Chapter 3

Pleiotropic Effects of Vitamin D in Kidney Disease

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Abstract

Vitamin D is metabolized in the liver and kidneys and then converted to the active form, 1.25-dihydroxyvitamin D [1.25(OH)2D]. Chronic kidney disease patients usually lack both 25-hydroxyvitamin D [25(OH)D] and 1.25(OH)2D due to impaired renal function and 1α-hydroxylase deficiency. Chronic kidney disease patients have a high incidence of cardiovascular and infectious morbidities. Increasing evidence indicates a relationship between vitamin D deficiency and cardiovascular and infectious mortality risks. Vitamin D may have significant biological effects beyond its traditional roles on mineral and bone metabolism. Many extrarenal cells have the capability to produce local active 1.25(OH)2D in an intracrine or paracrine fashion. Vitamin D has a significant association with nonskeletal diseases, such as immunodeficiency, metabolic syndrome, insulin resistance, diabetes, hyperlipidemia, cardiovascular disease, proteinuria, and acute kidney injury. This article aims to review and summarize the pleiotropic effects of vitamin D in patients with kidney disease, particularly the immunological, metabolic, cardiovascular, and renal effects.

Keywords: vitamin D, pleiotropic effects, immunity, metabolic, cardiovascular, acute kidney injury, chronic kidney disease

1. Introduction

Most animals cannot synthesize all vitamins. Vitamin D is a lipid-soluble vitamin and the only vitamin that can be synthesized by humans. Evolutionally, vitamin D has been synthesized by a photochemical process in land vertebrates to satisfy the requirement for a calcified skeleton for more than 350 million years [1, 2]. Vitamin D is metabolized by 25-hydroxylase and 1α-hydroxylase in the liver and kidneys, respectively, and converted to the active form, 1.25-dihydroxyvitamin D [1.25(OH)2D] [3]. Recently, the extrarenal conversion

of 25-hydroxyvitamin D (25(OH)D or calcidiol) to 1.25(OH)2D (calcitriol) may play important biological roles beyond its traditional roles [4]. Chronic kidney disease (CKD) patients usually lack both 25(OH)D and 1.25(OH)2D due to impaired renal function and 1α-hydroxylase deficiency. CKD patients have a high incidence of cardiovascular and infectious morbidities. Increasing evidence indicates a relationship between vitamin D deficiency and cardiovascular and infectious mortality risks [5].

Vitamin D plays new roles through activation of the vitamin D receptor (VDR), which involves several pleiotropic effects. Immune systems are clearly impaired in CKD patients [6, 7]. In innate immunity, the conversion of 25(OH)D to 1.25(OH)2D within monocytes and macrophages may produce cathelicidin and β-defensin to enhance the disinfectant effects [8, 9]. Vitamin D also has an inhibitory effect on the adaptive immune system by regulating the function of antigen-presenting cells (APCs), T lymphocyte activation and proliferation, and cytokine secretion [10, 11]. Therefore, vitamin D plays an essential role in immunomodulation.

The metabolic syndromes and insulin resistance are increased in CKD patients [12]. Recently, an association between insulin resistance, diabetes mellitus (DM), and vitamin D deficiency has been proposed [13]. Low vitamin D levels are associated with hypertension (HTN) and endothelial dysfunction [14]. Vitamin D also has protective effects on improving proteinuria and progression of renal function in CKD patients [15, 16]. Vitamin D deficiency is a biomarker to predict acute kidney injury (AKI) and is independently associated with increased morbidity and mortality in critical illness [17]. This review focuses on the influence of vitamin D on immunological, metabolic, cardiovascular, and renal effects in patients with kidney disease.

2. Vitamin D and immune regulation

Vitamin D has been used to treat infections such as tuberculosis for more than 100 years [6, 18]. Epidemiological experiments have shown that vitamin D deficiency is closely related to autoimmune and infectious diseases [2, 19–21]. Immune cells carry VDR and 1α-hydroxylase, which produces the active metabolite 1.25(OH)2D through local synthesis and heightens immunomodulatory properties [8]. Increasing evidence indicates that vitamin D deficiency may cause dysregulation of the innate and adaptive immune systems and promote microinflammation [22].

