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VITAMIN D: ROLES IN RENAL AND CARDIOVASCULAR PROTECTION

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Abstract

Purpose of review—Great progress has been made in recent years in understanding the expanding roles of the vitamin D endocrine system beyond calcemic regulation, including pathophysiological actions in the kidney and the cardiovascular system. The purpose of this review is to update the recent advance regarding the effects of vitamin D and its analogs on the renal and cardiovascular system.

Recent findings—Vitamin D-deficiency is not only widely associated with chronic kidney disease and cardiovascular disease in humans, but may also accelerate the disease progression. Dysregulation of vitamin D metabolism caused by renal insufficiency contributes to the low vitamin D status. Preclinical and clinical studies have demonstrated impressive therapeutic outcome with low-calcemic vitamin D analogs in renal and cardiovascular disease. The mechanism underlying the renal and cardiovascular protection involves regulation of multiple signaling pathways by vitamin D including NF- κ B, Wnt/ β -catenin and the renin-angiotensin system.

Summary—The renal and cardiovascular protective activity of vitamin D revealed in recent studies has profound clinical implications. Nutritional correction of vitamin D-deficiency and treatment with vitamin D analogs could be therapeutic options for renal and cardiovascular problems. New vitamin D analogs with better renal and cardiovascular therapeutic efficacy are highly desired. More randomized trials are needed to address these issues.

Keywords

Cardiovascular disease; Chronic kidney disease; Renin-angiotensin system; Vitamin D; Vitamin D-deficiency; Vitamin D analogs

Introduction

Vitamin D-deficiency (usually defined as serum 25-hydroxyvitamin D levels (25(OH)D) < 20 ng/mL or 50 nmol/L) is an emerging global health problem that is estimated to affect more than one billion people worldwide [1]. The vitamin D endocrine system, with 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) as the most active hormonal metabolite, is a pleiotropic hormonal system (figure 1). As such, vitamin D-deficiency has various adverse consequences [1], including detrimental impact on the renal and cardiovascular system.

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Studies in recent years have demonstrated strong renal and cardiovascular protective effects of vitamin D and its analogs. Renal and cardiovascular disorders are leading causes of death in humans, thus these findings have profound clinical implications. The main focus of this review is to update the most recent development in the understanding of the renal and cardiovascular effects of vitamin D.

High prevalence of vitamin D-deficiency in chronic kidney disease

High prevalence of vitamin D-deficiency or -insufficiency in patients with chronic kidney disease (CKD) has been well documented in recent epidemiological studies. Low serum 25(OH)D status, particularly low 1,25(OH)₂D₃ levels, is very common in patients with CKD even at early stages, and the severity of deficiency increases with the progression of kidney disease [2, 3]. Cross-sectional analyses showed that 25(OH)D-deficiency is associated with impaired glomerular filtration rate (GFR) in CKD [4], and 25(OH)D- and 1,25(OH)₂D₃-deficiency are independently associated with decreased hemoglobin levels and anemia in early CKD [5]. Data from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States revealed a correlation between low serum 25(OH)D (<15–17.8 ng/mL) and the risk of all-cause mortality in the general population [6] and in subjects with CKD who are not undergoing dialysis [7]. Recently data from the Ludwigshafen Risk and Cardiovascular (LURIC) Health Study confirmed that low vitamin D status is associated with all-cause mortality and cardiovascular mortality in CKD patients in Germany [8], and a meta-analysis of 10 prospective studies confirmed that high 25(OH)D levels are associated with significantly improved survival in patients with CKD [9]. Vitamin D-deficiency is closely correlated to kidney disease progression, and the serum vitamin D status is an independent inverse predictor of disease progression and death in CKD patients [10], suggesting that vitamin D-deficiency may in fact accelerate the progression of CKD. On the other hand, numerous retrospective observational studies in the last few years consistently reported reduced mortality in hemodialysis and non-dialysis CKD patients receiving vitamin D or its analog therapy [11]. Whether vitamin D-deficiency is in fact the cause of CKD progression and whether raising vitamin D levels or correcting vitamin D-deficiency indeed ameliorates CKD, however, require large randomized controlled clinical trials to address.

