Management of Vitamin D in Chronic Kidney Disease

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ABSTRACT

Vitamin D plays a vital role in numerous physiological processes, including immune function, cardiovascular health, and bone maintenance. The adequacy of its status has been strongly associated with morbidity and mortality across diverse populations, particularly among individuals with chronic kidney disease (CKD). Given the kidneys' critical role in vitamin D metabolism and homeostasis, deficiency is highly prevalent in this population and has been linked to adverse outcomes and poor survival. In this review, we provide a comprehensive overview of vitamin D, its sources, metabolism, physiological actions, and clinical management of its deficiency or insufficiency, with a specific focus on patients with CKD.

KEYWORDS: Vitamin D; CKD; end-stage kidney disease; dialysis; mortality

INTRODUCTION

Vitamin D plays a critical role in mineral metabolism, immune regulation, and cardiovascular health, and its dysregulation is particularly relevant in the context of chronic kidney disease (CKD).[1] As kidney function declines, multiple disruptions in vitamin D metabolism occur, resulting in altered calcium-phosphate homeostasis, elevated parathyroid hormone (PTH), and adverse cardiovascular and renal outcomes. Understanding the physiology of vitamin D, its unique actions in CKD, and available therapeutic strategies is crucial for optimizing the care of CKD patients.

VITAMIN D: FORMS AND METABOLISM

Vitamin D refers to a group of fat-soluble secosteroids, primarily vitamin D_3 (ergocalciferol), derived from plant sources, and vitamin D_3 (cholecalciferol), synthesized in the skin upon exposure to ultraviolet B radiation.[2] Both forms are biologically inactive and undergo sequential hydroxylation to become active. Following absorption or cutaneous synthesis, vitamin D is stored in adipose tissue and the liver, where it is first hydroxylated by hepatic 25-hydroxylase to 25-hydroxyvitamin D [25(OH)D], the major circulating and storage form.[3] It then binds with vitamin D-binding protein and is delivered to the kidneys, where, after glomerular filtration, it is picked up by proximal tubular cells with help of megalin receptor. It is then further hydroxylated by 1α-hydroxylase to produce 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], the hormonally active form,[4] and is released into the circulation. In addition to renal synthesis, extrarenal tissues—including immune cells, the parathyroid glands, and vascular smooth muscle—express 1α-hydroxylase, enabling local production of $1,25(OH)_2D$ for autocrine and paracrine signaling.[5] The degradation of both 25(OH)D and $1,25(OH)_2D$ is regulated by 24-hydroxylase, which initiates their conversion into inactive calcitroic acid derivatives, thereby maintaining metabolic balance.[6]

ACTIONS OF VITAMIN D IN CKD

Although nongenomic signaling via cell membrane receptor remains to be fully elucidated,[7] the diverse physiological actions of vitamin D are primarily mediated through the vitamin D receptor (VDR), a nuclear receptor present in numerous tissues, including the kidneys, intestines, bones, vessels, and immune system.[8] Upon ligand binding, VDR forms a heterodimer with the retinoid X receptor and modulates the gene transcription involved in calcium absorption, bone turnover, cell proliferation, and cytokine regulation. These actions span endocrine, autocrine, and paracrine pathways, making vitamin D functionally versatile. While the primary effects of vitamin D involve maintaining mineral homeostasis via its action on the intestine (to increase calcium and phosphate absorption), bone (to regulate remodeling), and parathyroid glands (to suppress PTH), emerging clinical evidence highlights its broader relevance in cardiovascular protection, immune modulation, and survival.[9] Observational studies have linked adequate vitamin D status with improved all-cause mortality and reduced cardiovascular events in the general population, reinforcing its potential utility in high-risk groups such as those with CKD.[10]

Bone mineral metabolism

Reduced vitamin D activity along with hypocalcemia and hyperphosphatemia lead to secondary hyperparathyroidism. Animal studies have shown that elevated PTH levels in CKD lead to bone loss, vascular calcifications (VC),[11] and

suppression of erythropoiesis, contributing to anemia.[12] In humans, although most patients with CKD are asymptomatic, uncontrolled hyperparathyroidism can adversely affect bone, muscle, and tendon, leading to pain, tendon rupture, or bone fractures. It may also cause calciphylaxis, neurotoxicity, and pruritus.[13]

