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Vitamin D and Its Role in Chronic Kidney Disease

By JIE TANG, MD, MSc

Vitamin D is crucial for a wide variety of organ systems; nevertheless, vitamin D deficiency is highly prevalent in the general population and especially in those with compromised renal function. It is important for physicians to be proactive in monitoring vitamin D status and in aggressively managing those who show signs of deficiency. This issue of *Nephrology Rounds* reviews recent clinical evidence regarding the pleiotropic effects of 1,25-dihydroxyvitamin D (1,25[OH]2D), the unique role of 25-hydroxyvitamin D (25[OH]D), and discusses the management of vitamin D deficiency in patients with chronic kidney disease (CKDs), including those requiring dialysis.

Vitamin D

Vitamin D is a fat-soluble vitamin that also acts as a pleiotropic hormone. There are 2 major forms of vitamin D: **vitamin D₃** is normally produced in the skin after sun exposure and can also be acquired from diet, and **vitamin D₂** is only obtained exogenously. It is formed from the irradiation of ergosterol, a plant and fungal sterol.

Both Vitamins D₂ and D₃ are used as dietary supplements in the United States (US). Vitamin D undergoes sequential hydroxylations through the liver and kidney to reach its final active form, 1,25(OH)2D. This active agent interacts with its nuclear receptor, and becomes a transcription factor to modulate gene expression and biological actions.¹ A vitamin D receptor (VDR) is present in a wide variety of cells including enterocytes, osteoblasts, renal tubular cells, cardiac myocytes, parathyroid and pituitary gland cells, promyelocytes, and lymphocytes.²

The important final step of 1,25(OH)2D synthesis is 1 α -hydroxylation, which is catalyzed by 1 α -hydroxylase. The enzyme is present in renal tubular cells, and is also expressed in a variety of extrarenal tissues.³ Under normal circumstances, extrarenal 1 α -hydroxylase appears to act in an autocrine or paracrine fashion by modulating cellular and tissue actions at a local level, whereas renal 1 α -hydroxylase provides 1,25(OH)2D for systemic (endocrine) actions.⁴

In the human body, the storage form of vitamin D is 25(OH)D; it is also the predominant circulating form of vitamin D in the blood and, therefore, is considered the most reliable index of human vitamin D status. Despite possible direct effects of 25(OH)D on calcium and phosphate homeostasis, in both animal models and humans, 1,25(OH)2D is the most biologically active form of vitamin D in terms of affinity for VDR, and in stimulating intestinal calcium transport and bone calcium mobilization.^{5,6} The kidney is able to maintain an adequate serum 1,25(OH)2D level, which is regulated primarily by serum parathyroid hormone (PTH), calcium, and phosphate. Both 25(OH)D and 1,25(OH)2D can be inactivated through hydroxylation at C-24, resulting in 24,25(OH)2D or 1,24,25(OH)3D. Studies using 24-hydroxylase knockout mice provided strong evidence for the role of 24-hydroxylase in the catabolism of 1,25(OH)2D and indicated that 24-hydroxylated vitamin D was a relatively inactive metabolite,⁷ although that is still debated by other investigators.

Currently available vitamin D compounds

Two groups of vitamin D compounds are available on the market. The first group includes ergocalciferol (vitamin D₂) and its analogs, doxercalciferol (1 [OH] D₂) and paricalcitol (19-nor-1,25 [OH]2 D₂). The second group includes cholecalciferol (vitamin D₃) and its analogs, calcidiol (25 [OH] D₃), alfalcidol (1 [OH] D₃, currently unavailable in the US), and calcitriol (1,25 [OH]2 D₃). Both calcitriol and paricalcitol have similar potencies in parathyroid gland suppression,⁸ but unlike calcitriol, paricalcitol has less calcemic and phosphatemic effects due to its lack of carbon 19 and the exocyclic double bond.⁸ Ergocalciferol and cholecalciferol are routinely used to treat nutritional vitamin D deficiency, according to serum 25(OH)D levels. Ergocalciferol is as effective as cholecalciferol in repleting vitamin D stores;⁹ they both have good safety profiles, without significant risks for hypercalcemia or hypercalciuria.¹⁰ Alfalcidol and doxercalciferol are indicated for patients with compromised renal function but sufficient hepatic function, whereas calcidiol is primarily for patients with intact renal function. The

effects of alfacalcidol and doxercalciferol on calcium homeostasis differ markedly. In animal studies, doxercalciferol demonstrates at least equal or higher bone-protective activity with distinctly less pronounced effects on calcium homeostasis compared with alfacalcidol.¹¹ The data on calcidiol are limited.