Altered vitamin D metabolism in kidney disease

Recent studies provide evidence that dysregulation of vitamin D metabolism is a main cause for vitamin D-deficiency in CKD. The majority of vitamin D in the body comes from *de novo* synthesis in the skin, catalyzed by ultraviolet light from the sunlight. Once synthesized, vitamin D is quickly converted in the liver to 25(OH)D, the predominant circulating metabolite. In the circulation 25(OH)D complexes with vitamin D binding protein (DBP). Following glomerular filtration the 25(OH)D-DBP complex is reabsorbed via megalin-mediated endocytosis in the proximal tubules [12], where 25(OH)D is converted to 1,25(OH)₂D₃ by renal 1 α -hydroxylase (CYP27B1) [1]. In renal insufficiency, the decline in megalin-mediated endocytotic activity and renal 1 α -hydroxylase activity and the loss of 25(OH)D-DBP into the urine because of proteinuria contribute to the development of 25(OH)D and 1,25(OH)₂D₃ deficiency. This notion is supported by recent experimental data that demonstrate dysregulated vitamin D metabolism in kidney disease. Urinary excretion of DBP was found elevated in type 1 diabetes patients [13], and levels of megalin, DBP and 25(OH)D increased in the urine of type 1 diabetic mice [14]. In Zucker diabetic fatty rats, the expression of megalin and Dab2 was decreased in the kidney and renal reuptake of 25(OH)D-DBP was compromised, accompanied by reduced levels of 25(OH)D and 1,25(OH)₂D₃ in the serum and elevated urinary excretion of 25(OH)D, 1,25(OH)₂D₃ and DBP [15]. Moreover, renal 24-hydroxylase (CYP24A1), the catabolic

enzyme involved in 25(OH)D and 1,25(OH)₂D₃ degradation, was found markedly elevated in uremic rats and diseased human kidney biopsies, together with reduction in serum 1,25(OH)₂D₃ [16]. This suggests that increased CYP24A1 activity also contributes to vitamin D-deficiency in kidney disease.

Another factor that contributes to the low vitamin D status in CKD is fibroblast growth factor (FGF) 23, a major phosphatonin that promotes renal phosphate excretion and suppresses 1,25(OH)₂D₃ production via inhibition of CYP27B1 and stimulation of CYP24A1 [17]. Circulating FGF23 levels are elevated along with the decline of GFR and the increase in serum creatinine and phosphate levels [18–20]. In advanced CKD persistent phosphate retention due to impaired kidney function greatly induces FGF23, leading to suppression of 1,25(OH)₂D₃ production. In addition, conventional risk factors such as reduced sunlight exposure and poor dietary vitamin D intake also contribute to vitamin D insufficiency in the CKD population.

Anti-proteinuric activity of vitamin D

Albuminuria is a major risk factor for CKD progression, renal failure, cardiovascular events and death [21], thus reduction of albuminuria is a crucial therapeutic target for CKD. A cross-sectional analysis of the NHANES III data revealed a correlation between vitamin D-insufficiency and increased prevalence of albuminuria in the US adult population [22], suggesting that vitamin D has an intrinsic anti-proteinuric activity. A number of clinical studies have demonstrated therapeutic efficacy of vitamin D analogs to reduce proteinuria. Following an early report that activated vitamin D analog paricalcitol has significant anti-proteinuric activity in CKD [23], two small randomized pilot trials were conducted to evaluate the anti-proteinuric effect of oral paricalcitol treatment in CKD patients (n=24 and n=61, respectively) [24, 25]. These trials showed that paricalcitol significantly reduced albuminuria independent of its effect on hemodynamics or parathyroid hormone suppression. Most recently, a large randomized placebo-controlled clinical trial (the VITAL Study, n=281) confirmed that paricalcitol is able to reduce albuminuria and blood pressure in patients with diabetic nephropathy who were already on renin-angiotensin inhibitor therapy [26]. Together these clinical data provide a strong case to argue for the use of low-calcemic vitamin D analogs as a complementary therapy for treatment of proteinuria. Given the importance of podocytes in the regulation of glomerular filtration, it is speculated that podocytes are important anti-proteinuric target of vitamin D [27].

Renoprotective mechanisms

Recent research with different experimental models of kidney disease has provided good insights into the reno-protective mechanism for vitamin D and its analogs. The reno-protective activity of vitamin D is mediated by the vitamin D receptor (VDR) and appears to act by regulating multiple pathways including the renin-angiotensin system (RAS), NF-κB, Wnt/β-catenin and some key structural proteins (Table 1).

