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REVIEW

Role of vitamin D in diabetes mellitus and chronic kidney disease

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Abstract

Approximately 30%-50% of people are recognized to have low levels of vitamin D, and insufficiency and deficiency of vitamin D are recognized as global health problems worldwide. Although the presence of hypo-vitamin D increases the risk of rickets and fractures, low vitamin D levels are also associated with hypertension, cancer, and cardiovascular disease. In addition, diabetes mellitus (DM) and chronic kidney disease (CKD) are also related to vitamin D levels. Vitamin D deficiency has been linked to onset and progression of DM. Although in patients with DM the relationship between vitamin D and insulin secretion, insulin resistance, and β-cell dysfunction are pointed out, evidence regarding vitamin D levels and DM is contradictory, and well controlled studies are needed. In addition, vitamin D influences the renin-angiotensin system, inflammation, and mineral bone disease, which may be associated with the cause and progression CKD. There is increasing evidence that vitamin D deficiency may be a risk factor for DM and CKD; however, it remains uncertain whether vitamin D deficiency also predisposes to death from DM and CKD. Although at this time, supplementation with vitamin D has not been shown to improve glycemic control or prevent incident DM, clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed. This review focuses on the mechanism of vitamin D insufficiency and deficiency in DM or CKD, and discusses the current evidence regarding supplementation with vitamin D in patients with these diseases.

Key words: Vitamin D; Vitamin D deficiency; Diabetes mellitus; Chronic kidney disease; Cardiovascular disease

Core tip: Vitamin D plays an essential role in diabetes

mellitus (DM) and chronic kidney disease (CKD). The relationship between vitamin D and insulin secretion, insulin resistance, and β-cell dysfunction are pointed out. Vitamin D deficiency has been linked with the renin-angiotensin system and inflammation, which may be associated with the cause and progression CKD. There is increasing evidence that vitamin D deficiency may be a risk factor for DM and CKD. Clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed.

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INTRODUCTION

Diabetes mellitus (DM) and chronic kidney disease (CKD) are common diseases worldwide, and their prevalence continues to increase[1,2]. Vitamin D deficiency is also recognized as a worldwide health problem[3], and is associated with rickets and fracture. In addition, hypovitamin D has recently been considered a responsible factor in the onset and progression of DM and CKD. There has been increasing evidence suggesting that an inverse vitamin D status is prevalent in patients with DM or CKD[4]. Furthermore, supplementation of vitamin D in patients with DM or CKD has been reported in several trials and a meta-analysis[5]. In this review, we provide current clinical data on the mechanism of vitamin D deficiency and the effects of vitamin D on patients with DM or CKD.

VITAMIN D PHYSIOLOGY

Vitamin D is a fat-soluble steroid hormone derived from dietary intake as well as synthesis through the skin *via* exposure to sunlight (Figure 1). Vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are produced through solar ultraviolet B radiation (UVB; wavelength 290 to 315 nm). Vitamin D_3 is manufactured from previtamin D_3, which is changed through UVB irradiation from provitamin D_3[6]. Most 25-hydroxyvitamin (25[OH]D) is derived from skin conversion. An alternative source is from dietary intake, mainly from foods of plant or animal origin. In general, animals and fish contain vitamin D_3, and mushrooms contain vitamin D_2[7]. Vitamin D from the skin and diet is either stored in adipose tissue or converted to 25(OH)D in the liver. Vitamin D metabolism requires two hydroxylations to form its active metabolite. The first hydroxylation of vitamin D takes place in the liver where vitamin D is metabolized to 25(OH)D by cytochrome P 2R1 (CYP2R1). 25(OH)D binds to vitamin D-binding protein (DBP) and can flow into the blood in a stable form. 25(OH)D-DBP complex is excreted into the urine and reabsorbed through megalin, a multiligand scavenger receptor in the proximal tubules[8,9], where the complex is converted by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) and changed to its active form 1,25-dihydroxyvitamin $(OH)_2D$, although other tissues have 1α-hydroxylase enzymatic activity[10]. CYP27B1 gene expression in the kidney is mediated by various factors. Parathyroid hormone (PTH), hypocalcemia, hypophosphatemia, and calcitonin affect the activation of CYP27B1 and can increase 1,25-$(OH)_2D$ levels. On the other hand, 1,25-$(OH)_2D$ and fibroblast growth factor-23 (FGF-23) inhibit CYP27B1 and can decrease 1,25-$(OH)_2D$ levels[11].