2.1. Vitamin D and innate immunity

Vitamin D can stimulate the differentiation of monocytes into mature phagocytic macrophages to enhance the effects against pathogens [23]. During infection, macrophages and monocytes are exposed to pathogen-associated molecular patterns (PAMPs), which may activate Toll-like receptor (TLR) 1/2 heterodimer and sequentially upregulate 1α-hydroxylase activity and VDR expression to produce 1.25(OH)2D [24]. 1.25(OH)2D inhibits the release of the proinflammatory cytokine tumor necrosis factor α (TNF-α), regulates the activity of nuclear factor κB (NF-κB), and suppresses the expressions of TLR2 and TLR4 in human mono-

cytes, which reduces cytokines release [25]. Lipopolysaccharide (LPS) can induce TLR4, interferon-γ (IFN-γ), and CD14 activity to increase 1α-hydroxylase expression. When serum 25(OH)D levels are above 30 ng/mL (75 nmol/L), 25(OH)D can convert to its active form, 1.25(OH)2D, via 1α-hydroxylase in macrophages in an intracrine or autocrine manner [23]. Consequently, 1.25(OH)2D enters the nucleus by binding VDR complexes with retinoid X receptor (RXR), which causes direct signaling on the transcription of cathelicidin and β-defensin 2 [24]. Both the above peptides can cleave microbial membranes and promote innate immunity in response to infectious agents. Hence, the macrophage's functions deteriorate, which decreases its antibacterial effect in vitamin D-deficient patients compared with people with adequate vitamin D [24, 26].

25(OH)D supplements increase induction of cathelicidin, which is associated with the capacity for killing *Mycobacterium tuberculosis* and promoting antibacterial activity [18, 24, 26]. Vitamin D binding to VDR can also upregulate the expression of β-defensin 4A (DEFB4A) through nucleotide-binding oligomerization domain 2 (NOD2) activation and NF-κB stimulation [23]. Autophagy is an important macrophages defense mechanism against intracellular pathogens by the elimination of materials, which acts as a dynamic recycling system that yields new components and energy for cellular renovation and homeostasis [18]. Antibacterial cathelicidin, β-defensin 4A, and maturation of autophagosomes cooperate to enhance bacterial killing, which is highly dependent on vitamin D status [27]. Therefore, in innate immunity, vitamin D promotes macrophages to produce cathelicidin and β-defensin 2 and enhances the capacity for autophagy via TLR activation.

2.2. Vitamin D and adaptive immunity

VDR are presented in activated T cells and B cells; therefore, vitamin D plays a functional role in modulating adaptive immunity [27]. 25(OH)D or 1.25(OH)2D suppresses the maturation of professional APCs and dendritic cells (DCs) by decreasing costimulatory marker expression and affecting the binding ability and expression of VDR, thereby reducing antigen presentation and regulating adaptive immune responses [28–31]. Furthermore, vitamin D can influence T cell function through endocrine, paracrine, and intracrine mechanisms. Vitamin D directly influences T-cell proliferation and cytokine production [27]. Vitamin D increases anti-inflammatory T-helper 2 (Th2) cytokine production and suppresses Th1 cytokines, which shifts from Th1 to Th2 axes [30, 32].

The suppression of DC maturation by 1.25(OH)2D has the potential to induce Treg cells, which exhibit anti-inflammatory effects [29–31, 33]. Vitamin D can significantly increase the percentage of Tregs through direct endocrine systemic calcitriol effects or intracrine conversion of 25(OH)D to 1.25(OH)2D by Tregs themselves, or indirectly through the APCs remaining in an immature status. Vitamin D also inhibits the development of Th17, which is associated with tissue damage, inflammation, and host-graft rejection in autoimmune diseases [34]. In humoral immunity, 1.25(OH)2D results in reduced proliferation and differentiation of B lymphocytes, and immunoglobulin production [35].

