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Vitamin D supplementation in chronic kidney disease; effects on proteinuria, disease progression, and cardiovascular outcomes

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ABSTRACT

Chronic kidney disease (CKD) is commonly accompanied by vitamin D deficiency, largely due to impaired renal conversion of 25-hydroxyvitamin D [25(OH)D] to its biologically active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. In addition to its classical role in calcium–phosphate homeostasis and bone metabolism, vitamin D exerts multiple extra-skeletal effects, including modulation of renal function, cardiovascular health, and endocrine pathways, primarily through activation of the vitamin D receptor (VDR) and suppression of the renin–angiotensin–aldosterone system (RAAS). This narrative review synthesizes current evidence on the impact of vitamin D supplementation encompassing nutritional forms (cholecalciferol and ergocalciferol) and active or analog forms (calcitriol, paricalcitol, and calcifediol) on proteinuria, CKD progression, and cardiovascular outcomes. A targeted literature search was conducted across PubMed, Web of Science, Scopus, DOAJ, and Google Scholar. Evidence from multiple randomized trials and meta-analyses indicates that active vitamin D analogues, particularly paricalcitol, are associated with consistent reductions in proteinuria among patients with CKD. Nutritional vitamin D, especially cholecalciferol, has also demonstrated potential antiproteinuric effects in selected populations. Observational data consistently show that vitamin D deficiency is independently associated with accelerated decline in estimated glomerular filtration rate (eGFR) and increased risk of progression to end-stage renal disease (ESRD); however, interventional studies have not conclusively demonstrated that vitamin D supplementation slows CKD progression. Similarly, while observational studies link low vitamin D levels with increased cardiovascular morbidity and higher mortality, randomized trials have not consistently shown significant improvements in major cardiovascular outcomes. Overall, vitamin D supplementation, particularly active analogues, appears beneficial for proteinuria reduction. Still, its effects on renal disease progression and cardiovascular endpoints remain uncertain, underscoring the need for larger clinical trial studies.

Implication for health policy/practice/research/medical education:
Vitamin D deficiency is common in chronic kidney disease (CKD) due to impaired renal activation. It contributes to adverse renal and cardiovascular outcomes through mechanisms involving vitamin D receptor (VDR) signaling and suppression of the renin–angiotensin–aldosterone system. Evidence that active vitamin D analogues, particularly paricalcitol, consistently reduce proteinuria, while nutritional vitamin D (especially cholecalciferol) may also provide antiproteinuric benefits in selected populations. Studies show that vitamin D deficiency is independently correlated to more decrease in estimated glomerular filtration rate (eGFR) and increased risk of end-stage renal disease (ESRD); however, interventional trials have not conclusively demonstrated that supplementation slows CKD progression. Similarly, although low vitamin D levels are consistently linked to higher cardiovascular morbidity and mortality, randomized evidence has not confirmed significant improvements in major cardiovascular outcomes, highlighting the need for large, well-designed trials with clinically meaningful endpoints.

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Introduction

Approximately 10–14% of adults worldwide are affected by chronic kidney disease (CKD) and is associated with progressive loss of kidney function, excess cardiovascular morbidity, and premature mortality (1-5). Vitamin D deficiency is among the most prevalent and clinically consequential metabolic abnormalities in CKD (5,6). Studies have documented that vitamin D deficiency is associated with the progression from CKD stage 3 to stage 5, with the proportion increasing directly as renal function declines (7). The kidneys play a central role in the activation of vitamin D, converting circulating 25-hydroxyvitamin D [25(OH)D] into the biologically active hormone 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] or calcitriol via the enzyme 1α-hydroxylase. As kidney function deteriorates, this conversion is impaired, creating a vicious cycle in which vitamin D deficiency further accelerates renal injury and exacerbates complications (8,9).

Vitamin D was historically viewed exclusively as a regulator of calcium, phosphate, and parathyroid hormone (PTH) homeostasis, and management of CKD mineral and bone disorder (CKD-MBD) remains a key indication for supplementation (5). However, it is now recognized that virtually every cell in the body expresses the vitamin D receptor (VDR), and that vitamin D governs a remarkably wide range of biological processes relevant to CKD, including suppression of the renin–angiotensin–aldosterone system (RAAS), inhibition of renal fibrosis via the transforming growth factor-β (TGF-β)/Smad pathway, anti-inflammatory effects through nuclear factor-κB (NF-κB) inhibition, and direct modulation of podocyte integrity (10,11). These observations have generated substantial interest in whether vitamin D supplementation can reduce proteinuria, slow disease progression, and improve cardiovascular outcomes in patients with CKD, questions that remain subjects of active investigation (12). This narrative review critically examines evidence from PubMed-indexed peer-reviewed literature on these three domains: effects of vitamin D on proteinuria, on CKD disease progression, and on cardiovascular outcomes, with attention to the type of vitamin D agent used, the CKD stage studied, and the quality of available evidence.