The binding of 1,25$(OH)_2D$ to the vitamin D receptor (VDR) in the nuclear receptor affects gene transcription. In general, 1,25$(OH)_2D$ promotes dietary calcium and phosphorus absorption in the intestine and regulates reabsorption of calcium in the renal tubules. Because VDR is expressed in a variety of organs, such as the heart, liver, blood vessels, and the central nervous system, 25-hydroxyvitamin D-1α-hydroxylase is also expressed in these tissues[12].

It is widely believed that 25(OH)D is the only precursor of 1,25$(OH)_2D$ and does not influence individual tissues. However, recent reports revealed that 25(OH)D has a weak binding capacity for VDR and affects several tissues in the autocrine or paracrine system[13,14]. In addition, extrarenal 1α-hydroxylase enzymatic activity is controlled in different ways that that in renal tubular cells[15].

EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

Because 1,25$(OH)_2D$ has a short half-life (approximately 15 h), 1,25$(OH)_2D$ levels are not considered a good indicator of vitamin D levels. As 25(OH)D is more stable in the blood than 1,25$(OH)_2D$, blood concentrations of 25(OH)D are 500 to 1000 times higher than 1,25$(OH)_2D$ concentrations. Therefore, to evaluate vitamin D deficiency and insufficiency, serum 25(OH)D concentrations are considered an adequate biomarker. The United States Institute of Medicine defines vitamin D deficiency as 25(OH)D levels less than 20 ng/mL and greater than 20 ng/mL is sufficient upon evidence related to bone health[16]. Several studies reported that people with 25(OH)D levels less than 20 ng/mL is the risk factor of fracture[17] and have greater subsequent rates of bone loss[18]. On the other hand, the Endocrine Society's guidelines, which are based on patients with endocrine disorders, define vitamin D insufficiency as 25(OH)D levels of 21-29 ng/mL[19,20]. Despite these different definitions, both guidelines agree that vitamin D insufficiency and deficiency are common problems in certain populations.

About 1 billion people worldwide lack vitamin D[21,22]. Vitamin D deficiency and insufficiency are prevalent conditions not only in elderly people but also

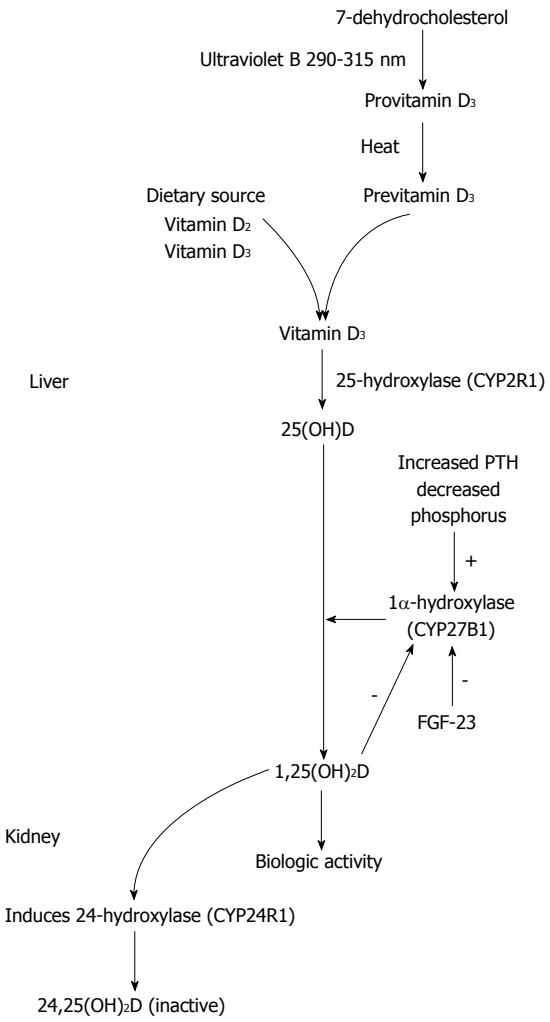

Figure 1 Mechanism of vitamin D synthesis. FGF-23: Fibroblast growth factor-23.

