

In-Depth Clinical Review

The use of vitamin D analogues in chronic kidney diseases: possible mechanisms beyond bone and mineral metabolism

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Abstract

Chronic kidney disease (CKD) is a common and costly medical condition, and currently available therapeutic options remain unsatisfactory. Vitamin D analogues are widely used for the bone and mineral disorder associated with CKD. However, accumulating evidence suggests that vitamin D analogues may have actions other than their effects on bone and mineral metabolism. In this article, we review the following aspects on the use of vitamin D analogues for the treatment of CKD: (1) epidemiological studies showing that patients with late-stage CKD have better survival than untreated patients; (2) animal studies showing that vitamin D analogues may retard the progression of CKD; (3) human studies on the anti-proteinuric and possibly renal protecting effects of vitamin D analogues in CKD and (4) the potential mechanisms of its therapeutic benefit. Nonetheless, definitive proof of the clinical benefits by randomized control trial would be necessary before one could advocate the routine use of vitamin D analogues for the treatment of CKD patients.

Keywords: calcitriol; cardiovascular disease; paricalcitol; proteinuria; renal failure

Chronic kidney disease (CKD) is a debilitating and costly medical condition. The clinical course is characterized by persistent proteinuria after an initial insult to the kidney, followed by progressive decline in renal function [1]. CKD patients are not only at risk of progressing to dialysis-dependent renal failure; they are at high risk of developing renal bone disease [2] and cardiovascular disease (CVD) [3,4]—the latter represents the major cause of mortality and morbidity in CKD patients. Unfortunately, the optimal therapy of CKD remains unknown. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) reduced proteinuria in short-term trials [5–7] and retard the rate of progression of renal function deterioration in chronic proteinuric nephropathy [8]. There is also evidence that these therapies may have a beneficial effect on the inflammatory component of CKD [9,10].

However, ACE inhibitor and ARB may not completely abrogate the renal function deterioration among high-risk patients.

In this respect, there is an increasing interest in the use of vitamin D analogues for the treatment of CKD patients. The reduction of renal 1α -hydroxylase activity and the circulating level of 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃), the active form of vitamin D, are prominent features of CKD. Vitamin D is a primary regulator of calcium homeostasis. Deficiency of 1,25-(OH)₂D₃ plays an important role in the pathogenesis of renal bone disease. Genetic inactivation of either the vitamin D receptor (VDR), a member of the nuclear receptor superfamily that mediates the action of 1,25-(OH)₂D₃, or 25-hydroxyvitamin D₃ 1α -hydroxylase, the rate-limiting enzyme for the biosynthesis of 1,25-(OH)₂D₃, results in impaired calcium homeostasis, leading to hypocalcaemia, secondary hyperparathyroidism and rickets [11–14]. Vitamin D deficiency in adults without CKD can precipitate or exacerbate osteopaenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture [15]. However, the wide tissue distribution of vitamin D receptor (VDR) suggests that the vitamin D endocrine system has additional physiological functions beyond calcium homeostasis. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases and CVD [15], all being relevant in normal population as well as CKD patients.

Vitamin D analogue and mortality in CKD

The use of vitamin D analogues in CKD patients is not new. In fact, replacement of activated vitamin D has been the cornerstone of therapy for secondary hyperparathyroidism, the cardinal manifestation of mineral bone disorder in CKD. While the only current indication for the use of activated vitamin D and its analogues in patients with CKD is the treatment of secondary hyperparathyroidism, the impact of vitamin D therapy may extend beyond lowering parathyroid hormone (PTH) levels and include potential cardiovascular

Table 1. Observational studies examining outcomes associated with treatment of activated vitamin D in patients with chronic kidney diseases