The renin-angiotensin system

The intrarenal RAS is a major mediator of renal damage. Many pathological conditions such as hyperglycemia, renal insufficiency and vitamin D-deficiency can activate the local RAS in the kidney, leading to increased local concentration of angiotensin (Ang) II, the effector of the RAS cascade that has a broad range of pathogenic activities that promote renal injury [28]. It is well established that the vitamin D hormone is a negative regulator of the RAS by suppressing renin expression [29, 30]. VDR-null mutant mice develop more severe renal damage (e.g. increased albuminuria, glomerulosclerosis and interstitial fibrosis) than wild-type counterparts in diabetic state [31] or under unilateral ureteral obstruction (UUO) [32],

because of enhanced activation of the RAS in the kidney. In rats with 5/6 nephrectomy paricalcitol treatment attenuated glomerular and tubulointerstitial damage and reduced blood pressure and proteinuria by blocking the activation of the local RAS in the kidney remnant [33]. Vitamin D analog doxercalciferol modulated high fat-induced renal disease by targeting the RAS and lipid metabolism [34]. Moreover, many studies proved that combination therapy with one vitamin D analog (paricalcitol or doxercalciferol) and one RAS inhibitor (ACE inhibitor or ARB) produced synergistic or additive therapeutic effects in blocking renal damage in experimental models of type 1 and type 2 diabetes mellitus [35–38], UO [39] and 5/6 nephrectomy [40]. The basis for the enhanced reno-protective efficacy of the combination therapy is the blockade of the compensatory renin induction usually encountered in the use of RAS inhibitors by the vitamin D analog. Inhibition of the renin induction and Ang II accumulation within the kidney leads to significantly better therapeutic outcomes [41]. The combination strategy demonstrated in these preclinical studies explains why vitamin D analogs are still effective in reducing proteinuria in CKD patients who are already on RAS inhibitor therapy [24, 26]. Given that RAS inhibitors are standard of care for CKD and many other diseases, an important implication of the combination therapy is that vitamin D analogs can be used as complementary therapy in many human diseases.

NF- κ B activation and inflammation

NF- κ B is a family of transcription factors that functions as a master regulator of immune response. NF- κ B regulates a wide range of genes involved in inflammation, proliferation and fibrogenesis that are known to play important roles in kidney disease [42]. Vitamin D suppresses NF- κ B activation, partly by disrupting DNA binding of NF- κ B [43]. Serum vitamin D status is inversely associated with increased renal inflammation in patients with a variety of kidney disorders [44]. Recent investigations showed that paricalcitol protects against kidney damage by blocking NF- κ B activity and reducing renal inflammation in experimental models of kidney disease such as UO [45], cyclosporine-induced nephropathy [46] and gentamicin-induced renal injury [47]. At the molecular level, 1,25(OH) $_2$ D $_3$ inhibits the expression of high glucose-induced MCP-1 and angiotensinogen and inflammation-induced PAI-1 by blocking the activation of NF- κ B [48–50]. These factors are involved in renal disease progression. For example, MCP-1 induces infiltration of macrophages in the kidney, which release factors that can promote kidney disease progression. Ang II activates NF- κ B, whereas NF- κ B mediates high glucose induction of angiotensinogen, the substrate of renin for Ang II production. This vicious circle, which enhances the local accumulation of Ang II in diabetic nephropathy, can be disrupted by vitamin D [51].

Wnt/ β -catenin pathway

Recent studies implicated that activation of the Wnt/ β -catenin pathway induces podocyte injury and albuminuria in adriamycin nephropathy [52]. 1,25(OH) $_2$ D $_3$ can block the Wnt/ β -catenin pathway by promoting the physical interaction between VDR and β -catenin, thus preventing β -catenin nuclear translocation [53]. The molecular basis underlying liganded VDR and β -catenin interaction has been established [54]. Most recently, paricalcitol was shown to prevent podocyte dysfunction and ameliorate proteinuria by blocking Wnt/ β -catenin signaling via VDR- β -catenin interaction [55].