in adolescents[23] and children[24]. One study reported that almost one half of participants had 25(OH)D levels less than 40 nmol/L during the winter and spring[25]. In this study, 7437 people from a British birth cohort study who were 45 years old had 25(OH)D levels measured. Although the prevalence of hypovitamin D, defined as levels below 40 nmol/L, was 15.4% during the spring and summer, the proportion was 46.6% during the winter and autumn. Other studies showed that vitamin D deficiency was especially common in older persons (67-95 years)[26,27], and more than 50% of postmenopausal women taking medication for osteoporosis had 25(OH)D levels below 30 ng/mL[28]. Various factors, including age, sex, location, nutrition status, and physical fitness, affect vitamin D status[29]. In addition, diabetes, renal function, hypoalbuminemia, and albuminuria are also risk factors for vitamin D deficiency[30,31].

Recently, the relationship between 25(OH)D levels and genetic polymorphisms of DBP were reported[32]. It was previously known that 25(OH)D concentrations differed between black Americans and whites[33]. Although it was generally thought that nutritional, environmental, and hormonal factors affected racial differences[34], the detailed mechanisms behind these differences are unknown. Powe *et al*[32] reported that although total 25(OH)D and DBP were lower in black subjects than in white subjects, concentrations of estimated bioavailable 25(OH)D were similar between black and white subjects. In addition, because the affinity of DBP to 25(OH)D differs in the DBP gene polymorphism, genetic polymorphisms of DBP genes (rs7041 and rs4588) provide a likely explanation for racial variations in levels of DBP and 25(OH)D[35]. The combination of rs7041 and rs4588 produces amino acid changes resulting in variant DBPs (Gc1F, Gc1S, and Gc2). The phenotype of Gc1F, which is common in black homozygotes, was associated with the lowest levels of DBP (Gc1F/Gc1F homozygotes). On the other hand, Gc1S, which is common in white subjects, was associated with the highest DBP levels (Gc1S/Gc1S homozygotes). The Gc2/Gc2 homozygotes and Gc1F/Gc1S heterozygotes were associated with intermediate DBP levels. These findings suggest that racial differences in the distribution of DBP and total 25(OH)D are caused by DBP polymorphisms, and low total 25(OH)D levels do not indicate vitamin D deficiency. For purposes of cross-racial evaluations of vitamin D deficiency, it might be appropriate to estimate serum total 25(OH)D concentrations using DBP polymorphisms and DBP.

Associations between vitamin D levels and mortality have been shown by several observational studies[36,37]. Low vitamin D levels have also been shown to be associated with obesity, fractures, and infections[38]. Several observational studies have revealed potential links between low vitamin D levels and cardiovascular disease[39]. It is well known that people who live at high altitudes are at higher risk for hypertension and cardiovascular disease[40,41]. In a study of patients with hypertension who were exposed to UVB radiation three times a week for 3 mo, 25(OH)D concentrations increased by about 180%, and blood pressure became normal[42]. A prospective, nested, case-control study of 1484 women without hypertension and with low 25(OH)D levels showed that women with lower 25(OH)D levels had a higher rate of incident hypertension than controls. Low 25(OH)D concentrations have been shown to be inversely related to developing hypertension[43]. A recent Mendelian randomization study of vitamin D status and blood pressure concluded that increased plasma concentrations of 25(OH)D might reduce the risk for hypertension[44]. Cardiovascular disease such as coronary arterial disease[45], myocardial infarction[46], heart failure[47], and stroke[48] are also associated with vitamin D deficiency. However, a recent study showed that high levels of 25(OH)D were also associated with cardiovascular disease mortality[49]. This prospective, observational, cohort study analyzed 247574 citizens from Denmark and showed that a 25(OH)D level below 12.5 nmol/L was associated with a higher risk for mortality [hazard ratio (HR) = 1.59] compared with the reference range (50-75 nmol/L); however, those with

levels higher than 125 nmol/L had the highest mortality risk (HR = 1.95). There is a possibility that maintaining adequate vitamin D levels is essential for human health.