2.3. Vitamin D and immune dysfunction in CKD

CKD patients usually have obvious immune dysregulation, which may play a role in infection and contributes to an important cause of morbidity and mortality [36]. Vitamin D deficiency causes dysregulation of the innate and adaptive immune systems and promotes microinflammation. Low 1.25(OH)2D levels have been related to elevated mortality rates in CKD patients [36]. Consequently, CKD leads to a diminished response to infection and misapplied inflammatory response as in a state of immune dysregulation and sustained inflammation [6]. On the one hand, strong associations have been shown between the prevalence of vitamin D deficiency and susceptibility to infection [37], and on the other hand, vitamin D also has an antioxidative effect. Both immunomodulatory and antioxidative activities may contribute to immune dysfunction in CKD. It is difficult to clarify whether the immunomodulatory or antioxidative effect of vitamin D is more predominant during the process. However, the results of vitamin D supplementation trials did not always demonstrate consistent protective effects [38]. Prevention through vaccination remains the best strategy to minimize the adverse consequences associated with infections. Patients with CKD demonstrate inadequacies of immunity for generating a protective vaccine response. Vitamin D might influence immune responsiveness and its potential modulating role in vaccine immunogenicity [39]. Can we translate vitamin D immunomodulating effect on innate and adaptive immunity to vaccine response? According to current evidence, it is still premature to recommend vitamin D for practical therapeutic or preventive use to enhance vaccine response. More research and large trials are needed for further confirmation.

3. Roles of vitamin D in metabolic disturbance

3.1. Vitamin D and metabolic syndrome

Metabolic syndrome is a condition characterized by the presence of at least three of the following: abdominal obesity, increased blood pressure (BP), impaired glucose tolerance or diabetes, dyslipidemia (elevated levels of triglycerides), and low concentration of high-density proteins [40]. Metabolic syndrome is associated with an increased risk of renal injury, cardiovascular disease, type 2 diabetes, and all-cause mortality [41]. The relationship between metabolic syndrome and CKD is complex and bidirectional. Low 25(OH)D3 levels are associated with metabolic syndromes. A meta-analysis of observational studies showed a significantly inverse association between blood 25(OH)D levels and the risk of metabolic syndrome [42]. There is a 51% reduction in the prevalence of metabolic syndrome with a high level of vitamin D. Furthermore, another meta-analysis provided a dose-response relationship between the blood vitamin D concentration and metabolic syndrome risk. A 25 nmol/L increase in 25(OH) D levels was associated with a 13% decrease in the risk of metabolic syndrome. However, there was some heterogeneity among the studies. The association was somewhat stronger in the elderly populations with metabolic syndrome [43]. Although the observational (epidemiological) studies demonstrated significant associations between vitamin D and metabolic syndrome, their causal relationship is still undetermined. Further

studies, particularly longitudinal randomized clinical trials, are needed to determine whether vitamin D supplementation plays a role in the prevention of metabolic syndrome.

3.2. Vitamin D, insulin resistance, and DM

3.2.1. Vitamin D and insulin resistance

CKD patients experience impaired insulin secretion and enhanced insulin resistance [12, 44]. Vitamin D deficiency, secondary hyperparathyroidism, inflammation, and oxidative stress all can alter glucose metabolism and contribute to insulin resistance. Active vitamin D (1.25(OH)2D) may stimulate pancreatic insulin secretion directly through the interaction of the 1.25(OH)2D3-RXR-VDR complex, thus increasing insulin synthesis [45, 46]. Insulin secretion is a calcium-dependent process and vitamin D may indirectly increase the calcium concentration by alternating calcium flux within the β islet cells; therefore, it has adverse effects on β islet cells' secretary function. In addition, vitamin D and calcium regulated insulin sensitivity by stimulating the insulin receptor and activating peroxisome proliferative-activated receptor γ (PPAR-γ) [47]. Extrarenal 1α-hydroxylase leads to the local production of 1.25(OH)2D, which has a role in ensuring calcium influx into cells, and may be essential to the actions of insulin in skeletal muscle and adipocytes [48, 49].

Chronic inflammation is involved in the development of insulin resistance. Vitamin D has immunoregulatory effects by decreasing inflammatory responses to reduce insulin resistance and the risk of diabetes [13]. Therefore, parathyroid hormone (PTH) may negatively affect insulin sensitivity through altering body composition and inhibiting insulin signaling by reducing the number of glucose transporters to promote glucose uptake, suppress insulin release, and promote insulin resistance in adipocytes [50, 51].

However, there appears to be a need for randomized trials to evaluate the definite effects of vitamin D supplementations in insulin resistance and whether supplementations of vitamin D may be a suitable management strategy to ameliorate insulin resistance.