Search strategy

A comprehensive literature search was conducted in PubMed, Web of Science, Scopus, DOAJ, and the Google Scholar search engine to identify relevant studies. The search strategy combined controlled vocabulary and free-text terms related to vitamin D and its various forms, including vitamin D, cholecalciferol, ergocalciferol, calcitriol, paricalcitol, calcifediol, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D, with terms describing chronic kidney disease and related conditions such as CKD, renal insufficiency, and kidney failure. Additional targeted searches were performed to evaluate specific outcomes, including proteinuria (proteinuria, albuminuria, urinary albumin-to-creatinine ratio), CKD progression (estimated glomerular filtration rate [eGFR] decline, end-stage renal disease), and cardiovascular outcomes (left ventricular hypertrophy, cardiovascular mortality, major adverse cardiovascular events) in the context of CKD. Filters were applied to include studies published in English, conducted in human populations, and limited to peer-reviewed articles.

Vitamin D metabolism in CKD; pathophysiology

Disrupted vitamin D activation

The metabolism of vitamin D in CKD is profoundly disrupted at multiple levels. Under normal physiological conditions, dietary and cutaneous synthesized vitamin D_3 undergoes hepatic hydroxylation to 25(OH)D, the primary circulating storage form, before renal conversion to 1,25$(OH)_2$D by 1α-hydroxylase (CYP27B1) (8,9). In CKD, the progressive loss of functional nephron mass reduces CYP27B1 activity, leading to a fall in circulating 1,25$(OH)_2$D levels even when 25(OH)D stores are adequate. As a result, patients with CKD face a dual burden: nutritional deficiency of 25(OH)D (further exacerbated by reduced sun exposure, dietary restrictions, and urinary losses) compounded by impaired renal activation of what 25(OH)D remains (1).

Role of FGF23 and the RAAS

The fibroblast growth factor 23 (FGF23)–vitamin D axis adds another layer of complexity. FGF23, a bone-derived phosphaturic hormone, is an early and potent inhibitor of 1α-hydroxylase; its levels rise progressively with declining GFR, contributing to the suppression of calcitriol synthesis even in the early stages of CKD (13). FGF23 elevation independently predicts adverse outcomes, including ESRD, cardiovascular disease, and left ventricular hypertrophy (LVH) in CKD patients, and paradoxically, active vitamin D compounds stimulate FGF23 secretion, raising concerns about the net clinical effect of these agents in advanced disease (14). Simultaneously, the RAAS is a key target of vitamin D signaling: 1,25$(OH)_2$D acts on the VDR to suppress renin gene transcription, thereby limiting angiotensin II production and its downstream pro-fibrotic, pro-inflammatory, and pro-proteinuric effects. Vitamin D deficiency is thus associated with stimulation of RAAS activity, which in turn perpetuates hypertension, glomerular injury, and CKD progression (15,16).

Anti-fibrotic and anti-inflammatory properties

Active vitamin D inhibits TGF-β_1–mediated signaling, a dominant driver of renal interstitial fibrosis and tubular epithelial-to-mesenchymal transition (17). In experimental models, 1,25$(OH)_2$D and VDR activation preserve E-cadherin expression on tubular epithelial cells, suppress α-smooth muscle actin and fibronectin,

and upregulate hepatocyte growth factor — collectively opposing the fibrogenic program (17,18). By inhibiting the NF-κB pathway, vitamin D suppresses the production of pro-inflammatory cytokines including interleukin-6 and monocyte chemotactic protein-1, and tumor necrosis factor-α, which are central mediators of CKD-associated inflammation and fibrosis. These mechanistic insights provide a strong biological rationale for studying vitamin D interventions as renoprotective strategies in CKD (19).