As mentioned above, vitamin D status and cardiovascular disease are strongly associated. Animal models offer several mechanisms to explain this association. Activation of the renin-angiotensin-aldosterone system (RAAS) has been seen in VDR knockout mice[50], and vitamin D has been shown to regulate the nuclear factor kappa beta pathway in renal failure model mice[51]. In vascular endothelial cells, transcription of nitric oxide synthase has been shown to be inhibited by vitamin D in mice[52]. In addition, vitamin D has been shown to activate the Keap1-Nrf pathway, which opposes oxidative stress, in renal failure model mice[53].

VITAMIN D AND DM

Type 1 DM

Type 1 DM is caused by a complex autoimmune destruction of pancreatic islet β-cells, leading to absolute insulin deficiency. The autoimmune nature of type 1 DM has been clarified with the detection of autoantibodies against islet β-cells and their infiltration by T cells, B cells, and macrophages[54]. Vitamin D has been shown to have immunomodulatory properties as well. Many immunomodulatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease have been reported to be associated with vitamin D deficiency[55,56]. Type 1 DM is also said to be related to vitamin D deficiency[57]. As VDR are expressed in human T and B lymphocytes, vitamin D is thought to modify the Th1/Th2 cytokine profile[58]. In addition, vitamin D is also thought to be associated with the immune system *via* its inhibition of lymphocyte proliferation[59]. Non-obese diabetic (NOD) mice with vitamin D deficiency showed an increased incidence and severity of diabetes[60]. Using $1,25(OH)_2D$ reduced the manifestation of diabetes in NOD mice by decreasing the number of effector T cells[61,62]. Another study reported that $1,25(OH)_2D$ also counteracted cytokine-induced expression of Fas, which regulates cell death in human islet cells[63].

The relationship between sunlight exposure and the incidence of type 1 DM has been reported[64]. One study showed that providing vitamin D supplements to infants in North Europe, where daylight hours are shorter than in other countries, decreased the risk for new-onset type 1 DM[65]. Although children suspected of having rickets during the study period had a relative risk (RR) of 3.0 (1.0-9.0) for type 1 DM, children who had taken 2000 IU vitamin D daily had a RR = 0.22 (0.05-0.89). Some studies were designed to clarify the effect of vitamin D on the preservation of β-cell function after the onset of type 1 DM[66]. Two studies found no significant effects of administration on vitamin D in protecting β-cell function[67,68]. However, another study reported significant effects of vitamin D administration on maintaining β-cell function after the development of type 1 DM. Thirty-eight patients with new-onset type 1 DM were randomly assigned to receive daily oral therapy with cholecalciferol, 2000 IU, or placebo[69]. The cumulative incidence of progression to undetectable ($\leqslant$ 0.1 ng/mL) fasting C-peptide and stimulated C-peptide levels was lower in the cholecalciferol group than in the placebo group. In another study, alfacalcidol (0.25 μg/d) preserved β-cell function in children with newly diagnosed type 1 DM[70]. Further studies are needed to clarify whether the administration of 25(OH)D or $1,25(OH)_2D$ can inhibit the onset of type 1 DM.

Type 2 DM

As VDRs in pancreatic β-cells play an important role in the progression of type 2 DM[71], vitamin D deficiency is related to insulin secretion, insulin resistance, and β-cell dysfunction in the pancreas[72] (Figure 2). The secretion of pancreatic insulin is inhibited by vitamin D deficiency in the diabetic animal model[73,74]. Administration of vitamin D restores glucose-stimulated insulin secretion and promotes β-cell survival by modulating the generation and effects of cytokines[75,76]. Insulin secretion is also influenced by calcium concentration and flux through the β-cells[77]. Vitamin D regulates the function of calbindin, a systolic calcium-binding protein found in pancreatic β-cells, and acts as a modulator of depolarization-stimulated insulin secretion *via* regulation of intracellular calcium[78]. PTH, which has its concentration regulated by vitamin D, is associated with insulin synthesis and secretion in the pancreas[79].

Insulin sensitivity is also associated with vitamin D. By stimulating the expression of insulin receptors, vitamin D regulates insulin sensitivity[80,81]. In addition, vitamin D enhances insulin sensitivity by promoting the expression of peroxisome proliferator-activated receptor (PPAR) delta, which is a widely expressed member of the PPAR family of nuclear receptor fatty acid sensors and regulates fatty acids in skeletal muscle and adipose tissue[82]. Intracellular calcium is a key factor of peripheral insulin resistance *via* an impaired signal transduction pathway leading to decreased glucose transporter activity[83,84].