Study	Patients	Treatment	Follow-up	AHR of all-cause mortality	Comments
Shoji <i>et al.</i> [16]	242, prevalent HD	Oral alphacalcidol	61 months	No difference	Lower cardiovascular mortality
Teng <i>et al.</i> [17]	51 037, prevalent HD	Any analogue	24 months	0.74 (95% CI 0.71–0.79)	
Melamed <i>et al.</i> [18]	1007, incident HD and PD	Calcitriol	36 months	0.62 (95% CI 0.44–0.86)	
Kalantar-Zadeh <i>et al.</i> [19]	58 058, prevalent HD	Paricalcitol	24 months	Lower all-cause mortality	Possibly a dose-dependent effect
Tentori <i>et al.</i> [20]	7731, prevalent HD	Any analogue	37 weeks	0.83 (95% CI 0.77–0.91)	No difference between all three different analogues
Teng <i>et al.</i> [21]	67 399, prevalent HD	Paricalcitol	36 months	0.84 (95% CI 0.79–0.90)	Versus calcitriol
Kovesdy <i>et al.</i> [22]	520, CKD stages 2–5	Calcitriol	2.1 years	0.35 (95% CI 0.23–0.54)	Pre-dialysis patients ^a
Shoben <i>et al.</i> [23]	1418, CKD stages 3 and 4	Calcitriol	1.9 years	0.74 (95% CI 0.58–0.95)	Pre-dialysis patients ^a

HD, haemodialysis; PD, peritoneal dialysis; CKD, chronic kidney diseases; AHR, adjusted hazard ratio; CI, confidence interval.

^aBoth showed a trend of lower risk of dialysis. See the text for detailed description.

Table 2. Animal studies examining the renal protective effect of vitamin D analogues

Study	Model	Treatment	Benefit			Remarks
			Proteinuria	Renal function	Histology	
Schwarz <i>et al.</i> [24]	Subtotally nephrectomy	Calcitriol	Reduce	n/a	Less glomerulosclerosis	No change in BP; benefit not related to PTH
Hirata <i>et al.</i> [25]	Subtotally nephrectomy	22-oxacalcitriol	Reduce	n/a	Less glomerulosclerosis	
Mizobuchi <i>et al.</i> [26]	Subtotally nephrectomy	Paricalcitol	Reduce	Improve	Less glomerulosclerosis	Possibly a higher TI volume
Migliori <i>et al.</i> [27]	Thy1.1 glomerulonephritis	Calcitriol	Reduce	n/a	Less glomerular damage	
Tan <i>et al.</i> [28]	Obstructive nephropathy	Paricalcitol	n/a	n/a	Less TI damage	

BP, blood pressure; PTH, parathyroid hormone; TI, tubulointerstitial; n/a, not assessed.

and metabolic benefits. Several large observational studies examining outcomes associated with the use of activated vitamin D therapy in patients on maintenance dialysis and in patients with CKD not yet on dialysis have suggested that the benefits of vitamin D receptor activators may include direct cardiovascular and metabolic benefits (Table 1). These studies incorporated data from a very large number of patients and consistently showed that patients treated with any kind of vitamin D receptor activators experienced significantly lower all-cause and cardiovascular mortality rates compared with patients not receiving any treatment. Furthermore, the survival benefit of vitamin D analogues generally did not change quantitatively after adjusting for serum calcium, phosphate and parathyroid hormone levels in these studies [16–21], suggesting that the effect on survival is almost entirely explained by some non-traditional pleiotropic effects.

It is important to recognize that most of these studies examined CKD patients on maintenance dialysis. Nonetheless, two studies showed a similar benefit in pre-dialysis CKD patients [22,23]. Kovesdy *et al.* [22] examined the association of oral calcitriol treatment with mortality and the incidence rate of dialysis in 520 male US veterans with CKD stages 3–5 and not yet receiving dialysis; 258

patients received treatment with calcitriol, 0.25–0.5 µg/day, for a median duration of 2.1 years. The incidence rate ratios for mortality and combined death and dialysis initiation were significantly lower in treated patients. In this study, treatment with calcitriol was also associated with a trend towards a lower incidence rate of dialysis. In another study, Shoben *et al.* [23] evaluated associations of oral calcitriol use with mortality and dialysis dependence in 1418 non-dialysis patients with CKD and hyperparathyroidism in the Veterans' Affairs Consumer Health Information and Performance Sets database. After adjustment for various clinical confounders, oral calcitriol use was associated with a 26% lower risk for death and a 20% lower risk for death or dialysis. Taken together, these two studies suggest that vitamin D analogues may have some renal protective effect in pre-dialysis CKD patients.