Definition and prevalence of vitamin D deficiency

Although there is no consensus regarding optimal serum 25(OH)D level, they are inversely associated with PTH levels until 25(OH)D reaches 30–40 ng/mL, at which point PTH levels begin to level off (at their nadir).¹² Generally, 25(OH)D levels of <20 ng/mL are considered vitamin D deficient, whereas a level of 21–29 ng/mL is considered insufficient. Vitamin D deficiency is now regarded as an epidemic, with 1 billion people worldwide estimated as vitamin D deficient or insufficient.¹³ A recent study found that more than 70% of individuals aged ≥ 12 years have serum 25(OH)D levels <32 ng/mL.¹⁴ Martins et al,¹⁵ using National Health and Nutrition Examination Survey (NHANES) III data, reported that the prevalence of vitamin D deficiency or insufficiency, defined as a 25(OH)D level <30 ng/mL, was >40% regardless of the differences in age, sex, and ethnicity. Usually, 25(OH)D deficiency results from lack of sun exposure or inadequate nutrition, and the prevalence of vitamin D deficiency was higher in women, elderly persons, and ethnic minorities.¹⁵

In patients with CKD, both proteinuria and uremia increase the risk of low serum 25(OH)D.^{16,17} In proteinuric patients, especially heavy proteinuria, the tubular uptake and activation of 25(OH)D by megalin-mediated endocytosis is compromised,¹⁸ leading to urinary loss of 25(OH)D complex with its vitamin D-binding protein (DBP). Uremia further decreases skin response to ultraviolet (UV) light and the production of vitamin D₃ from 7-dehydrocholesterol.¹⁷ The prevalence of 25(OH)D deficiency/insufficiency was reported to be as high as 86% in predialysis patients with estimated glomerular filtration rate (eGFR) ranging from 11–111 mL/min, and 97% in patients on dialysis.¹⁹ In addition to a high prevalence of 25(OH)D deficiency or insufficiency, patients with CKD also demonstrate profound reductions in 1,25(OH)₂D levels, especially those reaching end-stage renal disease (ESRD) requiring dialysis.²⁰ Decreased renal 1 α -hydroxylase activity is the primary cause, and this activity is not only affected by the reduction of functional renal mass,²¹ it is also suppressed by hyperuricemia,²² metabolic acidosis,²³ and uremic toxins,²⁴ disorders commonly seen in advanced CKD. In patients with eGFR <30 mL/min, >60% demonstrated 1,25(OH)₂D deficiency (defined as <22 pg/mL).²⁵

Actions of vitamin D

Calcium homeostasis and bone health (Table 1)

The kidney and intestine are the 2 major organs involved in calcium balance, where bone serves as a vast reservoir. In the kidney, most of the filtered calcium is reabsorbed in the proximal tubule, and the fine-tuning of final calcium excretion occurs in the distal nephron. In the intestine, the calcium transport involves both paracellular and transcellular pathways. The paracellular pathway is largely passive, whereas the transcellular pathway involves special-

ized calcium channels specifically ECaC2 and, to a lesser extent, ECaC1. Once calcium enters the cell, it binds to intracellular proteins, mainly microtubule-associated calbindin, and finally exits the cell through membrane calcium adenosine triphosphatase (ATPase) plasma membrane calcium ATPase [PMCA] and sodium calcium exchanger [NCX]) or alternatively by exocytosis.²⁶

Vitamin D is essential for calcium homeostasis and bone health. VDR- or 1 α -hydroxylase-knockout mice have a bone- and growth-plate phenotype mimicking humans with severe vitamin D deficiency.²⁷ The mice were hypocalcemic, hypophosphatemic, and exhibited hyperparathyroidism and osteomalacia.²⁷ 1,25(OH)₂D induces the expression of calbindin, increases calcium entry into the enterocytes via calcium selective channels, and stimulates intestinal PMCA expression to enhance calcium extrusion at the basolateral side.^{28,29} 1,25(OH)₂D also has direct effects on bone by inducing osteocalcin whose synthesis is positively associated with new bone formation,³⁰ and osteopontin, which is important for bone resorption;³¹ furthermore, it regulates osteoblastic differentiation, resulting in enhanced bone formation.³² Given that 1,25(OH)₂D can promote osteoblast-mediated osteoclast formation, it affects both bone formation and resorption, maintaining dynamic bone balance.³³ A positive bone balance during pregnancy and childhood growth is maintained through stimulation of 1,25(OH)₂D production by sex hormones, growth hormone, and insulin-like growth factor.^{34,35}