3.2.2. Vitamin D and type 2 DM

The association between vitamin D and type 2 DM has been explored recently [52]. There is an inverse association between vitamin D status and glycemic outcomes [13]. Insulin resistance increases the risk of type 2 DM. Lower vitamin D status is associated with higher risk of incident type 2 diabetes in observational studies; however, the effect of vitamin D supplementation on glycemic outcomes was not evident in some studies [48]. In a large cohort of middle-aged women, both vitamin D and calcium intakes were additive and inversely associated with risk of type 2 DM development. For both vitamin D and calcium, intakes from supplements rather than from diet were significantly associated with a lower risk of type 2 diabetes [53, 54]. Hence, a high intake of vitamin D and calcium was associated with a lower risk of type 2 diabetes. An inverse association was shown between serum 25(OH)D levels and prevalence of diabetes and its complications, and the improvement of symptoms after vitamin D supplementation. Underlying mechanisms may be associated with the role of vitamin D in immunity, β-cell

function, and insulin sensitivity [13]. Overall, the available data are currently insufficient to support the contention that type 2 diabetes can be improved by raising 25(OH)D concentrations. The confirmation of a potential beneficial effect of vitamin D on type 2 diabetes is needed in large trials.

3.3. Vitamin D and lipid metabolism

Lipid metabolism abnormalities with alterations in lipid profiles are commonly seen in CKD patients; therefore, the prevalence of dyslipidemia in CKD is much higher than that in the general population [55, 56]. Markedly reduced high-density lipoprotein quantity and function is the key dyslipidemia leading to persistent chronic inflammation, increased oxidative stress, and subsequent progression of cardiovascular disease in CKD. CKD also induces downregulation of lipoprotein lipase and very low-density lipoprotein (VLDL) receptor contributing to further hypertriglycemia and elevated VLDL levels. The vitamin D binding to VDR may affect bile acid synthesis and reduce cholesterol levels in hepatocytes and serum. Activation of the VDR by 1.25(OH)2D may suppress the expression of small heterodimer partner (SHP) and the activation of cholesterol 7-α-hydroxylase (CYP7A1) which is the rate-limiting enzyme in bile acid synthesis, and its expression controls serum cholesterol levels [57–59]. In addition, VDR activation downregulated farnesoid X receptor (FXR) and SHP expression to inhibit CYP7A1, which is responsible for lowering cholesterol [60, 61]. The vast majority of intervention studies did not show a significant effect of vitamin D on blood levels of serum cholesterol levels in CKD patients. However, there is evidence for a triglyceride-lowering effect of vitamin D in CKD patients, a group with elevated triglyceride levels. Thus, adequately designed primary prevention trials are needed to provide more evidence for the clinical application of vitamin D.

4. Roles of vitamin D in cardiovascular disease

4.1. Vitamin D and endothelial dysfunction

The vascular endothelial function of CKD patients is dysregulated. Calcium deposition in atherosclerotic plaques or vessel walls participates in the vascular calcification process, which causes major cardiovascular morbidity and mortality. Vitamin D has been associated with increased vascular calcification and evidence conversely supports a protective effect. Recent studies have demonstrated the relationship between vitamin D status and endothelial function. Vitamin D therapy can improve endothelial function. Oral vitamin D (cholecalciferol) improves endothelial vasomotor and secretory functions in CKD patients [62, 63]. In a clinical trial of patients with type 2 DM, who were vitamin D deficient, a one-time large dose of vitamin D improved flow-mediated brachial artery vasodilation and significantly decreased systolic BP compared with placebo [64]. In 42 subjects with vitamin D insufficiency, normalization of 25(OH)D at 6 months was associated with increases in reactive hyperemia index and subendocardial viability ratio, and a decrease in mean arterial pressure [14]. However, the available

data are currently insufficient to support the reverse endothelial dysfunction by administrating vitamin D in the general population.

An *in vitro* study indicated that vitamin D may attenuate the adverse effects (including increased NF-κB expression) of advanced glycation end products on endothelial cells [65]. Inflammatory processes can also increase ischemic mediators like intercellular adhesion molecule-1, which increases neutrophil-endothelial interactions [66]. Endothelial injury directly affects afferent arterioles and results in endothelin release and further vasoconstriction, which together cause microcirculatory dysfunction. In addition, vitamin D3 administration enhanced vascular regeneration by inducing stromal cell-derived factor 1 expression in the healthy population. Active vitamin D may increase Klotho secretion and upregulate the expression of osteopontin, a calcification inhibitor, to inhibit vascular calcification and improve vascular endothelial function [67]. Therefore, vitamin D3 may be viewed as a new approach for promoting vascular endothelial repair in the future.