The indirect effect of vitamin D is exerted by regulating calcium flux through the cell membrane and intracellular calcium. While low vitamin D induces secondary hyperparathyroidism, increased PTH levels are also associated with diabetes. A recent observational study of 494 women undergoing serial metabolic characterization revealed that hypovitamin D levels with increased PTH levels were an independent predictor of β-cell dysfunction, insulin resistance, and glycemia[85]. Vitamin D affects insulin resistance through the RAAS. One animal study demonstrated that vitamin D negatively regulated expression of renin genes in a mice model[86]. Furthermore, low levels of $1,25(OH)_2D$ increased renal renin production and activated the RAAS system in an animal model[87]. Finally, angiotensin Ⅱ inhibited the action of insulin in vascular and skeletal muscle tissues, leading to impaired glucose uptake[88].

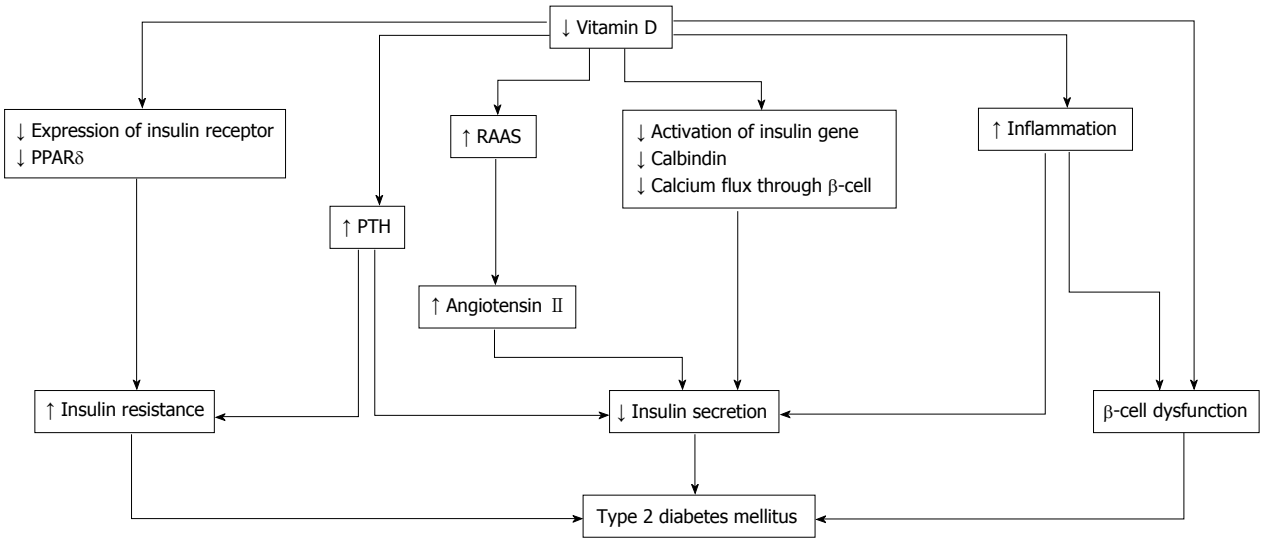

Figure 2 Putative scheme of effect of vitamin D on type 2 diabetes mellitus. PPAR: Peroxisome proliferator-activated receptor; PTH: Parathyroid hormone; RAAS: Renin-angiotensin-aldosterone system.

Systemic inflammation has an important role in insulin resistance and cardiovascular events in patients with type 2 DM[89]. As β-cells in the pancreas are affected *via* cytokine-induced apoptosis, high levels of inflammation cause worsening glycemic control. Vitamin D could decrease the effects of systemic inflammation and protect against β-cell cytokine-induced apoptosis by directly modulating the expression and activity of cytokines, as has been shown in animal models[90]. In patients with type 2 DM**,** incubation of isolated monocytes with 1,25(OH)$_2$D decreased the expression of inflammatory cytokines affecting insulin resistance, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α[91].