Cardiovascular and other extraskelatal benefits (Table 1)

Besides a presence in bone, kidney, and the gastrointestinal tract, VDRs have been identified in almost every other tissue and cell in the body, including the heart and blood vessels.^{13,36,37} In addition, 1 α -hydroxylase is also expressed in cardiac myocytes, fibroblasts, and vascular endothelial cells,^{38,39} indicating that heart tissue has the capacity to synthesize active vitamin D, and maintains an autocrine loop important for optimal cardiovascular (CV) function. In animal studies, vitamin D deficiency results in marked cardiac hypertrophy that is reversed by active vitamin D administration,^{40,41} as well, VDR-knockout mice reveal increased myocardial hypertrophy and fibrosis.⁴² Vitamin D supplementation protects against vascular calcification, blunts the deleterious impact of advanced glycation endproducts on endothelial cells, and lowers C-reactive protein (CRP) levels.^{43–45} Human subjects with adequate serum 25(OH)D levels are less likely to have CV risk factors, such as diabetes, hypertension, obesity, dyslipidemia, and microalbuminuria.¹⁵ A study in >1700 Framingham Heart Study participants revealed that low vitamin D was associated with increased risk of CV disease (CVD).⁴⁶ Another study in >18 000 men with no known CVD at enrollment, found a 2.42 relative risk of acute myocardial infarction (AMI) during 10 years of follow-up in those with 25(OH)D <15 ng/mL, even after adjusting for family history, diabetes, hypertension, dyslipidemia, and other known CV risk factors;⁴⁷ those with intermediate 25(OH)D levels were also at increased risk of AMI (relative risk 1.65–1.72).

In addition to its CV benefits, vitamin D has potent anti-cancer properties. It promotes cell differentiation, inhibits cell proliferation and angiogenesis, and reduces metastatic

Table 1: Direct effects of VDR activation by vitamin D treatment	
Tissue/organ system	Actions
Cardiovascular	<ol style="list-style-type: none"> 1. Reduces cardiac hypertrophy 2. Reduces myocardial fibrosis 3. Protects against vascular calcifications 4. Protects endothelium 5. Lowers risks of myocardial infarction 6. Suppresses renin production
Mineral	<ol style="list-style-type: none"> 1. Increases calcium absorption 2. Increases phosphate absorption
Musculoskeletal	<ol style="list-style-type: none"> 1. Enhances muscle mass/strength 2. Maintains normal bone formation
Endocrine	<ol style="list-style-type: none"> 1. Increases insulin sensitivity 2. Prevents parathyroid gland hyperplasia and suppresses PTH synthesis 3. Stimulates VDR and CaSR in parathyroid cells
Immune system & inflammation	<ol style="list-style-type: none"> 1. Reduces inflammation 2. Improves immune function
Renal	<ol style="list-style-type: none"> 1. Reduces nephrosclerosis/glomerulosclerosis 2. Reduces proteinuria 3. Delays progression of CKD 4. Reduces mortality in patients with CKD and ESRD
Tumor/cancer	<ol style="list-style-type: none"> 1. Promotes differentiation, inhibits proliferation 2. Inhibits angiogenesis 3. Reduces cancer risk and metastatic potential

VDR = vitamin D receptor; PTH = parathyroid hormone; CaSR = calcium sensing receptor; CKD = chronic kidney disease; ESRD = end-stage renal disease

potential.⁴⁸ Adequate levels have been associated with reduced risks of colorectal cancer,⁴⁹ breast cancer,⁵⁰ and non-Hodgkin lymphoma.⁵¹ Data from the Health Professionals Follow-Up Study⁵² revealed that low levels of vitamin D were associated with increased cancer incidence and mortality in men, particularly for gastrointestinal cancers. Currently, several ongoing prospective studies are further investigating the association between vitamin D and cancer prevention.