Renal protection in animal models

Several studies have shown that the administration of vitamin D analogues attenuates the renal damage in various experimental models of uraemia [24–28] and is summarized in Table 2. Schwarz *et al.* [24] studied subtotally

Table 3. Human studies examining the renal protective effect of vitamin D analogues

Study	Type	Patients	Treatment	Follow-up	Proteinuria	Renal function	Comments
Kovesdy <i>et al.</i> [22]	Cohort	520, CKD stages 2–5	Calcitriol	2.1 years	n/a	Incidence rate ratio of dialysis 0.67 (95% CI, 0.46 to 0.97)	
Shoben <i>et al.</i> [23]	Cohort	1418, CKD stages 3 and 4	Calcitriol	1.9 years	n/a	No difference in the incidence rate of dialysis	
Agarwal <i>et al.</i> [29]	Prospective	220, CKD stages 3 and 4	Paricalcitol	24 weeks	Reduced (OR 3.2, 95% CI 1.5–6.9)	n/a	Proteinuria tested by dipstick only
Szeto <i>et al.</i> [30]	Prospective	10, IgA nephropathy	Calcitriol	12 weeks	Reduced (1.98 ± 0.74 to 1.48 ± 0.81 g:g-Cr)	No difference before and after treatment	No difference in the serum AgII level
Alborzi <i>et al.</i> [31]	Prospective	24, CKD stages 2 and 3	Paricalcitol	1 month	Reduced by 46% (95% CI, 17–65%)	No difference between treatment and placebo groups	Reduction in serum CRP

CKD, chronic kidney diseases; AgII, angiotensin II; CRP, C-reactive protein; CI, confidence interval; OR, odds ratio; n/a, not assessed.

nephrectomized rats treated with 1,25-(OH)₂D₃ and found that vitamin D reduces renal cell proliferation and glomerular growth as well as glomerulosclerosis and albuminuria as indicators of progressive glomerular damage. With a similar subtotal nephrectomized rat model, Hirata *et al.* [25] showed that 22-oxacalcitriol treatment significantly suppressed urinary albumin excretion, prevented increases in serum creatinine and serum urea nitrogen and inhibited glomerular cell number, glomerulosclerosis ratio and glomerular volume. With the same model, Mizobuchi *et al.* [26] showed that paricalcitol can suppress macrophage infiltration, monocyte chemoattractant protein-1 (MCP-1) production, transforming growth factor-beta-1 (TGF-β1) mRNA and protein expression, and phosphorylation of Smad2, and these effects are amplified when blood pressure is controlled via renin–angiotensin system blockade.

Glomerular and tubulointerstitium have both been proposed as the target of vitamin D in renal protection. In a study of Thy1.1 experimental glomerulonephritis, Migliori *et al.* [27] found that treatment with 1,25-(OH)₂D₃ abrogated podocytes injury, detected as desmin expression, and loss of nephrin and zonula occludens-1 (two slit diaphragm-associated proteins) and glomerular polyanion staining, suggesting that vitamin D may revert proteinuria by counteracting glomerular podocyte injury. On the other hand, in a study of experimental obstructive nephropathy, a model that is characterized by predominant tubulointerstitial lesions, Tan *et al.* [28] showed that paricalcitol significantly attenuated renal interstitial fibrosis, as demonstrated by a reduced interstitial volume, decreased collagen deposition and repressed mRNA expression of fibronectin and type I and type III collagens. Paricalcitol also preserved E-cadherin and reduced alpha-smooth muscle actin expression *in vivo*. In addition, paricalcitol suppressed renal TGF-β1 and its type I receptor expression, underscoring its ability to block directly the epithelial to mesenchymal transition of tubular epithelial cells.

Renal protection in human CKD

Despite a wealth in animal data, human study on the renal protective effect of vitamin D analogues is scarce (Table 3).