A prospective cohort study designed in the United Kingdom showed that baseline 25(OH)D concentrations in patients without diabetes were inversely related with the risk for hyperglycemia and insulin resistance at 10 years of follow-up visits[92]. Moreover, a similar study reported that low 25(OH)D levels were a risk factor for type 2 DM[93]. This prospective, cohort study was conducted over 29 years among 9841 subjects without diabetes. Lower vitamin D levels were a risk factor for incident type 2 DM. However, a recent Mendelian randomization approach study found that low 25(OH)D levels were not genetically associated with the risk for type 2 DM[94]. This result suggests that the association between 25(OH)D concentrations and type 2 DM is not causal. A meta-analysis of 16 studies reported that the odds ratio for type 2 DM was 1.5 (1.33-1.70) for the bottom *vs* top quartile of 25(OH)D levels[95]. Numerous randomized controlled studies have investigated whether vitamin D supplementation influences glycemic homeostasis[96,97]. As described above, vitamin D is thought to improve insulin resistance and promote insulin secretion. Therefore, clinical trials often use outcomes such as homeostasis model assessment of insulin resistance, fasting plasma glucose levels, and hemoglobin A1c levels. Some clinical trials have assessed the combined effects of vitamin D and calcium supplementation on glucose homeostasis of patients with diabetes[98,99] and without diabetes[100]. These studies suggest that vitamin D plus adequate calcium levels might be needed for an improvement in glycemic status. However, a recent meta-analysis concluded that vitamin D supplementation given to address concerns with glycemic control and insulin resistance in patients with diabetes is not recommended, although the doses of vitamin D supplementation may not have been optimal; almost all of the included trials used vitamin D doses of at least 2000 IU/d[101]. Because most trials focused on glycemic status and insulin resistance over short durations (12 mo or less), we should await the results of ongoing trials with longer follow-up periods to provide new evidence regarding the potential role of vitamin D supplementation in type 2 DM[102].

One study was designed to examine the protective effect of vitamin D against the development of type 2 DM[103]. A total of 2447 older people (mean age, 77 years) were allocated to 800 IU daily vitamin D$_3$ and 1000 mg calcium both, or placebo for 24-62 mo. Vitamin D in combination with calcium was not able to prevent the development of diabetes or an increase in the need for medication in patients with diabetes. The Women's Health Initiative Calcium/Vitamin D Study, a randomized, placebo-controlled trial of 33951 postmenopausal women, followed participants receiving 1000 mg elemental calcium plus 400 IU of vitamin D$_3$ daily, or placebo for 7 years. Calcium plus vitamin D$_3$ supplementation did not reduce the risk for developing diabetes over 7 years[104]. These results suggest that vitamin D supplementation at doses of 400 to 800 IU/d, with or without calcium, does not prevent new-onset type 2 DM.

Although at this time, supplementation with vitamin D has not been shown to improve glycemic control or

