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STATE OF THE ART REVIEWS

Vitamin D supplements in chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a significant public health problem and Vitamin D deficiency is prevalent in CKD and might be associated with calcium and phosphate metabolism, cardiovascular disease, infections as well as the progress of kidney dysfunction. Emerging evidence implies that Vitamin D supplements may be of benefit to CKD. Based on existing laboratory and clinical evidence, this review intends to discuss the effectiveness of Vitamin D supplements and controversy in clinical practice. The effect of Vitamin D in CKD patients is summarized in detail from CKD–mineral bone disease, the progression of renal function, cardiovascular events and immune system. Considerable disputes exist for the Vitamin D supplements in CKD, and a growing amount of experimental evidence and some clinical evidence are now gathering from *in vitro*, animal and epidemiological studies.

Keywords

CKD, Vitamin D, Vitamin D deficiency, Vitamin D supplements, Vitamin D analogs

History

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Introduction

Recent studies have focused on the role of Vitamin D supplements in the general population and special populations such as chronic kidney disease (CKD) patients,¹ not only because of the effects of Vitamin D on bone and mineral metabolism,² but also the significant influence on the other physiological functions: regulation of blood pressure via inhibition of the renin–angiotensin–aldosterone system (RAAS) directly;³ effects on modulation of the immune system;⁴ anti-inflammatory actions⁵ and regulation of insulin secretion⁶ and lipid metabolism⁷ due to the widespread expression of Vitamin D receptors (VDR) in many organ systems; and the potential to alter the progression of kidney disease, diminish cardiovascular disease (CVD) and even improve the prognosis of patients.

Synthesis and metabolism of Vitamin D

Vitamin D, a fat-soluble vitamin, has many forms, of which Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol) are two biologically inert precursors. Vitamin D2 is mainly generated by plants via ultraviolet light irradiation from the sunlight and Vitamin D3 converts from the pre-Vitamin D3 which is synthesized with 7-dehydrocholesterol in the epidermis of animals by solar ultraviolet B radiation. Few foods are naturally rich in Vitamin D, except cod-liver oil, and only 10–20% of Vitamin D in blood circulation comes from

diet and dietary supplements.⁸ Therefore, humans derive Vitamin D mostly from skin-exposure to sunlight and may have Vitamin D deficiency without regular Vitamin D3 supplementation and daily exposure to sunlight.

In human body, the characterization of Vitamin D is a kind of endocrine hormone.⁹ The Vitamin D from diet could not meet the needs of the body and could be self-synthesized. In these cases, Vitamin D would not be a kind of vitamin, but a pro-hormone.¹⁰ Once Vitamin D3 synthesized, it is transported with the Vitamin D-binding protein (diastolic blood pressure, DBP) to the liver where it is quickly converted to 25-hydroxyvitamin D (25(OH)D) by cytochrome P450 Vitamin D 25-hydroxylases, CYP2R1 and CYP27A1. In the circulation 25(OH)D has a strong affinity with DBP, and once binding, the complex can keep a stable state and has a longer half-life, nearly 2–3 weeks. Therefore, 25(OH)D-DBP is the main storage form of Vitamin D and commonly used for monitoring the body's Vitamin D status.¹¹ After glomerular filtration, the 25(OH)D is converted to 1,25-dihydroxyvitamin D (1,25(OH)₂D) by renal 25-hydroxyvitamin D 1 α -hydroxylase (CYP27B1) in the proximal tubular cells. This is the hormonally active form of Vitamin D that acts on VDR in different target organs.¹² As a biologically active form, its half-life is short, only 8–12 h, which provides essentially no information about the body's nutritional Vitamin D status.¹³ The 1,25(OH)₂D synthesis in the kidney is affected by diverse regulatory hormones and genetic factors,¹⁴ such as parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), calcium phosphorus metabolism. The active Vitamin D can further be degraded to an inactive state by the renal enzyme 24-hydroxylase (CYP24A1) (Figure 1).