Hyperparathyroidism secondary to CKD is characterized by parathyroid gland hyperplasia and elevated PTH levels.[14] Elevated PTH can increase vitamin D levels by stimulating the activation enzyme 1-α hydroxylase and inhibiting the degradation enzyme 24-hydroxylase.[15] This response is insufficient to restore vitamin D adequacy. Moreover, the progressive loss of VDR further compromises the inhibitory effect of $1,25(OH)_2D$ on PTH synthesis.[14] To date, there is no conclusive evidence showing a complete reversal of these pathological processes in parathyroid gland or bone through vitamin D therapy. However, Fukagawa et al[16] demonstrated a regression in parathyroid gland volume measured by ultrasound, after 12 weeks of treatment with 4 µg of oral calcitriol administered twice weekly in nine patients on hemodialysis. Additionally, Andress et al[17] have shown an improvement in bone histology among 10 hemodialysis patients treated with a mean dose of 0.28 µg calcitriol for 12 months.

HYPERTENSION AND CARDIOVASCULAR OUTCOMES

Renin-Angiotensin-Aldosterone System (RAAS)

Renin-Angiotensin-Aldosterone System (RAAS) plays a key role in both the control of blood pressure and target-organ damage, especially in the heart and kidneys. Its dysregulation, which is highly prevalent in CKD, can lead to hypertension,[18-20] heart failure,[18,20] and CKD progression.[21-23] Vitamin D has a direct negative effect on RAAS activity.[24] This effect is likely mediated via plasma renin activity (PRA). Using a promoter-linked luciferase reporter assay, Yuan et al[25] showed a direct inhibition of renin gene transcription by $1,25(OH)_2D$. Indeed, animals lacking vitamin D 1α-hydroxylase gene exhibited elevated PRA, which could be normalized following $1,25(OH)_2D$ administration.[26] In human subjects with hypertension, a continuous negative correlation exists between plasma $1,25(OH)_2D$ levels and PRA.[27] However, existing prospective interventional trials failed to confirm a causal relationship.[28] It is likely that, in humans, the effect of vitamin D on renin is confounded by the individual variations in comorbid conditions and vitamin D metabolism.

Vascular health

Endothelial dysfunction promotes inflammation, contributes to hypertension and is a significant risk factor for cardiovascular diseases.[29-31] Studies have shown that as kidney function declines, there is a progressive worsening of flow-mediated dilatation and increased intima-medial thickness, indicating more severe endothelial dysfunction in patients with CKD.[32] Both endothelial cells and smooth muscle cells are key cell types to maintain vascular health and function, and they possess both 1α-hydroxylase and VDR locally, allowing autocrine, paracrine and endocrine actions of vitamin D.

Vitamin D regulates nitric oxide (NO) bioavailability, promotes its release, and supports endothelial cell survival, proliferation, and angiogenesis.[33] This is particularly relevant in CKD where NO activity is markedly diminished. Animal studies have demonstrated that vitamin D deficiency impairs NO-mediated endothelial dilation,[34] while vitamin D supplementation can improve endothelial function.[35,36] Similarly, in humans, low serum 25(OH)D levels have been associated with endothelial dysfunction in patients with CKD.[37] Clinical trials using cholecalciferol have demonstrated improvements in endothelial function in this population.[38] These findings were further supported by a recent umbrella review of interventional meta-analyses.[39]

In addition to its effects on nitric oxide, vitamin D is also a potent modulator of oxidative stress[40] —another key pathogenic factor contributing to endothelial dysfunction and tissue inflammation, particularly in patients with CKD. Vitamin D supplementation has been shown to reduce oxidative biomarkers such as malondialdehyde and advanced oxidation protein products via enhancing endogenous antioxidant defenses—including glutathione, superoxide dismutase, and catalase.[41,42] Although a single, high-dose administration of vitamin D has not been effective in reducing oxidative stress in healthy individuals, sustained supplementation in populations with a high-oxidative stress burden—such as those with CKD or diabetes—has been associated with decreased lipid peroxidation and improved antioxidant capacity.[43]