Neither of the observational studies described earlier on the outcomes associated with treatment of activated vitamin D in patients with pre-dialysis CKD provides a conclusive answer [22,23]. In the study reported by Shoben *et al.* [23], the incidence rate of dialysis was 10.4 and 10.1 events per 100 person-years among calcitriol users and nonusers, respectively. In contrast, Kovesdy *et al.* [22] found an insignificant trend between calcitriol treatment and the incidence rate of dialysis-dependent renal failure alone (without mortality) in unadjusted and fully adjusted models (adjusted hazard ratio 0.73, 95% CI 0.50–1.12). In fact, the association was statistically significant in the case-mix-adjusted model, with an incidence rate ratio of 0.67 (95% CI 0.46–0.97). Although the result seems encouraging, it is important to note that the study of Kovesdy *et al.* [22] had a smaller sample size and involved a more heterogeneous group of CKD patients than the one reported by Shoben *et al.* [23] (see Table 1).

How about prospective studies? In three double-blind, randomized, placebo-controlled studies to evaluate the safety and efficacy of oral paricalcitol, Agarwal *et al.* [29] studied 220 CKD stage 3 and 4 patients with secondary hyperparathyroidism who were randomized to oral paricalcitol (mean dose 9.5 μg/week) or placebo and followed up for up to 24 weeks. At the final visit, 51% of the paricalcitol patients compared to 25% placebo patients had a reduction in proteinuria (odds for the reduction in proteinuria 3.2 times greater for paricalcitol patients, 95% CI 1.5–6.9). The reduction of proteinuria favoured patients on paricalcitol regardless of the use of therapies to block the renin–angiotensin–aldosterone system. However, the actual amount of proteinuria, which was not the primary objective of those original trials, was not fully quantified. It could also be argued that the qualitative difference in proteinuria may be mediated by the difference in the achieved parathyroid hormone level between groups, for which the study was designed.

Two prospective human studies specifically examined the renal protective effect of vitamin D analogues. In a recent open-label prospective uncontrolled trial of 10 patients with biopsy-proven IgA nephropathy and persistent proteinuria despite ACE inhibitor or ARB therapy, we found that

calcitriol treatment, 0.5 μg twice weekly for 12 weeks, resulted in a progressive decrease in urine protein-creatinine ratio during the first 6 weeks that persisted throughout the study period [30]. This study, however, did not have a control group, and the duration of follow-up was too short to access the benefit on renal function deterioration. In this study, there was a simultaneous decrease in the serum TGF- β level, and the percentage of decrease in the serum TGF- β level significantly correlated with the percentage of change in proteinuria. The serum angiotensin II level, however, did not change throughout the study, indicating that the anti-proteinuric effect of calcitriol may not be related to the effect on the renin-angiotensin system.

In another recent pilot trial, 24 CKD patients (mostly stage 3) were randomly allocated to receive 0, 1 or 2 μg oral paricalcitol [31]. After 1 month, the treatment-to-baseline ratio of 24-h albumin excretion rate was 1.35 (95% CI, 1.08–1.69) with placebo, 0.52 (95% CI, 0.40–0.69) with a 1 μg dose and 0.54 (95% CI, 0.35–0.83) with a 2 μg dose. In addition, there was a significant reduction in the serum C-reactive protein level in the treatment groups. In this study, no difference was observed in renal function, 24-h ambulatory blood pressure or parathyroid hormone between groups. It was concluded that paricalcitol-induced reduction in albuminuria and inflammation may be mediated independent of its effects on haemodynamics or parathyroid hormone suppression. Taken together, these two studies showed an anti-proteinuric effect of vitamin D analogues by short-term treatment. Since both of the studies had very short follow-up, the long-term effect on renal function deterioration remains undetermined.

Diabetic nephropathy: a special case?