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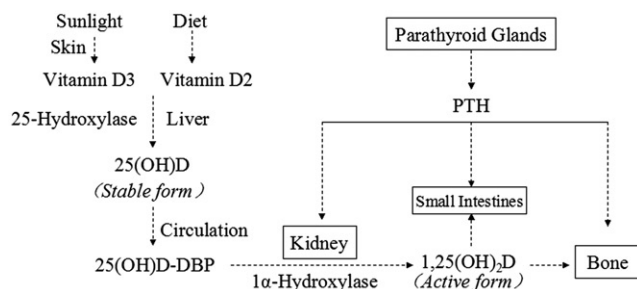


Figure 1. Sources and metabolism of Vitamin D.

Vitamin D deficiency/insufficiency in CKD

Metabolism of Vitamin D in CKD

Kidneys as the mainly organs convert the 25(OH)D to the active forms of Vitamin D, 1,25(OH)₂D. The Vitamin D deficiency or insufficiency is prevalent in patients with CKD which can decline renal production of 1,25(OH)₂D.¹⁵ There are several mechanisms for the dysregulation of Vitamin D metabolism during the progress of CKD.¹⁶ The limitation of 25(OH)D-DBP in the circulation is not only because of the reduced glomerular filtration rates (GFR),¹⁷ but also due to the loss of protein into the urine,¹⁸ that restrict the production of 1,25(OH)₂D which is one of the most active hormonal and a pleiotropic metabolite in human. FGF-23 as a counter-regulatory phosphaturic hormone for Vitamin D is another key factor which increase early in CKD, contributing by directly suppressing the activity of 1,25(OH)₂D via inhibition of 1- α -hydroxylase and degradation of 1,25(OH)₂D via the stimulation of 24-hydroxylase.¹⁹ Carboxyl (C)-terminal fragments of PTH may have potential suppressive effects on 1,25(OH)₂D synthesis.²⁰ Since the altering of FGF-23 and the PTH levels involves in the progression of CKD, Vitamin D insufficiency or deficiency could be the consequence of CKD as well the cause of CKD.²¹

The diagnosis of Vitamin D deficiency

Serum 25(OH)D is commonly recognized as a valuable biomarker to roughly reflect the patient's nutritional Vitamin D status.²² At present there is no unified criterion to define Vitamin D deficiency because most of the evidence for Vitamin D comes from population studies. These suggest a positive relation between high blood levels of the vitamin and a reduced risk of disease without providing explanations. The International Osteoporosis Foundation suggests that serum 25(OH)D levels should reach up to 75 nmol/L (30 ng/mL) to suppress the maximum of PTH.²³ The American Geriatrics Society published a consensus that serum 25(OH)D levels about <75 nmol/L (30 ng/mL) could increase the risk of falls especially among older populations.²⁴ However, United States Institute of Medicine reported that Vitamin D deficiency at serum 25(OH)D levels between <50 nmol/L (20 ng/mL) and under 75 nmol/L (30 ng/mL) is considered an insufficient amount.²⁵ Some experts suggested that serum 25(OH)D levels above 30 ng/mL could be desirable for optimal health and above 50 ng/mL should raise potential adverse effects, such as increased the risk for pancreatic cancer. This is proved

by some studies, that revealed that people with the highest Vitamin D levels seemed to have a higher, rather than lower,²⁶ chance of developing breast cancer.²⁷ Otherwise one study concluded that higher 25(OH)D levels were associated with significantly reduced mortality in patients with colorectal and breast cancer.²⁸ Therefore, there is no consensus on a cut-off point to define Vitamin D deficiency and the serum levels of 25(OH)D signifying deficiency or sufficiency are disease dependent, moreover the specific therapeutic levels for Vitamin D sufficiency in different diseases and the dose–response characteristics of Vitamin D will ensure progress in research, clinical medicine and public health.²⁹