Vitamin D also stimulates insulin secretion, inhibits renin production, and modulates immune cells, including T and B lymphocytes and macrophages;⁵³⁻⁵⁵ this has significant implications for the management of diseases such as diabetes, hypertension, autoimmune diseases, and infection control.

Vitamin D and PTH

Vitamin D and PTH are closely associated; PTH is a major regulator of vitamin D 1 α -hydroxylase activity,⁵⁶ affecting vitamin D synthesis, and vitamin D is a strong and effective modulator of PTH. Vitamin D therapy reduces serum PTH by preventing parathyroid gland hyperplasia, increasing calcium-sensing receptor expression on the parathyroid gland, and raising serum calcium concentrations.^{57,58}

In addition to the high prevalence of 25(OH)D deficiency, the levels of 1,25(OH)2D begin to decline at stage 2 CKD with a mean GFR of 65.1 \pm 6.1 mL/min.^{21,59} Two recently discovered molecules, fibroblast growth factor 23 (FGF23) and klotho, also play important roles in vitamin D metabolism, especially in patients with CKD. FGF23 is a 251 amino acid protein produced by osteoblasts and osteocytes that was originally identified in patients with tumor-induced osteomalacia and hypophosphatemia. FGF23

inhibits 1 α -hydroxylase activity, resulting in decreased synthesis of 1,25(OH)2D;⁶⁰ serum FGF23 levels are markedly increased in patients with advanced CKD, including those on hemodialysis.⁶¹ Klotho is an important cofactor essential for FGF23 actions;⁶² it is encoded by a putative antiaging gene identified in 1997. Mice with the mutated gene reveal hyperphosphatemia, hypercalcemia, and high serum 1,25(OH)2D levels.⁶⁰ Klotho is a 1012 amino acid cell-surface protein, which can be released as a circulating form after cleavage by metalloproteinases. Through modulating FGF23 action, klotho regulates urinary phosphate excretion and 1,25(OH)2D synthesis.

While 1,25(OH)2D levels start declining in stage 2 CKD, PTH levels begin to rise, usually becoming significantly elevated by stage 4-5 CKD.⁵⁹ In a large cross-sectional study of patients with early CKD,²⁵ 12% of subjects with eGFR \geq 80 mL/min and ~40% with eGFR between 40–49 mL/min had elevated serum PTH levels. Intact PTH levels may reach as high as 800-900 pg/mL in some untreated patients with late-stage CKD and, although the underlying etiology is likely multifactorial, the most common causes are low levels of vitamin D, hyperphosphatemia, and hypocalcemia. Local 1 α -hydroxylase expression in the parathyroid cell is now recognized, and active vitamin D is likely to have both autocrine and endocrine activities on the parathyroid gland.⁶³ As CKD progresses (GFR <45 mL/min), more serum phosphate accumulates and serum calcium drops, each acting by separate mechanisms to stimulate parathyroid gland growth, PTH synthesis and release.⁶⁴ In addition to acting on vitamin D metabolism, klotho also binds to Na⁺,K⁺-ATPase in parathyroid cells and regulates calcium-stimulated PTH secretion.^{60,61}

The clinical effects of high PTH and low vitamin D are difficult to distinguish because the 2 processes coexist in patients with stage 2-5 CKD or ESRD; however, high PTH is thought to have specific effects on bone turnover and CVD. Elevated PTH levels are catabolic for cortical bone, and chronic exposure to high PTH leads preferentially to cortical bone loss and deterioration in cortical architecture.⁶⁵ Since cortical bone contributes substantially to bone mechanical competence,⁶³ these changes could account for the increased fracture susceptibility noted in patients with CKD.⁶⁵ Cinacalcet, effective in suppressing PTH, was associated with a significant fracture risk reduction of 54%, in a pooled analysis of 4 randomized trials involving patients with ESRD and severe hyperparathyroidism.⁶⁷

Elevated PTH levels are also associated with CVD. Animal models indicate that high PTH levels can induce intense medial calcification independent of uremia or hyperphosphatemia.⁶⁸ In addition, significant myocardial hypertrophy is observed in animal CKD models, where PTH activates protein kinase C of cardiomyocytes and leads to hypertrophic growth and re-expression of fetal-type proteins.⁶⁹ Furthermore, PTH has been characterized as a permissive factor in the development of interstitial fibrosis in myocardial tissue.⁷⁰ These findings from animal studies are consistent with clinical observations that dialysis patients who underwent total or subtotal parathyroidectomy experienced improved left-ventricular function.⁷¹ For these reasons, it is important to manage secondary hyperparathyroidism

aggressively in the CKD population using current Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines.