CKD PROGRESSION

Renal inflammation

In CKD, alongside endothelial activation, there is an increased release of pro-inflammatory chemokines mediated by nuclear factor-κB (NF-κB), which is predominantly activated in the renal mesangium.[44,45] Therefore, chronic inflammation is highly prevalent in patients with CKD and is associated with both cardiovascular effects and renal fibrosis. Chronic inflammation also stimulates FGF 23, and they are both independently associated with risk of death.[46] FGF 23 signaling requires Klotho, an essential co-factor, which is downregulated in CKD, leading to FGF 23 resistance in the kidney. This further downregulates vitamin D production by inhibiting 1α-hydroxylase, and increases its catabolism via upregulation of 24-hydroxylase.[47] Vitamin D deficiency upregulates TNF alpha-converting enzyme, further suppressing Klotho, and worsening FGF 23 resistance, which leads to a vicious cycle of inhibition of vitamin D activation.[48]

Animal studies have demonstrated an inverse relationship between blood vitamin D levels and the accumulation of macrophages and T cells in the renal cortex.[49] Treatment with vitamin D[45,50,51] and its analogs[52] suppresses NF-κB, T cell proliferation and stimulates anti-inflammatory cytokines. Paricalcitol also improves thrombomodulin level, which optimizes endothelial response to inflammation.[53]

Renal fibrosis

Renal fibrosis is a hallmark of progressive CKD and is characterized by myofibroblast recruitment or formation via epithelial-mesenchymal transition (EMT), primarily mediated by transforming growth factor β (TGFβ).[54,55] In addition to its anti-inflammatory and RAAS-regulating effects, active vitamin D inhibits partial or complete renal EMT, myofibroblast activation, renal EMT, and subsequent extracellular matrix production. It has been shown that pretreatment with active vitamin D inhibits indoxyl sulfate-induced EMT in human tubular epithelial cells via Akt and β-catenin pathway.[56] In an animal model of diabetic nephropathy, vitamin D was also shown to shift macrophage activity from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, reducing inflammation and fibrosis.[57] Therefore, existing evidence supports the notion that achieving adequate levels of vitamin D is important for the preservation of normal kidney structure and function.

Integrity of podocytes and renal tubular cells

Podocytes, a highly specialized cell population essential for maintaining the glomerular filtration barrier, are frequently injured in various glomerular diseases. Maintenance of these healthy podocytes requires adequate vitamin D.[58] Studies have shown that active vitamin D inhibits both transient receptor potential cation channel C6 (TRPC6), a slit diaphragm protein upregulated in proteinuric kidney diseases, and urokinase-type plasminogen activator receptor (uPAR), a protein critical in foot process effacement.[59,60] In addition, in vitro and animal studies[61] utilizing a mouse model of diabetic nephropathy have demonstrated that autophagy, which is beneficial for podocyte health, is regulated by VDR. Vitamin D enhances autophagosome formation via VDR, whereas autophagy is downregulated in VDR knockout mice. Furthermore, active vitamin D inhibits apoptosis[62] via the RAAS, Wnt/β-catenin[58] or phosphatidylinositol 3-kinase (PI3K)/Akt-signaling[63] pathway and restores podocyte morphology.[64] Taken together, podocyte represents one of many key targets for the protective effects of vitamin D in CKD.

Renal tubular epithelial (RTE) cells are another specialized, highly metabolic cell population that are crucial for proper kidney function. Rich in mitochondria, a key organelle for vitamin D metabolism in the proximal nephron, renal tubular epithelial cells are particularly susceptible to injury resulting from mitochondrial dysfunction. Vitamin D plays a critical role, both directly and indirectly, in preserving mitochondrial integrity. It enhances the production of potent antioxidant enzymes and strengthens the defense against reactive oxygen species,[65] promotes adaptive responses to endoplasmic reticulum stress, and supports mitophagy—an essential process for the removal of damaged mitochondria.[66]