The above discussion considered CKD, irrespective of the underlying renal diagnosis, as a whole group. As to the use of vitamin D analogues, diabetic nephropathy needs special considerations because it is the leading cause of dialysis-dependent end-stage renal disease, and the renin-angiotensin system (RAS) is a major mediator of progressive renal injury in diabetic nephropathy. As discussed above, vitamin D negatively regulates the RAS, and the renal protective role of vitamin D in diabetic nephropathy has been specifically studied [32]. Diabetic VDR knockout mice developed more severe albuminuria and glomerulosclerosis due to increased glomerular basement membrane thickening and podocyte effacement [33]. More fibronectin and less nephrin were expressed in the VDR knockout mice compared to diabetic wild-type mice. In receptor knockout mice, increased renin, angiotensinogen, TGF- β and connective tissue growth factor accompanied the more severe renal injury.

In cell culture models, Zhang *et al.* [33] showed that 1,25-(OH) $_2$ D $_3$ inhibited high glucose-induced fibronectin production in cultured mesangial cells and increased nephrin expression in cultured podocytes. The 1,25-(OH) $_2$ D $_3$ also suppressed high glucose-induced activation of the renin-angiotensin system and TGF- β in mesangial and juxtaglomerular cells. In another series of experiments, the same group of investigators showed that combination therapy

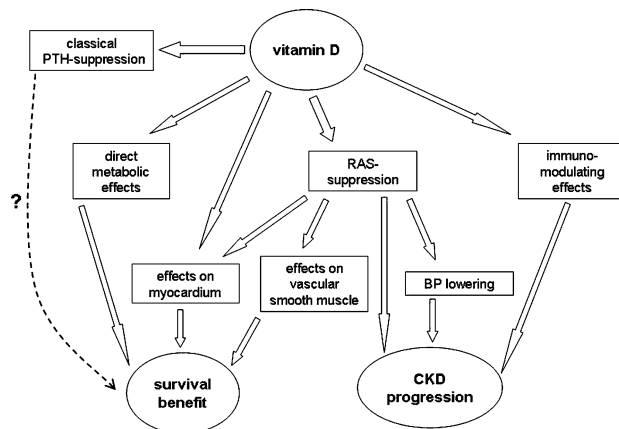


Fig. 1. Summary of putative mechanisms of action responsible for the lower mortality and progression of chronic kidney disease associated with vitamin D therapy. BP, blood pressure; CKD, chronic kidney diseases; RAS, renin-angiotensin system.

with an ARB and a vitamin D analogue markedly ameliorated renal injury in the streptozotocin-induced diabetes model due to the blockade of the compensatory renin rise by the vitamin D analogue, leading to more effective inhibition of the renin-angiotensin system [34]. The combined treatment suppressed the induction of fibronectin, TGF- β and MCP-1 and reversed the decline of slit diaphragm proteins nephrin, zonula occludens-1 and alpha-actinin-4. These were accompanied by blockade of intrarenal renin and angiotensin II accumulation induced by hyperglycaemia and losartan. Despite the above-mentioned experimental evidence, however, there are no human data in this area, and it seems probable that the renal protective effect of vitamin D is not specific for diabetic nephropathy [35].

Mechanisms of vitamin D-related benefits

A number of possible mechanisms have been proposed to explain the survival advantage of CKD patients treated with vitamin D analogues [36] (Figure 1). In addition to its primary role in calcium homeostasis and bone mineralization, the vitamin D endocrine system has additional physiological functions involving the immune and cardiovascular system and the protection of renal cellular integrity [37,38]. Most of the pleiotropic actions of vitamin D and its analogues are mediated by the VDR, a ligand-dependent transcription factor belonging to the steroid nuclear receptor gene family [38].

Effects on blood pressure and the renin-angiotensin system

In the last two decades, epidemiological studies have revealed an inverse relationship between the plasma 1,25-(OH) $_2$ D $_3$ concentration and the blood pressure or the plasma renin activity in both normotensive men and patients with essential hypertension [39–43]. Ultraviolet light exposure, which is required for vitamin D biosynthesis, is inversely related to the rise of blood pressure and the prevalence of hypertension in the general population and

was shown to have blood pressure-lowering effects [44,45]. Furthermore, it has been reported that vitamin D₃ supplementation reduces blood pressure in patients with essential hypertension [46,47], and 1,25-(OH)₂D₃ treatment reduces blood pressure, plasma renin activity and Ang II levels in hyperparathyroidism patients [48,49].