There are increasing epidemiological data published in recent years suggesting that Vitamin D deficiency is commonly found in the general population, especially prevalent in CKD patients. Based on the key statistics from the National Health and Nutrition Examination Survey (NHANESIII), the prevalence of 25(OH)D levels <20 ng/mL among adults with stages 1–3 CKD is 9–14%. Among adults with estimated GFR (eGFR) <30 mL/min/1.73 m², more than 27% had 25(OH)D deficiency.³⁰ Furthermore, nearly 80% of dialysis patients had Vitamin D deficiency or insufficiency (<30 ng/mL).^{31–33} Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for Bone Metabolism and Disease in CKD recommends that serum level of 25(OH)D <75 nmol/L (30 ng/mL) should be considered to provide prevention and treatment in patients with stages 3 and 4 CKD.³⁴ The treatment of Vitamin D insufficiency or deficiency when present in non-CKD patients according to corresponding meta-analysis is warranted since such therapy may reduce or prevent secondary hyperparathyroidism (SHPT) and decrease the incidence of hip fractures.²⁹

Vitamin D supplements and CKD

Vitamin D and derivatives

Vitamin D and derivatives have been widely used in a variety of medical areas, especially in the management of CKD, for example, the control of hyperparathyroidism.³ The different Vitamin D analogs have differential effects on physiological function, which could be classified by the activity.³⁵ Nutritional Vitamin D²⁵ since they can be supplemented by oral intake of vitamin D rich or fortified diets is non-biological active form such as ergocalciferol, cholecalciferol and traditionally the active forms, 1,25(OH)₂D, known as hormone are calcitriol and alfacalcidol. More recently, four Vitamin D analogs have been introduced in the nephrology area and play an increasingly important role in CKD treatment which is doxercalciferol, paricalcitol, oxacalcitriol and falecalcitriol.³⁶ Vitamin D receptor activator (VDRA) for any compound can activate VDR.³⁷ The different forms of Vitamin D compounds are listed in Table 1.

Vitamin D supplement in chronic kidney disease–mineral bone disease

Mineral bone disease as a systemic syndrome, contributing to the pathogenesis of renal osteodystrophy, is early and common complications in early stages of CKD associated

Table 1. Vitamin D and derivatives.

Vitamin D2	Vitamin D3
Nutritional Vitamin D	
Ergocalciferol (25-hydroxyVitamin D2)	Cholecalciferol (25-hydroxyVitamin D3)
Bioactive Vitamin D	
Classical active Vitamin D	
–	Calcitriol (1,25-dihydroxyVitamin D3) (VDRA)
	Alfacalcidol (1 α -hydroxyVitamin D3)
The new Vitamin D analogs	
Paricalcitol (19-nor-1,25-dihydroxyVitamin D2) (VDRA)	Maxacalcitol/22-oxacalcitriol (22-oxa-1 α ,25-dihydroxy Vitamin D3) (VDRA)
Doxercalciferol (1 α -hydroxyergocalciferol)	Falecalcitriol (F6-1 α ,25-dihydroxyVitamin D3)

with an increased risk of cardiovascular calcification and mortality although the rate of change and severity of abnormalities is highly variable among patients.³⁸ CKD patients with alteration in Vitamin D metabolism cannot make enough 1,25(OH)₂D to keep their bones mineralized normality, have abnormal calcium–phosphorus metabolism leading to SHPT which associated with an increased risk of cardiovascular calcification and mortality.² All these causes have significant correlation with prognosis.³⁹ The KDOQI guidelines have suggested that the treatment with nutritional or active Vitamin D is according to the target range of intact plasma PTH for the stage of CKD. In the dialysis population, the PTH target focuses on avoidance of risk at extremes of PTH, which is 2–9 times of the upper limit of the normal reference range.⁴⁰ It suggests that serum levels of calcium, phosphate, alkaline phosphatase, PTH and 25(OH)D in patients with CKD stages 4 and 5 should be monitored with a frequency based on stage, rate of progression and whether specific therapies have been initiated to avoid adverse reactions.⁴¹