Direct gene regulation

In the glomerular filtration barrier the slit diaphragm functions as the size-selective and charge-selective barrier to protein leakage. A number of proteins involved in the formation of the slit diaphragm are down-regulated in diabetes, and vitamin D therapy blocks the down-regulation [35, 37]. This vitamin D effect may result from direct stimulation on these

genes, or secondary to the prevention of podocyte loss. Nephritin, a key slit diaphragm protein produced by podocytes [56], is induced by $1,25(\text{OH})_2\text{D}_3$ in podocyte cultures [57]. Most recent work identified a vitamin D response element (VDRE) in the proximal promoter of the nephritin gene that mediates nephritin up-regulation by $1,25(\text{OH})_2\text{D}_3$ [58]. This regulation likely accounts for part of the anti-proteinuric mechanism of vitamin D.

Association of vitamin D-deficiency with cardiovascular disease

There is also a growing body of epidemiological evidence that links vitamin D deficiency to cardiovascular disease. By cross-sectional analysis of the NHANES III (1988–1994) and NHANES 2001–2004 databases that are representative of the US adult population, a number of studies consistently demonstrated an association of low serum $25(\text{OH})\text{D}$ levels with high blood pressure [59], increased prevalence of cardiovascular disease [60, 61] and cardiovascular risk factors including hypertension, diabetes, obesity and hyperlipidemia [62]. Prospective studies with cohorts from the Health Professionals' Follow-Up Study (HPFS) and the Nurses' Health Study (NHS) also showed an inverse correlation between serum $25(\text{OH})\text{D}$ levels and the risk of incident hypertension [63] and myocardial infarction even after adjusting for factors known to be associated with coronary artery disease [64]. Low serum $25(\text{OH})\text{D}$ is correlated with incident cardiovascular disease in Framingham Offspring Study participants without prior cardiovascular disease [65], and with high blood pressure in Hispanic and African Americans [66]. Vitamin D deficiency is also associated with coronary stenoses, coronary artery calcification and carotid atherosclerosis [67–69]. Moreover, the NHS and HPFS data suggest that higher vitamin D intake reduces the risk of cardiovascular disease in men [70], and a meta-analysis of 17 prospective studies also concludes that vitamin D supplements at moderate to high doses, but not calcium supplement, reduce the risk of cardiovascular disease [71].

Similar correlations are also reported in a variety of patient populations. Prospective analysis of a large electronic medical database demonstrated an association of vitamin D-deficiency with high prevalence of diabetes, hypertension, hyperlipidemia and peripheral vascular disease in a general US healthcare population [72]. Vitamin D-deficiency is associated with heart failure and sudden cardiac death in patients referred for coronary angiography in Europe [73]. A prospective cohort study showed that low serum $25(\text{OH})\text{D}$ levels are associated with increased risk of cardiovascular events in chronic peritoneal dialysis patients in Hong Kong [74]. A meta-analysis of 18 published studies confirms the inverse relationship between blood $25(\text{OH})\text{D}$ levels and hypertension [75]. Together these data indicate that vitamin D-deficiency is an important risk factor for cardiovascular disease.

Cardiovascular protective actions of vitamin D

Cardiovascular disease is common in the CKD population. A significant reduction in cardiovascular mortality was noticed in many retrospective observational studies that reported reduced mortality in CKD patients receiving vitamin D or its analog therapy (see references in [11]), suggesting that vitamin D has strong cardiovascular protective activity. This speculation is supported by animal studies conducted in recent years. In Dahl salt-sensitive rats paricalcitol treatment blocked high salt-induced cardiac hypertrophy [76]. More recent data showed that mono-treatment with paricalcitol or doxercalciferol or combination therapy with these analogs and RAS inhibitors (losartan or enalapril) prevented cardiac hypertrophy in spontaneously hypertensive rats [77] or prevented the progression of existing cardiac hypertrophy in Dahl salt sensitive rats [78]. As described above, the combination therapy blocked the compensatory induction of renin in the kidney and heart [77].

The cardio-protective mechanism of vitamin D remains to be fully defined. For the effect on cardiac hypertrophy, it is unclear if vitamin D directly acts on the heart via VDR. Although VDR expression was reported increased in hypertrophic heart in mice [79], whether VDR is indeed expressed in cardiomyocytes is controversial [80]. A VDR gene polymorphism is associated with left ventricular mass in patients with late stage CKD [81]. On the other hand, the effect of vitamin D on vascular disease is complex. While 1,25(OH)₂D₃ can induce vascular calcification in ApoE-null mice [82], it also inhibits foam cell formation, suppresses cholesterol uptake in macrophages from type 2 diabetes patients [83], and decreases atherosclerosis by regulating immune cells [84].