Experimental studies have highlighted the role of the VDR as a down-regulator of the renin-angiotensin system [50,51]. Li *et al.* [50] show that renin expression and plasma angiotensin II production were increased several folds in vitamin D receptor-null mice, leading to hypertension, cardiac hypertrophy and increased water intake. In wild-type mice, inhibition of 1,25-(OH)₂D₃ synthesis also led to an increase in renin expression, whereas 1,25-(OH)₂D₃ injection led to renin suppression. In this experiment, vitamin D regulation of renin expression was independent of calcium metabolism and that 1,25-(OH)₂D₃ markedly suppressed renin transcription by a VDR-mediated mechanism in cell cultures. Similarly, Zhou *et al.* [52] showed that in 1 α -hydroxylase knockout mice with a rescue diet that normalizes serum calcium and phosphorus levels, abnormalities in the renin-angiotensin system, blood pressure and cardiac structure-function problems remained, indicating that the repressing effect of vitamin D on the renin-angiotensin system is independent of extracellular calcium or phosphorus. Mechanistic analysis of VDR-mediated renin suppression suggests that VDR-mediated renin suppression likely acts through a transcriptional regulatory complex that binds to the CRE-like domain in the renin enhancer region [53].

The effect of a vitamin D analogue on the renin-angiotensin system, however, may not be directed on renin alone [54]. In rats with the remnant kidney model of chronic renal failure (5/6 nephrectomy), Freundlich *et al.* [55] showed that paricalcitol decreases angiotensinogen, renin, renin receptor and vascular endothelial growth factor mRNA levels in the remnant kidney by 30–50% as compared to untreated animals. Similarly, the protein expression of renin, renin receptor, the angiotensin type 1 receptor and vascular endothelial growth factor were all significantly decreased.

Other cardiovascular effects

Vitamin D has a direct effect on myocardium, independent of its suppressive effect on the renin-angiotensin system. It directly suppresses myocardial hypertrophy and could improve cardiac performance [56]. Walters *et al.* [57] demonstrated that the uptake of calcium by cardiac muscle cells is in part regulated by vitamin D, an effect that is receptor mediated, requiring transcription and protein synthesis. Vitamin D has also been shown to affect the growth of cardiac cells in culture. O'Connell *et al.* [58] showed that 1,25-(OH)₂D₃ reduces proliferation rate, PCNA levels and c-Myc levels of myocytes in culture through decreased entry into the S phase. Vitamin D deficiency also results in a shift in the tissue distribution of V1 and V3 myosin chains, favouring the V1 isotype [59]. Shifts in myosin isotypes have been shown to alter myocyte contractility [60].

In addition, vitamin D has a biphasic action on vascular smooth muscle cell and prevents its proliferation [61].

Carthy *et al.* [62] found that 1,25-(OH)₂D₃ suppresses VS vascular smooth muscle cell ³H-thymidine uptake; active vitamin D also suppresses the stimulatory effect of epidermal growth factor on vascular smooth muscle cell proliferation. At low dose, vitamin D may also stimulate the production of inhibitors of arterial calcification [63,64] and have an anti-thrombotic effect [65]. In contrast, active form of vitamin D applied in supraphysiological concentration of 10 nmol/l is a mitogenic factor for aortal smooth muscle cell [66].

Other metabolic effects

Vitamin D has also been reported to enhance insulin sensitivity and induce a favourable plasma lipid profile. In 126 healthy, glucose-tolerant subjects, Chiu *et al.* [67] found an independent correlation between serum 25(OH)D concentration and insulin sensitivity index, and an independent negative relationship of 25(OH)D concentration with plasma glucose concentration at fasting, 60, 90 and 120 min during the oral glucose tolerance test. In this study, subjects with hypovitaminosis D (below 20 ng/mL) had a greater prevalence of components of metabolic syndrome than did subjects without hypovitaminosis D. Vitamin D has also been reported to increase apolipoprotein A-I and high-density lipoprotein (HDL) cholesterol, resulting in a favourable plasma lipid profile [68]. In HepG2 cells treated 1,25-(OH)₂D₃, Apo AI secretion and mRNA levels were both suppressed in a dose-dependent manner [69]. This was accompanied by a similar decrease in apo AI promoter activity.