Vitamin D supplement and the progression of renal function in CKD

Emerging epidemiological studies have shown that Vitamin D deficiency may be associated with the progression of renal function in CKD.⁴² Previously, Melamed et al. suggested that after multivariable adjustment, participants with 25(OH)D levels <15 ng/mL were 2.6 times more likely to progress to end stage renal disease (ESRD) compared with participants with higher 25(OH)D levels.⁴³ A research from USA enrolling 5888 participants showed that each 10 ng/mL lower 25(OH)D was associated with a 25% greater risk of rapid GFR loss [95% confidence interval (CI) 5%, 49%, $p = 0.0$], adjusting for potential confounding characteristics and low 25(OH)D concentration was associated with eGFR loss with a magnitude similar to or stronger than that for diabetes or hypertension, the most important traditional risk factors for CKD.⁴⁴ Albuminuria as an important marker and major risk factor for progressive decline in renal function is considered by many to be the first step in an inevitable progression to nephropathy and renal failure. Multiple studies have shown an inverse relationship between the level of Vitamin D and degree of albuminuria.⁴⁵ NHANES III, in which 15,068 adults participating, showed that the patients with higher albuminuria were observed with lower Vitamin D.⁴⁶ These findings

suggest that low 25(OH)D concentration may be a modifiable risk factor for the progression of CKD.

Vitamin D supplement and proteinuria

Treatment with Vitamin D analogs for patients with proteinuric renal diseases could be helpful because Vitamin D has a very important role in regulating systems that could be important in the pathobiological state of proteinuria.⁴⁷ Fishbane et al. carried out a double-blind randomized study recruited 61 patients with CKD and concluded that oral paricalcitol can decrease urinary protein–creatinine ratios (UACR),⁴⁸ and plasma concentration of PTH level, C-reactive protein and TGF- β were reduced significantly, additional.⁴⁹ The Vitamins and Lifestyle (VITAL) study (NCT00421733), the multinational, placebo-controlled, double-blind trial, evaluated the anti-albuminuric effect of paricalcitol 1 or 2 μ g/day versus placebo in 281 patients with type 2 diabetes and albuminuria who were receiving angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers to control blood pressure and proteinuria and found that patients on 2 μ g/day paricalcitol showed an early, sustained reduction in UACR, ranging from –18% to –28% ($p = 0.014$ vs. placebo).⁵⁰ Furthermore, in a small group analysis, the effect of calcitriol on urinary protein excretion in patients with immunoglobulin A nephropathy was determined;⁵¹ Agarwal et al. reported that paricalcitol also has an anti-proteinuric effect on patients with CKD;⁵² recently a systematic review addressed that active Vitamin D analogs such as paricalcitol and calcitriol reduce residual proteinuria.⁵³ These researches indicated that Vitamin D supplement can reduce urinary protein in patients with CKD, and therefore it may exert protective effects on progression of renal function. But so far, there is no exact clinical evidence showing active Vitamin D has the effect in retarding the progression of renal function.

Vitamin D supplement and blood pressure

Mounting evidence from clinical studies has demonstrated an inverse relationship between serum Vitamin D levels and the blood pressure. Prospective studies with cohorts from the Health Professionals' Follow-Up Study and the Nurses' Health Study during 4 years of follow-up also showed that the multivariable relative risk of incident hypertension among patients whose measured plasma 25(OH)D levels were <15 ng/mL (i.e., Vitamin D deficiency) was three times compared with those whose levels were ≥ 30 ng/mL;⁵⁴ women

with low Vitamin D levels (17 ng/mL or 42 nmol/L) had a 67% increased risk of developing hypertension.⁵⁵ These studies implied that high blood pressure might benefit from Vitamin D supplement. A study was consisted of 148 women with 8 weeks of supplementation with Vitamin D3 (cholecalciferol) and calcium, and the supplementation resulted in a decrease in systolic blood pressure (SBP) of 9.3% ($p = 0.02$) and a decrease in serum PTH of 17% ($p = 0.04$).^{56,57} In the VITAL study, patients with high-dose 2 µg/day paricalcitol showed SBP with 3–9 mmHg reduction compared with placebo.⁵⁰ Therefore, Vitamin D may reduce the risk of hypertension and lower blood pressure. However, in meta-analyses of 10 trials, supplementation no significantly reduced SBP and did not affect DBP.⁵⁸ Thus, here is no consistent result in existing clinical trials giving confirmed evidence that Vitamin D supplementation may not have blood pressure benefits. Further research is needed to confirm these results.