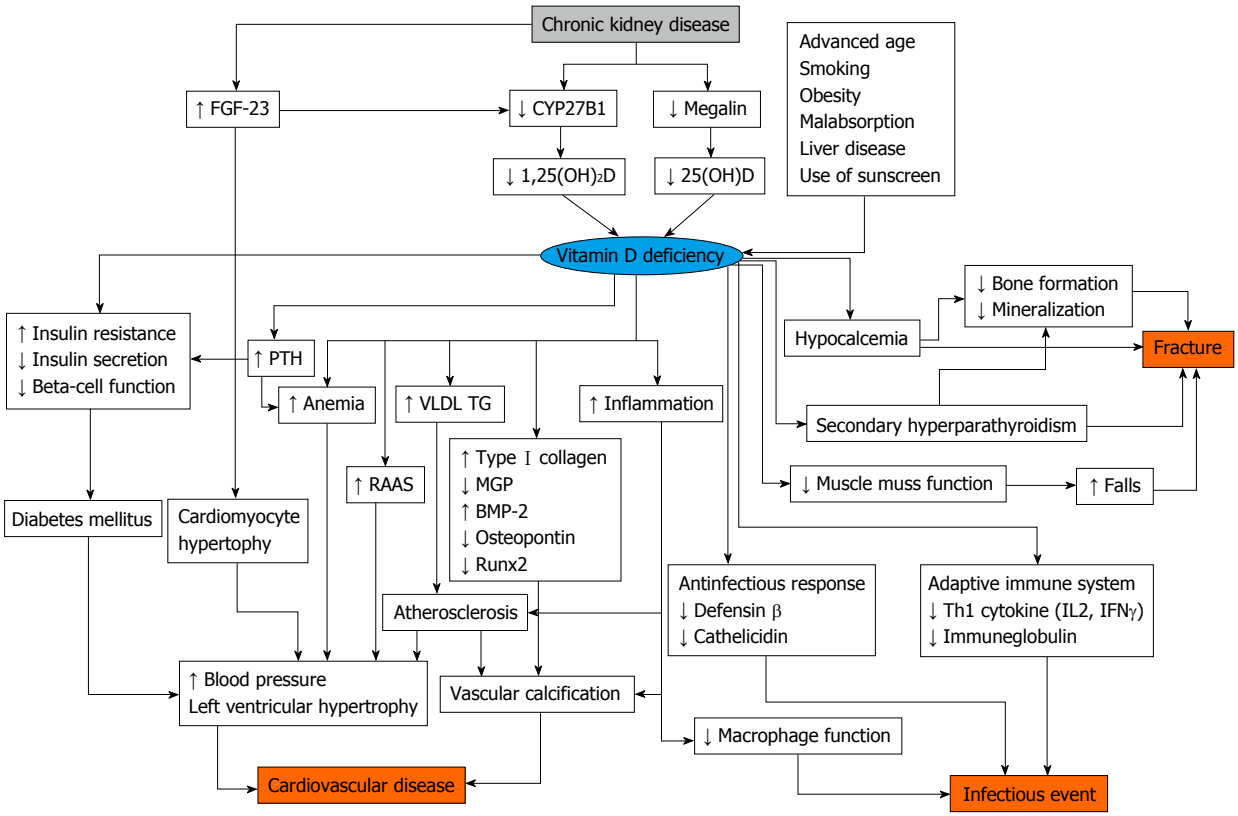

Figure 3 Vitamin D deficiency and cardiovascular disease. FGF-23: Fibroblast growth factor-23; PPAR: Peroxisome proliferator-activated receptor; PTH: Parathyroid hormone; RAAS: Renin-angiotensin-aldosterone system; VLDL: Very low density lipoprotein; TG: Triglycerides; IL: Interleukin; IFN: Interferon; MGP: Matrix gla protein; BMP: Bone morphogenetic protein.

prevent incident type 2 DM, clinical trials with sufficient sample size, study periods, and optimal doses of vitamin D supplementation are still needed. In addition, it is important that future studies of vitamin D use primary outcomes, such as all-cause mortality and cardiovascular disease, as endpoints.

VITAMIN D AND CKD

One study revealed that paricalcitol diminished residual albuminuria in patients with diabetic nephropathy[105]. In this study, patients were randomly assigned (1:1:1) to receive placebo, 1 μg/d paricalcitol, or 2 μg/d paricalcitol for 24 wk to investigate the effect on mean urinary albumin-to-creatinine ratio (UACR). Patients receiving 2 μg paricalcitol showed a nearly sustained reduction in UACR, ranging from -18% to -28% (P = 0.014 *vs* placebo). However, few trials have used a vitamin D receptor antagonist (VDRA) for patients with diabetes, and none has a sufficient number of patients or follow-up period. The effect of vitamin D_3 and VDRA on hard outcomes, such as progression of diabetes, cardiovascular disease, and all-cause mortality, requires larger and longer-term trials.

Some studies indicate that 1,25(OH)$_2$D levels decrease in patients with CKD[106]. There are the several theories about the pathogenesis of vitamin D deficiency in CKD. Megalin, which is present in endocytic receptors in proximal tubule cells, is involved in the reabsorption of DBP from glomerular ultrafiltrates[107]. In addition, megalin also mediates the subsequent intracellular conversion of 25(OH)D to its active form. As kidney function declines, megalin expression in the proximal tubule decreases[108]. Megalin function is also attenuated with reduced kidney function, because of damages from low molecular weight proteinuria. The activity of CYP27B1 is also associated with decreasing kidney function[109]. As FGF-23 reduces expression of cotransporters NaPi-Ⅱa and NaPi-Ⅱc, of the brush border in the proximal tubules, these mechanisms inhibit phosphorus absorption and CYP27B1 activity.