4.2. Vitamin D and the renin-angiotensin-aldosterone system (RAAS)

There is an inverse correlation between changes in vitamin D and changes in plasma renin activity [68]. Individual with 25(OH)D deficiency had higher circulating angiotensin II (Ang II) levels and significantly blunted renal plasma flow responses to infused Ang II when compared with individuals with sufficient 25(OH)D levels. Low plasma 25(OH)D levels may result in the upregulation of the renin-angiotensin-aldosterone system (RAAS) in otherwise healthy humans [69]. Animal and clinical studies have provided important mechanistic clues regarding the crosstalk between RAAS and vitamin D, which affects BP and volume regulation [70]. VDR-knockout mice demonstrated increased renin gene expression in the kidneys and had enhanced RAAS signaling in the blood, which led to significant sodium retention, vascular resistance, and HTN [69]. Conversely, treatment with calcitriol reduced renal renin production independent of calcium and PTH. Calcitriol binds to the VDR and blocks the formation of CRE-CREB-CBP complexes in the promoter region of the renin gene, thus reducing its level of expression [71].

4.3. Vitamin D and hypertension

The observation that people living at higher altitudes have a higher incidence of essential HTN during the winter raised the hypothesis that vitamin D deficiency may contribute to essential HTN [72, 73]. There is an inverse relationship between serum 25(OH)D concentration and HTN incidence, with an odds ratio of 0.73 for the highest versus the lowest category of blood 25(OH)D. In patients with HTN exposed to sufficient sunlight, the 25(OH)D levels were upregulated and subsequently BP was normal [73]. Another study showed that native vitamin D supplementation may improve HTN in type 2 diabetic patients [74]. Pooled data from previous clinical trials have produced mixed results [53, 75]. Data from normotensive individuals showed a small, but statistically significant, effect on reduction in BP with vitamin D intervention. In contrast, a meta-analysis to evaluate the effect of vitamin D supplementation on BP showed no significant BP-lowering effect of vitamin D supplements [75]. Hence, an appropriately high dose of vitamin D can normalize or nearly normalize blood 25(OH)D levels

and significantly reduce BP in hypertensive cohorts with vitamin D deficiency. Treatment of vitamin D-deficient or vitamin D-insufficient normotensive individuals with vitamin D for short period results in minimal effects on BP. Subgroup analysis displayed a significant reduction in diastolic BP in participants who had preexisting cardiometabolic disease.

The mechanisms underlying vitamin D's effect on HTN have not been elucidated yet. Several biological mechanisms relating vitamin D deficiency and HTN have been proposed. First, low vitamin D levels have been associated with increased vascular stiffness, endothelial dysfunction, inflammatory cytokines, and higher coronary artery calcium scores [72]. Other possible mechanisms concerning vitamin D deficiency leading to HTN include vitamin D deficiency leading to increased renin expression, high PTH and low calcium levels, and increased sympathetic nervous activity. Vitamin D deficiency is also an epigenetic risk factor that favors increased vascular tone, which may not play an important role in the regulation of normal BP homeostasis, but serves as a trigger to contribute to the development of HTN in vulnerable middle-aged people.

4.4. Vitamin D and anemia

Anemia due to erythropoietin deficiency or resistance is the major cause of renal anemia in CKD. Chronic inflammation, iron imbalance, and increased hepcidin production also contribute to anemia in CKD patients [76]. Several factors, such as the use of phosphate binders and antacids, loss of blood during hemodialysis, and intake of erythropoiesis-stimulating agents (ESA) cause iron deficiency. Vitamin D deficiency may increase inflammatory cytokines production (interleukin-6, IFN-γ, TNF-α), which stimulate hepcidin production, thus inhibiting ferroportin activity and limiting iron usability [77, 78]. In addition, secondary hyperparathyroidism will directly inhibit erythroid progenitors, endogenous erythropoietin synthesis, and red blood cell survival as well as indirectly promote bone marrow fibrosis and hyperphosphatemia [76, 79]. All of these factors will lead to ESA hyporesponsiveness. Providing vitamin D or active vitamin D may promote anti-inflammation and erythroid proliferation to correct ESA resistance, improving anemia, and reduce ESA requirements [80, 81]. Therefore, vitamin D levels and ESA requirements exhibit an inverse relationship in CKD patients.