VITAMIN D DEFICIENCY IN CKD

Vitamin D deficiency is defined based on the serum levels of 25(OH)D. Kidney Disease Outcomes Quality Initiative (KDOQI) defines vitamin D deficiency when the level is below 20 ng/mL, and vitamin D insufficiency when level is between 20–29 ng/mL.[67]

In the U.S., 28.9% of adults are vitamin D deficient, as per the National Health and Nutrition Examination Survey (NHANES), with an additional 41.4% being insufficient.[68] However, due to the dietary restriction, reduced sun exposure, and reduced conversion of 25(OH)D to 1,25$(OH)_2$D, the prevalence of vitamin D deficiency is higher in the CKD population and increases with each increasing stage of CKD.[69] The prevalence of vitamin D deficiency has not been reported in CKD or ESKD patients, but studies have estimated between 30% and 86% of patients to be vitamin D deficient.[70-74]

Multiple metabolic changes lead to vitamin D deficiency in CKD patients. First, limited sun exposure, malnutrition, reduced renal mass, decreased megalin expression in proximal tubular cells,[75] and loss of vitamin D binding protein due to proteinuria, lead to lower levels of 25(OH)D. Moreover, the conversion of 25(OH)D to its active form, 1,25$(OH)_2$D, is markedly impaired due to reduced nephron mass, tubular dysfunction and elevated fibroblast growth factor 23 (FGF 23), while vitamin D catabolism is accelerated due to increased 24-hydroxylase activity.[76] Therefore, it is common to observe deficiencies in both vitamin D stores and the active form, 1,25$(OH)_2$D, in patients with CKD

VITAMIN D THERAPY

Nutritional forms of vitamin D

Nutritional forms include vitamin D2 or ergocalciferol and vitamin D3 or cholecalciferol. Even though both forms may be absorbed equally well,[77] vitamin D2 binds to D-binding protein with lesser affinity and has a shorter half-life compared to vitamin D3.[78] This results in vitamin D3 being more effective in raising 25 (OH) D levels, which reflects total body vitamin D stores.[78] In fact, Wetmore et al[79] showed that cholecalciferol, when compared to ergocalciferol, was more effective in raising 25 (OH) D levels in patients with CKD stage 3-5 and serum 25 (OH) D levels below 30ng/ml. They were equally effective in raising 1,25 $(OH)_2$ D and in suppressing PTH levels. Despite animal and human retrospective studies showing clinical efficacy, prospective

interventional studies utilizing nutritional vitamin D agents have yielded mixed results.

PTH-lowering effect of nutritional vitamin D in CKD is well known, but the degree of effectiveness varies with studies, showing that it may not be as effective in advanced CKD, or when PTH level is significantly elevated.[80] Westerberg et al[81] supplemented 8000 units per day cholecalciferol for 12 weeks in 95 patients with CKD stage 3–4 and found a reduction in PTH in the treated group, while PTH level increased in the placebo group. Ergocalciferol supplementation has similar effects. Al-Aly et al[82] retrospectively studied 66 patients with CKD stage 3-4 and vitamin D insufficiency who received 50,000 units ergocalciferol weekly for 12 weeks and noted an improvement in PTH level (from 231 to 192 pg/mL, p<0.05). A recent meta-analysis confirmed this effect.[83] However, pooled data from four randomized controlled trials (RCTs), including 122 pre-dialysis CKD patients, did not find significant PTH lowering effect in nutritional vitamin D treated group compared to placebo. In fact, no PTH lowering effect was observed even among 568 dialysis patients from seven RCTs.[84]

Effect on albuminuria has also been mixed. Molina et al[85] randomly selected 101 patients with CKD stage 3–4 with at least 30mg/g of albuminuria and PTH level >70pg/mL to receive 666 IU/day cholecalciferol. A significant improvement in albuminuria (284mg/g to 167mg/g, p<0.001) occurred in the treatment group after six months. Susantitaphong et al[86] reported similar benefit of ergocalciferol. However, a large RCT by de Boer,[87] which included 1312 diabetic patients with CKD stage 2 or earlier, showed no effect on albuminuria reduction.