CKD progression and mortality in CKD/ESRD

Vitamin D may prevent nephrosclerosis and delay CKD progression through its anti-inflammatory and antiproliferative properties. In a subtotal nephrectomy animal model,⁷² treatment with 1,25(OH)₂D led to significantly less glomerulosclerosis and albuminuria, independent of PTH. Both vascular and tubular expressions of transforming growth factor (TGF)- β were significantly reduced in the animals treated with vitamin D.⁷² In patients with CKD stage 3-5, treatment with calcitriol was associated with a trend toward a lower incidence of dialysis initiation;⁷³ another similar study⁷⁴ in patients with stage 2-5 CKD found that those with higher baseline 25(OH)D levels had significantly better renal survival, independent of other risk factors associated with progressive kidney diseases, such as age, body-mass index, heart disease, diabetes, or proteinuria.

CVD is the leading cause of mortality in patients with advanced CKD and, given the CV benefits, adequate vitamin D is associated with prolonged survival in this unique patient population.^{73,74} Observational studies demonstrated a similar survival advantage with vitamin D therapy among ESRD patients on hemodialysis.⁷⁵⁻⁷⁸ In a retrospective analysis of incident hemodialysis patients, Teng et al⁷⁶ reported a 20% 2-year survival advantage for patients who received intravenous vitamin D therapy versus those who did not. Wolf et al⁷⁹ also demonstrated a similar survival advantage over 90 days with adequate vitamin D levels among incident dialysis patients, and noted significant interactions between vitamin D levels, subsequent active vitamin D therapy, and survival; untreated deficient patients were at significantly increased risk for early mortality.

Role of 25-hydroxyvitamin D

The unique actions of 25(OH)D are suggested to be independent of 1,25-(OH)₂D and may have direct physiological effects on bone health. Exposure to 25(OH)D can lead to increased intestinal calcium and phosphate transport,^{80,81} and increased renal calcium and phosphate reabsorption independent of 1,25(OH)₂D.⁸² Osteomalacia, for example, was found only in those CKD patients with relatively low levels of 25(OH)D, and bony mineralization improved after intravenous repletion.⁸³ In dialysis patients, 25(OH)D was independently linked to PTH, and was the only parameter associated with radiological bone disease independent of 1,25(OH)₂D.⁸⁴ 25(OH)D provides an important substrate for 24,25(OH)₂D, which has been shown to have independent effects on reduction of bone resorption,⁸⁵ 25(OH)D is also able to use VDR-independent pathways (eg, protein kinase A) for intracellular signalling.⁸⁶ Finally, an adequate store of 25(OH)D is necessary for autocrine/paracrine actions in tissues expressing 1 α -hydroxylase.

Under normal circumstances, the synthesis of 1,25(OH)₂D is not substrate (25[OH]D) dependent; however, in CKD patients, renal 1 α -hydroxylase becomes substrate (25[OH]D) dependent,² and a higher concentration of precursor 25(OH)D is likely needed to reach adequate 1,25(OH)₂D levels.

Vitamin D therapy in CKD

Since vitamin D deficiency or insufficiency is highly prevalent, especially in patients with CKD, it should be managed aggressively even in early CKD. Vitamin D supplementation with either ergocalciferol or cholecalciferol has been recommended to restore and maintain adequate vitamin D status before resorting to the use of the highly potent active vitamin D sterol. Nutritional causes of low serum 25(OH)D should be established in all CKD patients, and malnutrition should be corrected with a multidisciplinary approach. For many patients with mild vitamin D deficiency, 8 weekly doses of ergocalciferol (50 000 U) will raise serum 25(OH)D to normal levels,⁸⁷ but total repletion will take longer in patients with severe deficiency or those with nephrotic-range proteinuria.