Immunomodulating effects

A vitamin D analogue is also a potent regulator of the immune system, in particular, on T cell-mediated immunity [70,71]. Vitamin D receptor is found in significant concentrations in the T lymphocyte and macrophage populations. However, its highest concentration is in the immature immune cells of the thymus and the mature CD8 T lymphocytes. The significant role of vitamin D compounds as selective immunosuppressants is illustrated by their ability to either prevent or markedly suppress animal models of autoimmune disease. Results show that 1,25-(OH)₂D₃ can either prevent or markedly suppress experimental autoimmune encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus, type I diabetes and inflammatory bowel disease [71]. Vitamin D hormone stimulates TGF- β 1 and interleukin 4 (IL-4) production, which in turn suppresses inflammatory T cell activity [71]. Calcitriol attenuates the expression of experimental murine lupus [72]. In the kidney, 1,25(OH)₂D₃ also regulates mesangial cell smooth muscle phenotypes in a TGF- β 1-mediated manner [73] and ameliorates glomerular injury in rats with experimental glomerulonephritis [74].

Difference between compounds

Based on the available data, it is difficult to draw any conclusion on the difference between individual forms of a

vitamin D analogue. Two large cohort studies did attempt to perform head-to-head comparison between analogues. In an observational study of 7731 prevalent haemodialysis patients, Tentori *et al.* [20] found that mortality was significantly lower in patients treated with doxercalciferol and paricalcitol versus calcitriol in the unadjusted survival model. In adjusted models, however, this difference was not statistically significant. In another study of 67 399 prevalent haemodialysis patients, Teng *et al.* [21] found that the mortality rate was 16% lower (95% CI 10–21%) among paricalcitol-treated patients than calcitriol-treated ones. It could be argued that the latter study had a much larger sample size and longer follow-up as compared to the former one (36 months versus 9 months). Nonetheless, any observed difference between individual forms of a vitamin D analogue could equally be explained by the difference in the effective dosage. At this moment, it is impossible to recommend one product over another, although newer compounds with a lower risk of hypercalcaemia might be preferable if high-dose therapy is needed.

Further direction

Although the results seem promising, definitive proof of the clinical benefits by randomized control trial would be necessary before one could advocate the routine use of vitamin D analogues for the treatment of CKD patients. In fact, therapy with a vitamin D analogue is not without risk; hypercalcaemia or elevated calcium/phosphate product is always a concern. Around one-third of the ESRD patients treated with calcitriol for renal bone disease would have hypercalcaemia or elevated calcium/phosphate product [75,76]. It has been postulated that there exists some differential effect between calcitriol and other vitamin D analogues (for example, paricalcitol) on parathyroid hormone suppression and their relative incidence rate of hypercalcaemia and hyperphosphataemia [75–78]. Nonetheless, as many as 18% of dialysis patients treated with paricalcitol had persistent hypercalcaemia or elevated calcium/phosphate product [78]. In short, vitamin D therapy should not be taken lightly, and close monitoring of the biochemical profile is necessary.

Conclusions

While the only current indication for the use of activated vitamin D and its analogues in patients with CKD is the treatment of secondary hyperparathyroidism, a number of observational studies show that the use of activated vitamin D therapy in dialysis and pre-dialysis CKD patients is associated with a superior survival rate. In addition, animal studies and available, though limited, human data suggest that vitamin D therapy may have an anti-proteinuric effect and possibly reduce the rate of renal function deterioration. In addition to its primary role in calcium homeostasis and bone mineralization, vitamin D has a variety of additional functions including suppression of the renin–angiotensin system, direct cardiovascular, metabolic and immunomodulating effects. Putative mechanisms of action responsible

for the lower mortality and progression of CKD associated with vitamin D therapy are summarized in Table 1. The wealth of experimental evidence and observational studies shed light on potential areas of further clinical trials that are necessary to test whether vitamin D therapy would confer clinically meaningful benefits to CKD patients.

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