Among the dialysis population, nutritional vitamin D supplementation has not been shown to improve cardiac function or survival.[88,89]

Semi-active agents

Semi-active agents such as calcifediol (25-OH D3) bypass the 25-hydroxylation step and can be used in patients with liver disease. Others such as alfacalcidiol (1α-(OH) D3) and doxercalciferol (1α-(OH) D2) are synthetic prodrugs that bypass renal 1-hydroxylation and are activated by hepatic 25-hydroxylation.

Calcifediol (25-hydroxyvitamin D3) is a semiactive precursor of calcitriol. Russo et al[90] demonstrated an increase in 25 (OH) D levels within seven days of administration of calcifediol, and two RCTs conducted in vitamin D-deficient, post-menopausal women demonstrated a consistent benefit in raising 25 (OH) D levels when compared to cholecalciferol, where calcifediol was more effective and faster than cholecalciferol.[91,92] Calcifediol also had a higher rate of absorption and can be used in patients with malabsorptive states.[93] Subsequent studies have confirmed these findings in other patient populations.[94,95]

Furthermore, the effect of calcifediol on PTH has shown consistent benefits. For example, Germain et al[96] compared calcifediol, nutritional, and active vitamin D among 376 CKD stage 3–4 patients with vitamin D insufficiency and secondary hyperparathyroidism, and observed that only calcifediol reduced PTH and was not associated with hypercalcemia. Similarly, Sprague et al[97] demonstrated efficacy of calcifediol in a small CKD population with secondary hyperparathyroidism and vitamin D insufficiency, and subsequently[98] confirmed the findings in a larger cohort. They randomized 429 patients with CKD stage 3-4 vitamin D insufficiency and secondary hyperparathyroidism to receive 30 µg or 60 µg daily for 26 weeks and, when compared to placebo, were noted to have a significant reduction in level of PTH (p<0.001). Furthermore, response rates increased with duration of treatment and were independent of CKD stages. A post-HOC analysis of two RCTs involving 126 patients not only showed a consistent PTH lowering effect but also demonstrated a slower GFR decline in patients who achieved at least 30% reduction in PTH levels.[99]

There have been no studies on the effect of calcifediol on survival in the pre-dialysis CKD population, and most studies have combined different vitamin D formulations. However, among those on dialysis, the use of calcifediol did not appear to carry a survival benefit. In a phase III multicenter, randomized, open-label trial involving 284 adults on hemodialysis with vitamin D insufficiency, 24-month calcifediol supplementation did not reduce all-cause or cardiovascular mortality.[100] Similarly, use of other semi-active compounds also failed to show any significant benefit in cardiovascular or all-cause mortality.[101]

Doxercalciferol (1α-hydroxy D2) is another semiactive agent and a synthetic analog of ergocalciferol which is activated with hepatic hydroxylation and has been shown to increase $1,25(OH)_2D$ levels effectively.[102] It has shown consistent PTH lowering benefits among CKD population, including patients on hemodialysis. For example, Coburn et al[103] noted a 46% reduction in PTH after 24 weeks of titrating doxercalciferol among 55 patients with stage 3–4 CKD and secondary hyperparathyroidism. Similarly, Frazao et al[104] randomized 138 patients on hemodialysis to receive 10 µg doxercalciferol at each session, with dose adjusted to maintain PTH between 150–300 pg/ml. They found that PTH reduced to 44% of baseline value after 16 weeks of open-label treatment in the two groups, but only the treatment group showed persistent suppression. Yang et al[105] recently confirmed this finding with intravenous formulation. However, a survival benefit has not been noted, especially among the hemodialysis population.[106]

Active agents

$1,25(OH)_2D$ is also available as active agents like calcitriol for use in CKD patients, as it bypasses both hydroxylation steps in the liver and kidneys. Paricalcitol (19-nor-$1,25\ (OH)_2$ D2) is an analog which is widely used in the U.S. Several

others are available for use in certain countries, such as oxa-calcitriol (22-oxa-1,25$(OH)_2$ D3), falecalcitriol (1,25 $(OH)_2$-26,27-F6 D3), and eldecalcitol (2α- (3-hydroxypropoxy)-1,25 $(OH)_2$ D3).[107]