If serum PTH levels fall into the desirable range, therapy with additional hydroxylated vitamin D sterol will be unnecessary; however, if PTH levels remain elevated, active vitamin D therapy should be considered. Dihydroxylated vitamin D compounds (calcitriol, paricalcitol) or 1 α -hydroxylated analogs are commonly used in patients with CKD. Oral calcitriol is most commonly used; low doses (0.125–0.25 μ g/day) are usually well tolerated, but the risks of hypercalcemia, hyperphosphatemia, and/or hypercalciuria are increased with higher doses or as GFR declines.⁸⁸ Overall, its use is limited by a low therapeutic index and concerns regarding acceleration of kidney disease, ectopic calcification, and increased risk of cardiac death. Alfacalcidol is also effective in lowering PTH and increasing bone mineral density in CKD patients beyond stage 2; however, a significant 3% increase of serum calcium was noted in the alfacalcidol group (versus control).⁸⁹ Doxercalciferol was also tested in a randomized, controlled trial,⁹⁰ in patients with stage 3 or 4 CKD and intact PTH levels >85 pg/mL. At a starting dose of 1 μ g/day (maximum 5 μ g/day), doxercalciferol led to a 46% reduction of serum PTH levels after 6 months of treatment; there were no significant increases in serum or urine calcium, and serum phosphorus when compared with the control. Oral paricalcitol is the most promising vitamin D analog on the market, achieving its site selectivity via selective side chain modifications. It can be dosed daily at a starting oral dose of 1 μ g in individuals with PTH <500 pg/mL and 2 μ g in individuals with PTH >500 pg/mL; thrice-weekly dosing is also highly effective.⁹¹ Randomized trials have demonstrated that paricalcitol leads to effective suppression of PTH; furthermore, there were no significant differences between oral paricalcitol and placebo in the incidence of hypercalcemia, hyperphosphatemia, or elevated

calcium-phosphorus products.⁹² To date, no direct comparison has been performed between different vitamin D preparations in patients with CKD. Alfacalcidol and doxercalciferol appear to have safer side-effect profiles than calcitriol in stages 3 and 4 CKD, although they both produce higher rates of urinary calcium excretion than paricalcitol.⁹³ In addition, paricalcitol appears to have lower phosphatemic effects than doxercalciferol,⁹³ which is important, since high serum phosphate has been associated with reduced life expectancy in patients with compromised renal function.⁹⁴

Vitamin D therapy in ESRD

When compared with early CKD patients, those on dialysis are more likely to have low levels of 25(OH)D because of inactivity, uremia, poor oral intake, and compromised endogenous synthesis of vitamin D₃. Assumptions that 1 α -hydroxylase is significantly reduced in dialysis patients due to reduced renal mass and uremia, and that 25(OH)D will never be able to maintain adequate 1,25(OH)₂D despite high doses, allow many nephrologists to ignore 25(OH)D levels and concentrate on monitoring 1,25(OH)₂D and its replacement. Both ergocalciferol and cholecalciferol have proven effective in raising serum 1,25(OH)₂D levels in dialysis patients;^{95,96} however, despite positive findings with 25(OH)D, success is often suboptimal for raising 1,25(OH)₂D levels to goal and suppressing secondary hyperparathyroidism in dialysis patients.⁹⁷ There is also concern about possible hypercalcemia with prolonged use of either ergocalciferol or cholecalciferol.⁹⁸ Given resistant hyperparathyroidism in dialysis patients, active vitamin D therapy is often needed; both oral and intravenous pulse calcitriol are effective, but have been associated with hypercalcemia and hyperphosphatemia.⁹⁹ Data on intravenous paricalcitol suggest that this vitamin D analog is more effective in suppressing PTH in the dialysis population; it provides safer effects on calcium and phosphorus levels and is associated with improved morbidity and life expectancy compared with calcitriol.¹⁰⁰⁻¹⁰² Intravenous doxercalciferol is also effective in suppressing PTH, although like calcitriol, significant elevations in serum calcium and phosphorus have been noted.¹⁰³

Conclusion

Vitamin D is increasingly recognized for its important actions on a variety of organ systems with evidence of survival benefits, especially in those with compromised renal functions. It is important to monitor vitamin D status in patients with CKD, and the serum 25(OH)D levels should be maintained >30 ng/mL to maximize the beneficial effects of vitamin D on health. Several vitamin D preparations are effective and have excellent safety profiles; in particular, paricalcitol is associated with improved morbidity and prolonged survival in dialysis patients, but the long-term effects of its oral preparation in patients with CKD (predialysis) have yet to be studied. Despite progress made in under-

standing the biology and clinical implications for vitamin D, many recommendations in the current guidelines must be tested for evidence-based practice, and large-scale randomized, controlled trials are needed.

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