A general and likely mechanism underlying the cardiovascular effects of vitamin D is regulation of the RAS, a cascade that has a profound impact on the cardiovascular system. That 1,25(OH)₂D₃ functions as a negative regulator of the RAS has long been established. Null mutant mice lacking VDR or Cyp27b1 develop hyperreninemia and cardiac hypertrophy [29, 85]. Overexpression of human VDR in the juxtaglomerular cells suppresses renin expression in transgenic mice [86]. A recent study confirmed that vitamin D analog therapy can significantly suppress plasma renin activity in hemodialysis patients [77]. In healthy humans low vitamin D status may result in up-regulation of the RAS [87]. Data from the large cohort of patients (n>3000) in the LURIC study revealed that both serum 25(OH)D and 1,25(OH)₂D₃ levels are independently and inversely associated with plasma renin concentration and Ang II levels [88], strongly supporting the concept of vitamin D regulating RAS in humans. Having said that, the therapeutic efficacy of vitamin D and its analogs, either as primary or complementary therapy, in cardiovascular disease needs to be tested by randomized controlled clinical trials. In this regard, the ongoing PRIMO study, a randomized trial that investigates the effect of paricalcitol on the progression of left ventricular hypertrophy in stage 3 and 4 CKD patients (n=227) who are already on RAS inhibitors [89], is highly anticipated. This trial actually assesses the cardiac outcome of the combination of vitamin D analog and RAS inhibitor in humans. Studies like this are needed to fully understand the therapeutic potential of vitamin D and its analogs.

Conclusion

Research in the last few years has greatly advanced our understanding of the renal and cardiovascular effects of vitamin D. The evidence for vitamin D exerting renal and cardiovascular protection is abundant and strong, but the protective mechanism remains to be fully defined. Given the complexity of the disease and the pleiotropic nature of vitamin D activity, the protective effect is expected to be multi-factorial. This notion is supported by the mechanistic insights obtained so far from the experimental cell and animal models. With regard to the renal actions of vitamin D, great progress has been made with a variety of kidney disease models. In comparison, relatively few studies have been conducted to address the role of vitamin D-VDR signaling in vascular disease. An increasing body of epidemiological data has firmly established the correlation or association between low vitamin D status and renal and cardiovascular disease in humans, but clinical studies addressing causative relationship or therapeutic effects remain limited and thus are urgently needed. The prevalence of renal and cardiovascular diseases is increasing, yet disease treatment and management are costly with poor outcome. Better understanding of the renal and cardiovascular actions of vitamin D could stimulate the development of new vitamin D analog drugs for these diseases. One major shortcoming of the current vitamin D analog drugs is the relatively narrow therapeutic window mostly due to the hypercalcemic effect. Therefore, new analog drugs with less calcemic effect and better therapeutic efficacy for renal and cardiovascular diseases are highly desired.

Summary of key points

- Vitamin D-deficiency or insufficiency is associated with renal and cardiovascular disease. A rapidly growing body of evidence has suggested a role of vitamin D in renal and cardiovascular protection.
- Vitamin D-deficiency is partly caused by dysregulation of vitamin D metabolism in kidney disease.
- Reno-protective actions of vitamin D have been demonstrated in a variety of experimental models of kidney disease. The anti-proteinuric activity of vitamin D and vitamin D analogs is confirmed by randomized clinical trials.
- The cardiovascular protective effect of vitamin D is supported by strong epidemiological data. Anti-hypertrophic and anti-atherosclerotic activities of vitamin D and vitamin D analogs have been reported in a number of animal models.
- The renal and cardiovascular protective mechanism of vitamin D is multi-factorial and involves multiple regulatory pathways.

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* of special interest;

** of outstanding interest

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Figure 1.

Although 1,25 (OH) D₃ has the greatest affinity for the vitamin D receptor, because of their similar chemical structures and much higher levels, ergocalciferol is also a physiologically important agonist.

Table 1Potential renoprotective actions of 1,25(OH)₂ vitamin D

Suppression of the renin angiotensin system.
Reduced NF- κ B activation and inflammation.
Inhibition of the Wnt/ β -catenin pathway.
Direct effects on the expression of slit diaphragm proteins