Clinical studies using active agents have demonstrated some benefits in CKD patients. For instance, Ritz et al[108] randomized 45 patients with CKD to receive 0.125 µg per day of calcitriol and noted that PTH levels were lower in this group compared to placebo. Subsequently, Isakova et al[109] demonstrated that supplementing 0.25 µg calcitriol daily for one week reduced PTH levels among 12 patients with CKD stage 3–4. Similar benefits of calcitriol have been demonstrated among patients with ESKD on hemodialysis.[110,111]

Calcitriol has also been shown to reduce albuminuria in pre-dialysis CKD patients. For example, Szeto et al[112] enrolled 10 patients with biopsy-proven IgA nephropathy already on ACEi or ARB to receive 0.5 µg twice weekly oral calcitriol for 12 weeks and noted a reduction in albuminuria (–0.26 g/g, 95% CI, –0.03 to –0.49). While this study lacked a control arm, Liu et al[113] subsequently confirmed this finding by random allocation of 50 patients with IgA nephropathy to receive similar dose of oral calcitriol or placebo for 48 weeks.

The effect of calcitriol on cardiovascular outcomes has been inconclusive. Gnudi et al[114] randomized 55 patients with CKD stage 3 and type 2 diabetes mellitus to receive 0.5 µg calcitriol daily or placebo and measured left ventricular mass with an MRI at baseline and at 48 weeks of treatment. However, they did not find a significant difference between the treatment arm and the placebo arm (median difference 1.84, 95% CI: –1.28–4.96). Similarly, no effect was noted on vascular stiffness after treatment with calcitriol.[115-117] However, calcitriol supplementation has been shown to lead to a reduction in myocardial hypertrophy in ESKD patients on hemodialysis.[118,119]

The potential benefit of calcitriol must be carefully weighed against the risks of hypercalcemia, hyperphosphatemia, and ectopic calcifications. In a study by Coyne et al[120] involving patients with stage 3–4 CKD and secondary hyperparathyroidism who received 0.25 µg of calcitriol daily, 1 out of 54 patients developed hypercalcemia (calcium >10.5mg/dl) and 28 patients developed hyperphosphatemia (phosphorus >4.5mg/dl). Among patients undergoing hemodialysis, calcitriol has been associated with a higher incidence of hypercalcemia. A study by Maxwell et al[121] randomized 22 hemodialysis patients to receive either 0.5 µg calcitriol daily or vitamin D3 and reported a peak calcium of 13.2mg/dl in 2 out of 13 patients. While calcitriol use has been linked with ectopic calcifications in animal studies, this has not been confirmed in human clinical studies.[122,123]

While an inverse relationship between vitamin D levels and mortality has been observed,[124-129] studies on supplementation with active vitamin D analogs have reported inconsistent results. In a study of 520 patients with CKD stage 3–5, supplementing with 0.25 µg/d to 0.5 µg/d of calcitriol was associated with a lower risk of progression to ESKD, the need for dialysis, and a lower risk of death.[130] Furthermore, Shoben et al[131] demonstrated that even lower doses of calcitriol (<0.25 µg/d–0.25 µg/d) in 1418 patients with CKD stage 3–4 were still associated with a 26% reduction in the risk of death (p = 0.016) and a 20% reduction in the combined risk of death or dialysis (p = 0.038). However, a recent meta-analysis which included 11,270 participants failed to corroborate the cardiovascular or all-cause mortality benefit of vitamin D supplementation.[132]

Similar to calcitriol, paricalcitol has also been shown to have beneficial effects on the bone mineral axis, CKD progression, and survival. It effectively reduces PTH levels among both CKD and hemodialysis patients. In the PENNY trial,[133] 88 patients with CKD stage 3–4 were randomized to receive 2 µg/d paricalcitol or placebo for 12 weeks. Paricalcitol was effective in reducing PTH (–75.1 pg/mL, 95% CI: –90.4 to –59.8; p <.001). These findings were also confirmed in head-to-head comparisons with both ergocalciferol[134] and calcitriol.[120] In a meta-analysis of nine RCTs including 832 patients with CKD stages 2–5, paricalcitol significantly suppressed PTH compared to placebo (risk ratio 6.37; 95% CI, 4.64–8.74; P<0.001).[135] Similar PTH lowering effect was demonstrated in a meta-analysis in patient on hemodialysis.[136]