Clinical and epidemiological studies have suggested that Vitamin D analog may suppress proteinuria and hypertension; however, there is no evidence from controlled clinical trial data. In a meta-analysis of subgroup analysis including four small clinical studies, data indicated that Vitamin D (paricalcitol, maxacalcitol, doxercalciferol) cannot reduce the risk of ESRD and Vitamin D therapy may be independently associated with reduced mortality in CKD.⁵⁹ Therefore, more high quality controlled clinical trials with clinical endpoints as ESRD are needed to prove that Vitamin D supplement could attenuate the progression of renal function directly.

Laboratory studies indicate that Vitamin D analogs suppress the renin–angiotensin system (RAS) and inhibit production of inflammatory cytokines for improving the renal function. In animal models studies, Li et al. found that mice with Vitamin D deficiency elevated production of renin as well as in cell culture, whereas injection of 1,25(OH)₂D reduces renin synthesis which is independent of calcium metabolism.⁶⁰ Furthermore, they have found that mice lacking the VDR increased renin synthesis and angiotensin (Ang) II, leading to hypertension, cardiac hypertrophy.⁶¹ In addition, the 5/6 nephrectomy uremic rat model treated with an ACEI and a paricalcitol, suppressed urinary protein excretion, reduced both mesangial cell proliferation and the degree of glomerulosclerosis via mediation of the TGF-β signaling pathway and matrix-regarding molecules and this effect was amplified when blood pressure was controlled via RAAS blockade.⁶² Tan et al. demonstrated that the Vitamin D analog paricalcitol ameliorates renal interstitial fibrosis in a mouse model of obstructive nephropathy.⁶³ Thus, these evidence supported that the potential renoprotective effects of Vitamin D supplement include suppression of the RAAS and a reduction in proteinuria through negative regulation of the RAAS and directly the protection of glomerulus via the activation of VDR and anti-proliferation, pro-differentiation and anti-inflammation which may be attributed to a suppression of the NF-κB pathway promoting both inflammation and fibrogenesis by regulating gene expression of cytokines, chemokines and adhesion molecules including interleukin-6 (IL-6), MCP-1 and tumor necrosis factor-α (TNF-α).⁶⁴

Vitamin D supplement and cardiovascular events in CKD

Animal experiments demonstrated that VDR knockout mice can develop cardiac hypertrophy and high blood pressure due to excessive stimulation of the RAS and spontaneously hypertensive rats,⁶¹ treated with paricalcitol or doxercalciferol, have the reduction in left ventricular hypertrophy (LVH), attenuation of cardiac and cardiomyocyte hypertrophy, improvement of left ventricular diastolic function, and suppression of episodes of heart failure.⁶⁵

Clinical and epidemiological studies have found that Vitamin D deficiency/insufficiency has been recently associated with important CVD risk factors such as obesity, hypertension, and diabetes mellitus in CKD and in the general population⁶⁶ and inversely associated with risk for developing coronary artery calcification.⁶⁷ A study with 1739 participants reported that individuals with Vitamin D deficiency (25(OH)D < 15 ng/mL) had 1.62 times increased in incident cardiovascular events compared with those without Vitamin D deficiency, and the effect was evident in participants with hypertension.⁶⁸ But Mehrotra et al. analyzed CKD patients from NHANESIII that low serum Vitamin D predicts a higher mortality and has no significant with cardiovascular events in CKD patients undergoing dialysis.⁶⁹ Therefore, Vitamin D might be a determinant of cardiovascular mortality, but without cogent evidence directly related to cardiovascular endpoints.