In addition to the decline of 1,25(OH)$_2$D levels, 25(OH)D levels also decrease in patients with CKD. There are the several plausible mechanisms that explain the decreases in 25(OH)D. The complex of 25(OH)D and DBP leaks with proteinuria. Uptake of 25(OH)D decreases due to down-regulation of megalin levels. One study showed that 25(OH)D concentrations in patients with CKD were low[110]. The prevalence of vitamin D deficiency is 35% among about 4000 patients with CKD in the United States[111].

There is some evidence that vitamin D status is associated with poor clinical outcomes in patients with CKD[112] (Figure 3). Low 25(OH)D levels are associated with all-cause mortality and cardiovascular disease in patients with CKD[113]. The risk for end stage renal disease is higher in patients with low vitamin D status. Among patients undergoing hemodialysis and peritoneal

dialysis, low 25(OH)D levels are also associated with cardiovascular disease[114].

There is some evidence regarding restitution of vitamin D in patients with CKD[115,116] and as well as in patients undergoing dialysis [117,118]. As previously described, patients with kidney failure usually have insufficient 1,25(OH)$_2$D levels, and a VDRA is used for these patients. One study revealed that paricalcitol diminished albuminuria in patients with diabetic nephropathy[105]. In the VITAL study, which was designed to compare the effectiveness between paricalcitol and placebo, the paricalcitol group showed a decreased UACR of -16% compared with placebo[105]. However, as of yet, no other studies have investigated the effectiveness of vitamin D supplementation for protection of kidney function; thus, future studies are needed. Another study showed that paricalcitol led to decreases in levels of brain natriuretic peptide (BNP) in patients with CKD[119]. On the other hand, a recent study reported that treatment with paricalcitol did not improve left ventricular mass and function in patients with CKD[120]. There is controversial evidence regarding the role of VDRA to cardiovascular disease and surrogate makers. It is thought that as 1,25(OH)$_2$D inhibits activation of the RAAS, it leads to organ protection[121]. In addition, there is some evidence regarding VDRAs in patients undergoing hemodialysis. A retrospective cohort study showed that VDRA users had a lower mortality rate than non-VDRA users[122]. However, the Dialysis Outcomes and Practice Patterns Study revealed that taking vitamin D agents did not improve clinical outcome in patients undergoing dialysis. In addition, a recent study reported that pharmacological doses of alfacalcidol were associated with accelerated progression of aortic stiffness in patients undergoing hemodialysis[123]. To date, various discussions have taken place regarding the use of VDRA in patients undergoing dialysis, but adequate clinical studies are needed before any recommendations can be made.

According to the Kidney Disease Improving Global Outcomes guidelines, 25(OH)D levels should be determined in patients with CKD stage 3-5, and if levels are low, physicians should consider vitamin D supplementation[124]. Low 25(OH)D levels are associated with all-cause mortality and cardiovascular disease in patients with CKD as well as in patients undergoing dialysis[125]. Another study showed that among these patient groups, those with low levels of 25(OH)D and high levels of FGF-23 have worse outcomes[38]. However, there is not sufficient evidence regarding vitamin D supplementation for patients with CKD and those undergoing dialysis[126]. Although studies have reported that cholecalciferol decreases albuminuria[127,128] and improves PTH levels[129] in patients with CKD, there is no study with set clinical outcomes such as all-cause mortality or cardiovascular disease. In patients undergoing dialysis, cholecalciferol decreases BNP levels and reduces left ventricular hypertrophy[130]. As VDRAs increase calcium and phosphorus levels in patients undergoing dialysis, it is usually recommended that physicians only need to monitor calcium and phosphorus levels when using a VDRA[131]. On the other hand, vitamin D$_3$, such as cholecalciferol, does not increase calcium and phosphorus levels[132,133]. As with patients with CKD, there is no evidence with hard endpoints regarding the use of vitamin D$_3$ supplementation in patients undergoing hemodialysis.

CONCLUSION

Emerging evidence is accumulating on the important role of vitamin D in the pathogenesis of diabetes and CKD. Many prospective studies have shown associations between vitamin D status and chronic disease, including diabetes and CKD. However, there are contradictory findings regarding whether restitution of normal vitamin D levels modifies the occurrence or clinical course of these diseases. Although there is a concern that vitamin D may be a surrogate marker for poor health status, further well-designed clinical trials are needed in this area.

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