5. Roles of vitamin D in renal disease

5.1. Vitamin D and chronic kidney disease (CKD)

Vitamin D deficiency is a prominent feature of CKD. Vitamin D deficiency is related to albuminuria, CKD progression, and subsequent cardiovascular diseases [15, 16]. VDR is highly expressed in the kidney; therefore, the kidney can be considered a classic vitamin D target organ [82, 83]. Vitamin D has been prescribed for renal patients to prevent osteodystrophy and increased attention has focused on its renoprotective activity in recent decades. Molina et al. reported that vitamin D supplements may effectively reduce albuminuria at CKD stages 3–4 [84]. In the VITAL study, the administration of paricalcitol in addition to RAAS blockade further reduced albuminuria compared with RAAS blockade alone in patients with diabetic

nephropathy [85]. A meta-analysis study showed a higher risk for nephropathy in vitamin D–deficient patients with diabetes, but these association studies did not show causality. However, pooling the results of available clinical trials showed no significant change in proteinuria after vitamin D supplementation. More vitamin D research is needed for a more comprehensive and precise conclusion.

Activation of the VDR is essential in reducing proteinuria [85]. Traditionally, using RAAS blockers can reduce albuminuria [86]. 1.25(OH)2D3 is known as a RAS inhibitor by its negative regulatory effect on renin production to provide additional renoprotection [69]. The renoprotective effects of vitamin D can improve proteinuria, glomerulosclerosis, and interstitial infiltration and reduce renal oxidative stress [87]. Combined treatment with paricalcitol and losartan suppressed the induction of fibronectin, transforming growth factor β (TGF-β) and monocyte chemoattractant protein-1 (MCP-1), and reversed the decline of the slit diaphragm proteins nephrin, Neph-1, ZO-1, and alpha-actinin-4 [88]. VDR knockout in diabetic mice was associated with severe albuminuria and glomerulosclerosis [69]. Alternatively, vitamin D might slow the progression of diabetic nephropathy by improving insulin secretion, delaying destruction of β islet cells, affecting osteocalcin, and consequently assisting in glucose metabolism. TGF-β, MCP-1, hepatocyte growth factor, thrombospondin-1, and plasminogen activator inhibitor are other possible molecular targets of vitamin D action [87, 89, 90].

5.2. Vitamin D and acute kidney injury (AKI)

A significantly lower plasma 25(OH)D concentration was associated with low plasma cathelicidin level in patients with sepsis compared with healthy controls. A low 25(OH)D level was a biomarker to predict AKI and has a significant impact on length of stay, organ dysfunction, infection rates, and survival in critically ill patients [17, 91, 92]. Vitamin D deficiency was independently associated with increased morbidity and mortality as well as significantly associated with AKI with RIFLE-Injury and -Failure stages in intensive care units (ICU) [93]. The levels of bioavailable 25(OH)D were strongly and inversely associated with the severity of sepsis and inversely associated with hospital mortality. Because the levels of the major metabolite of vitamin D, 24R.25(OH)2D3, were not elevated in AKI, the reduced levels of 25(OH)D resulted from decreased production and not enhanced catabolism related to FGF23. The strong association between bioavailable 25(OH)D versus total 25(OH)D levels and severity of sepsis may be related to the selective uptake of bioavailable 25(OH)D by macrophages and nontraditional target organs [94].

The exact mechanism is unknown. 1.25(OH)D can modulate the levels of inflammatory cytokines and may play a role in LPS-induced immune activation of endothelial cells during Gram-negative bacterial infections. Renoprotective effects of vitamin D has been identified in several AKI animal models, including contrast-induced AKI, gentamicin-induced AKI, cisplatin-induced AKI, cyclosporine-induced AKI, ischemia-/reperfusion-induced AKI, and the obstructive nephropathy model [95–99]. The data from experimental AKI studies suggest that vitamin D analogs protect the kidney by targeting three major pathways: the local RAS, antioxidation, NF-κB and PPAR-γ pathways to suppress inflammatory, fibrotic, apoptotic, and proliferative factors [95, 100–102]. In contrast to the role of vitamin D in CKD patients, the role

of vitamin D in AKI is not as well defined. It is reasonable to hypothesize that the predisposition of vitamin D-deficient critically ill patients to AKI is related to the innate and adaptive immune response.