Recently, convincing data demonstrate the effect of Vitamin D supplementation in the benefit of the cardiovascular system and reduction for any cardiovascular event. Active Vitamin D can attenuate myocardial hypertrophy in hemodialysis patients with SHPT.⁷⁰ A meta-analysis of prospective studies performed by Wang et al. showed that Vitamin D supplements may reduce the risk for cardiovascular events and improve cardiovascular health in adults, especially in dialysis patients.⁷¹ However, a surprise finding came from the Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity (PRIMO) trial (NCT00497146): it was a double-blind, randomized placebo-controlled trial among 227 patients with pre-dialysis patients with mild to moderate left ventricular hypertrophy and preserved left ventricular ejection fraction was randomly assigned to receive 2 µg/day of oral paricalcitol (115 patients) or placebo (112 patients) for 48 weeks; left ventricular mass index, echocardiographic changes in left ventricular diastolic function, CVD events leading to hospitalization or death and change in cardiac biomarkers were observed and analyzed, and the results showed the surprise finding that 48 weeks therapy with paricalcitol did not alter left ventricular mass index or improve certain measures of diastolic dysfunction in patients but who had fewer hospitalizations for CVD events.⁷² These results differ from reports of Vitamin D therapy in animal models and human observational data. One potential explanation for the results is that Vitamin D might be associated with a reduction in mortality among patients on dialysis, but PRIMO study did not include patients on dialysis. The other explanation is FGF23, which was mentioned in “Metabolism of Vitamin D in CKD”. FGF23 as a hormone that regulates phosphate which might be increased by paricalcitol is related

with mortality and cardiovascular events from many epidemiological data in CKD patients.⁷³ Therefore, further randomized, controlled trials are needed to conclusively determine whether Vitamin D supplementation reduces CVD, CVD-related morbidity and all-cause mortality in CKD.

Vitamin D supplement and immune system in CKD

It is well known that CKD is a state of microinflammation, which might be contributed by Vitamin D deficiency besides the uremic milieu.⁷⁴ Vitamin D deficiency is associated with dysfunction of both innate and adaptive immunity in patients with CKD who have abnormal inflammatory response, increased susceptibility to infection and increased prevalence of malignancies.⁷⁵ Some studies unraveled that treatment with Vitamin D can alter immune function in CKD patients, enhance Th2 cell differentiation,⁷⁶ decrease IL-6, IL-8, IL-1 and TNF- α expression,⁷⁷ attenuate oxidative stress, even reduce platelet activating factor/thrombin activity and metabolism in hemodialysis patients.⁷⁸ Therefore, the immune regulatory function of Vitamin D supplement is well evaluated, associated with a decreased risk of infection, as well as reduced all-cause mortality. The study “Dialysis Infection and Vitamin D in New England” DIVINE is a ongoing randomized, placebo-controlled trial (NCT00892099) could provide a well understanding of the immune regulatory function of vitamin D in hemodialysis patients via evaluating cathelicidin, cytokine levels, and the incidence of infections in future.

Controversy for vitamin D in CKD

Controversy remains regarding the causality between Vitamin D deficiency and poor prognosis for patients with CKD. Patients who have serious condition could have low Vitamin D levels due to lack of adequate daylight outdoor exposure, malnutrition and abnormal Vitamin D metabolism.⁷⁹ A notable factor concerned is the socioeconomic status. In developing countries, the prevalence of Vitamin D deficiency varies widely by and within regions, and the prevalence ranges between 30% and 90%.⁸⁰ Lack of large-scale, epidemiologic studies and heterogeneity with respect to genetic, nutritional, lifestyle and socioeconomic status accounts for this variability. Based on the evidence from the Ludwigshafen Risk and Cardiovascular Health study, some researchers presumed that many various parameters might contribute to a poor Vitamin D status, and Vitamin D deficiency might only be a sign of no health status, rather than the direct cause of poor prognosis in patients with CKD.⁸¹

