that oral paricalcitol appears to have an anti-proteinuric effect in three pooled, double-blind, randomized, placebo-controlled studies

in CKD Stages 3 and 4 patients. Patients were randomized to paricalcitol capsules ($n=107$, mean dose 9.5 mcg/week) or placebo ($n=113$) and followed for up to 24 weeks. In conjunction with other safety measures, proteinuria was measured by dipstick and read by an automated reader in a central lab at the beginning and end of trial. At the final visit, 51% of the paricalcitol patients compared with 25% of the placebo patients had reduction in proteinuria, and these findings were independent of RAS blockade by ACEi/ARBs therapy. Although the method of detection of proteinuria is a limitation of this study, the outcome is at least hypothesis-generating. Clearly, more rigorous studies on the effect of active vitamin D on proteinuria are needed, followed by studies on hard end points.

It should be noted that the potential adverse consequences of vitamin D administration include alterations in serum minerals (hypercalcaemia, hyperphosphataemia and over-suppression of PTH), potential for soft tissue and arterial calcification, and adynamic bone disease. New vitamin D analogues with less calcaemic effects may decrease the risk of these potential adverse effects and more studies are needed in this area to confirm and clarify any beneficial effects of active vitamin D in CKD patients.

Conclusion

Active vitamin D is produced in the normal kidney and reduced serum levels of 1,25(OH)₂D₃ occur early in CKD. Active vitamin D has many important functions including immunomodulation, anti-proliferation and pro-differentiation as well as down-regulation of RAS. There is a growing amount of experimental evidence that vitamin D may be renoprotective, and some clinical evidence is now gathering. Whether this renoprotection is independent of the effects of RAS-intervention remains to be resolved. The currently available data, however, urge us to further study the potential role of active vitamin D or its analogues as a drug class, to be added to the current renoprotective (and potentially cardioprotective) pharmacological armamentarium. Well-designed clinical studies are needed to confirm this.

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Vitamin C deficiency in dialysis patients—are we perceiving the tip of an iceberg?

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Summary of the problem

The occurrence of vitamin C deficiency has complicated the management of dialysis patients since the beginning of renal replacement therapy [1]. The major portion of dietary vitamin C is provided by potassium-rich foods such as orange juice, strawberries and broccoli, but these foods are restricted for haemodialysis (HD) patients because HD removes potassium

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