6. Conclusion

Vitamin D is a critical substance for bone and mineral regulation and is also a hormone with pleiotropic functions. Vitamin D exerts beneficial effects on immunomodulatory effects, alleviates metabolic syndrome, improves insulin resistance, maintains regular blood pressure, increases vascular endothelial cell function, and manages renal anemia (**Figure 1**). Vitamin D has protective effects on improving proteinuria and progression of renal function in CKD patients. Vitamin D deficiency is independently associated with increased morbidity and mortality in critical illness and a biomarker to predict AKI. Thus, more trials are needed to provide more evidence for clinical application of the pleiotropic influence of vitamin D on the immunological, metabolic, cardiovascular, and renal effects in patients with kidney disease.

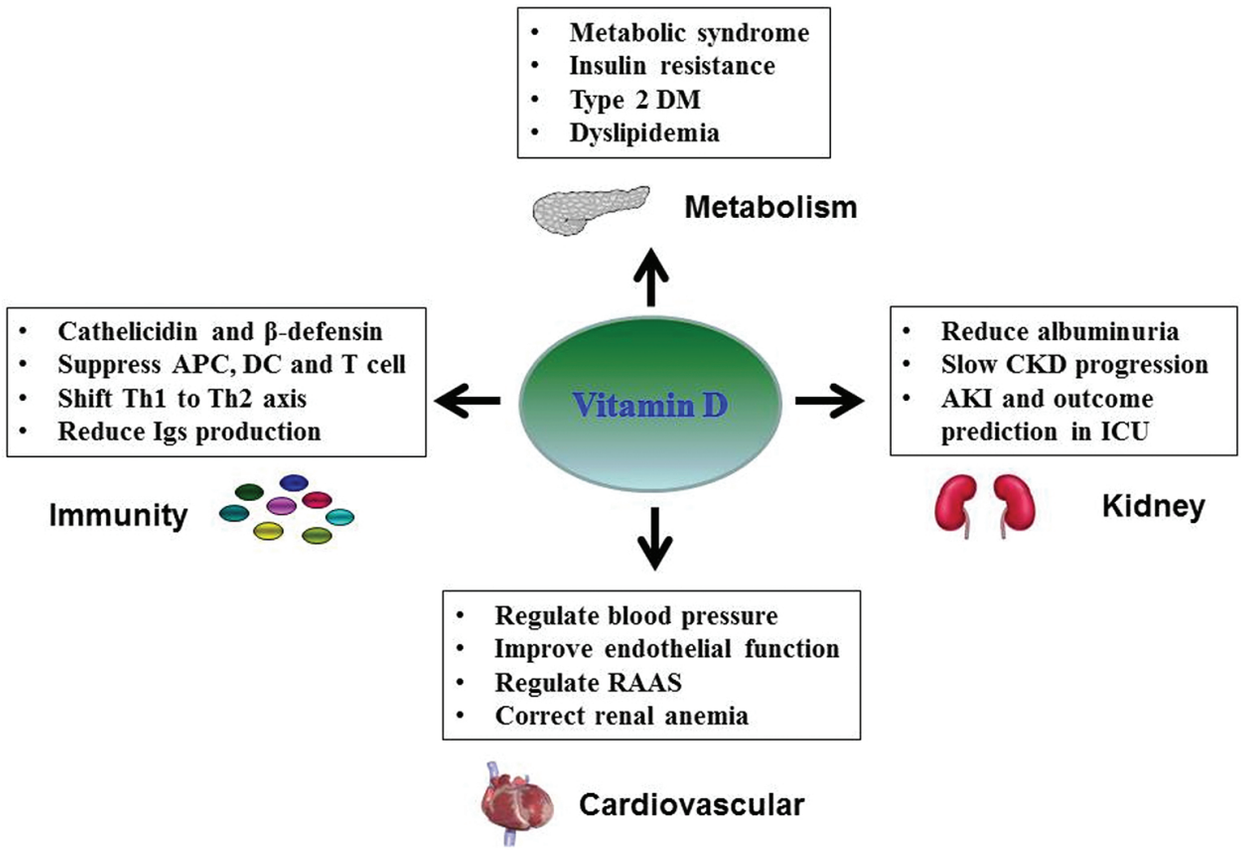

Figure 1. Pleiotropic effects of vitamin D in kidney disease. Vitamin D exerts beneficial effects on immunological, metabolic, cardiovascular, and renal effects in patients with kidney disease.

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