It remains to be established that optimal serum concentrations of Vitamin D for bone and general health in different diseases which would be variety depending on the different physiological states. Currently, the optimal Vitamin D status, >30 ng/mL (75 nmol/L) in CKD depends on the effect for preventing a rise in iPTH levels.⁸² But a serum concentration of 100 nmol/L Vitamin D appears to reduce the risk of hip and other nonvertebral fractures.⁸³ Actually, the establishment of an optimal Vitamin D should also consider the non-calcemic effects of Vitamin D that effect on VDR, resulting in inhibition of RAS, suppression of inflammatory reaction and modulation of immune system.⁸⁴

Increasing confusion exists as to which Vitamin D compounds are more appropriate for persons with CKD. The controversy about nutritional Vitamin D and active Vitamin D heats up. Some opinion-based guidelines recommend administration of such nutritional Vitamin D agents as ergocalciferol or cholecalciferol as the first therapy in hyperparathyroidism associated with low circulating levels of 25(OH)D (<30 ng/mL) in non-dialysis dependent CKD patients.⁸⁵ The deficiency of serum 25(OH)D can increase 1- α hydroxylation secretion in many extrarenal sites as a compensation for loss. Dusso et al. reported that 1,25(OH)₂D deficiency, but not hyperparathyroidism, may play a role in the stimulation of 1,25(OH)₂D production by macrophages which display higher rates of 1,25(OH)₂D synthesis and lower rates of catabolism in chronic renal failure.⁸⁶ Several studies have concluded the potential benefits of ergocalciferol in CKD, including satisfactory to inadequate lowering of PTH level to target ranges, improving response to erythropoietin stimulating agents, and salutary effects on glycemic controls, even suppress the risk of infection by increasing cathelicidin.^{59,87,88} Compared with nutritional Vitamin D agents, active Vitamin D compounds appear to more effectively lower the circulating levels of alkaline phosphatase, and PTH in CKD patients.^{89,90} Epidemiologic studies have almost consistently indicated the survival benefit of active Vitamin D agents across all stages of CKD, including among dialysis patients with 25(OH)₂D deficiency, for example, proteinuria decrease, improvement of the cardiovascular system and the risk of death reduction.³⁷

In addition, the controversy surrounding the potential clinical applications of new Vitamin D derivatives and classical active Vitamin D is discussed in many researches.^{91–93} VDRA analogs have been developed with enhanced affinity for the VDR and diminishing or even abolishing the calcemic and phosphatemic effects,³⁶ while calcitriol appears to be more potent than paricalcitol in mobilizing calcium resorption from bone and was thought to be associated with increasing serum calcium level resulting in hypercalcemia.⁹¹ Recently, in an investigator-initiated multicenter randomized clinical trial, researchers reported that there was no difference between alfacalcidol and paricalcitol in the treatment of SHPT in hemodialysis patients.⁹³ As a result, there has been increasing confusion as to whether Vitamin D agents are more or less appropriate for CKD patients or which type nutritional versus active Vitamin D preparations should be used.³⁷ Thus, the effects of different forms of Vitamin D may differ from metabolism and mechanisms which should cause practice attention in clinical.

Despite considerable disputes exist for the Vitamin D supplements in CKD, a growing amount of experimental evidence and some clinical evidence are now gathering from *in vitro*, animal, and epidemiological studies and suggesting that Vitamin D supplements may be of benefit to CKD patients. However, current guidelines only recommend Vitamin D treatment in patients with moderate CKD accompanied by SHPT and Vitamin D insufficiency. The ideal Vitamin D therapy for CKD patients should be the one that improves survival irrespective of suggested or imposed target ranges for arbitrary or opinion-based surrogate endpoints.³⁷ Consequently, the randomized clinical trials, in which are ongoing, are needed to determine whether

Vitamin D supplementation could reduce future CVD events, the rate of progression of kidney disease and mortality risk in individuals with CKD as well more accurately define the precise therapeutic agent, dose, timing, monitoring parameters and indications for Vitamin D therapy.

Declaration of interest

No conflict of interest exists in the submission of this manuscript.

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