Additionally, paricalcitol also has a protective effect on proteinuria. Agarwal et al[137] randomly selected 220 patients with CKD stage 3–4 to receive 9.5 µg/week of oral paricalcitol for 24 weeks. The results demonstrated a qualitative reduction in proteinuria by dipstick compared to placebo. Several studies have since corroborated their results, demonstrating similar benefits quantitatively in the CKD population,[138,139] and in patients with diabetic nephropathy.[140] De Borst et al[141] also conducted a meta-analysis on 688 patients from six studies who were on ACEi or ARB. Four of these studies utilized paricalcitol, while the other two utilized calcitriol. There was a 16% reduction in proteinuria among patients treated with active vitamin D compared to the control. There was no significant difference based on drug or its dosage used, cause of CKD, or duration of follow-up. A subsequent meta-analysis by Cheng et al[135] included four trials with 469 stage 2–4 CKD patients on ACEi or ARB, who exclusively received paricalcitol as the active vitamin D agent, found that patients treated with paricalcitol were 68% more likely to achieve at least a 10% reduction in proteinuria compared to control or placebo (RR 1.68; 95% CI, 1.25–2.25; P<0.001).

The effect of paricalcitol on cardiovascular health and survival has been variable. While Zoccali et al[142] did find a beneficial effect of paricalcitol on endothelium function, there have been no beneficial effects demonstrated on left ventricle mass or hypertrophy. For example, the PRIMO trial[143] randomized 227 patients with CKD stages 3–4 and mild to

moderate left ventricular hypertrophy to receive 2 µg daily paricalcitol versus placebo for 48 weeks, but did not notice a reduction in left ventricular mass. Similarly, the OPERA trial[144] did not find a beneficial effect of paricalcitol on left ventricular mass. Regardless of these effects on surrogates of cardiovascular disease, a meta-analysis combining seven clinical trials on paricalcitol and calcitriol by Li et al[145] did show a reduction in cardiovascular events (RR 0.27; 95% CI, 0.13–0.59). Furthermore, a meta-analysis comparing paricalcitol to other vitamin D agents demonstrated better survival in the paricalcitol-treated CKD patents (HR, 0.95; 95% CI, 0.91–0.99; P <0.001).[146]

Among dialysis patient, paricalcitol has been associated with a lower risk of death.[147] In fact, patients given paricalcitol have been shown to have better survival outcomes even when compared to calcitriol.[146] Teng et al[148] conducted a retrospective review of 69,492 patients on hemodialysis who received either paricalcitol or calcitriol, and noted that there were 3417 deaths among the paricalcitol group as compared to 6805 deaths among those that received calcitriol (rate ratio: 0.80, 95%CI 0.77–0.84, p<0.001). Although a subsequent study did not find such benefit,[106] a recent meta-analysis[136] involving four observational studies again showed improved survival (pooled HR of 0.86 (95% CI 0.80–0.91; p < 0.00001).

With regard to the adverse effects, paricalcitol appeared to carry less risks of hypercalcemia or hyperphosphatemia. In a study of 53 patients with stage 3–4, there was no increased risks of hypercalcemia or hyperphosphatemia when compared to placebo.[120,149] Other studies utilizing paricalcitol in hemodialysis patients also demonstrated a reduction in PTH levels without causing hypercalcemia or hyperphosphatemia.[150]

CONCLUSION

Vitamin D has myriad effects in the general population, especially in patients with CKD, via its role in calcium, phosphorus, PTH, and FGF 23 metabolism, along with its effect on albuminuria, inflammation, vascular health, morbidity, and mortality. Supplementation of vitamin D or its analogues can be beneficial in the CKD population regardless of dialysis dependency. However, conclusive evidence demonstrating its impact on key clinical outcomes, particularly survival, remains limited. Large-scale, well-designed prospective trials are needed to clarify the role of vitamin D supplementation on hard outcomes in patients with CKD and ESKD.

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