Effects on proteinuria

Early clinical evidence with active vitamin D

Proteinuria is both a marker of glomerular injury and an independent predictor of CKD progression and cardiovascular events; its reduction is therefore a key therapeutic target. The first formal clinical demonstration that a vitamin D analogue could reduce proteinuria in CKD came from a secondary analysis of a randomized trial by Agarwal et al, in which 51% of paricalcitol-treated patients with CKD and baseline proteinuria showed a reduction in proteinuria compared to only 25% in the placebo (odds ratio 3.2, 95% CI 1.5–6.9). Crucially, this antiproteinuric effect was independent of PTH suppression and of concomitant RAAS blockade, suggesting a direct mechanism beyond PTH-mediated pathways (20).

The VITAL study and paricalcitol in diabetic nephropathy

The landmark VITAL (Selective Vitamin D Receptor Activation for Albuminuria Lowering) trial, conducted by de Zeeuw et al evaluated the antiproteinuric effect of paricalcitol in 281 patients with type 2 diabetes (T2DM) and CKD on background RAAS inhibition. Patients on paricalcitol 2 μg/day showed a −16% change in urinary albumin-to-creatinine ratio compared to −3% of the placebo cohort, with a dose-dependent relationship demonstrating a −18% to −28% sustained reduction in the 2 μg group (vs. placebo). The addition of paricalcitol to RAAS inhibition was safe, with similar rates of adverse events between groups, supporting its potential as an adjunct to standard-of-care treatment (21).

Randomized trials with paricalcitol

Fishbane et al conducted an RCT on CKD patients and proteinuric renal disease, demonstrating that paricalcitol reduced protein excretion by −17.6% versus +2.9% in controls, with a 10% decrease in proteinuria achieved in 57.1% of paricalcitol patients versus 25.9% of controls (22). De Nicola et al studied the add-on antiproteinuric effect of paricalcitol in CKD patients already receiving intensified anti-RAAS therapy: six months of paricalcitol significantly reduced proteinuria from baseline to 0.61 g/24 h (95% CI 0.40–0.93), achieving remission (<0.5 g/24 h) in 37.5% of patients, with a greater effect observed in patients with diabetes, higher GFR, and unrestricted salt intake (23). A placebo-controlled double-blind trial by Oblak et al in kidney transplant recipients further confirmed that 2 μg/day paricalcitol reduced the urine protein-to-creatinine ratio by −39% compared to a +21% increase in the placebo group (24).

Meta-analytic evidence

Meta-analyses have synthesized the available RCT data on paricalcitol and proteinuria. Cheng et al performed a meta-analysis of nine RCTs (832 patients) comparing paricalcitol versus placebo in CKD stages 2–5, reporting that paricalcitol significantly reduced proteinuria (risk ratio [RR] 1.68; 95% CI 1.25–2.25) without significantly increasing the risk of hypercalcemia or cardiovascular adverse effects (25). Han et al's meta-analysis demonstrated that paricalcitol therapy significantly reduced proteinuria compared to placebo in the three trials analyzed (26).

Nutritional vitamin D (cholecalciferol) and proteinuria

Interest in cholecalciferol as an antiproteinuric agent is growing, particularly given its favorable safety profile compared to active analogues. A systematic review by Sharma et al examining five RCTs of native vitamin D supplementation in diabetic kidney disease (DKD) found that four of the five trials reported significant between-group reductions in proteinuria, with improvements also observed in low-density lipoprotein and total cholesterol, though effects on kidney function were mixed (27). In a prospective study of 210 non-dialytic CKD patients, the prevalence of vitamin D deficiency was confirmed to be associated with higher baseline proteinuria, and cholecalciferol 1,000 IU/day successfully repleted 25(OH) D levels without significant adverse effects in most patients (28).

Effects on disease progression

Observational and epidemiological evidence

Epidemiological studies repeatedly demonstrate that vitamin D deficiency is associated with accelerated progression of CKD. A large observational study reported that 25(OH)D deficiency was associated with a 1.64-fold increased risk of renal events (composite of death, doubling of serum creatinine, or dialysis; HR 1.64, 95% CI 1.32–2.05) compared to non-deficient patients, with an even higher risk observed in patients with concurrent diabetes or overweight (29). Similarly, Shardlow et al demonstrated that in a cohort of predominantly older patients with CKD stage 3, vitamin D deficiency and elevated PTH were related with all-cause mortality, though associations with CKD progression were not independent after adjustment for eGFR and proteinuria (30).

Mechanistic plausibility and experimental data

Mechanistically, active vitamin D demonstrated that the key pathways driving CKD progression in experimental models. By suppressing the RAAS, specifically through VDR-mediated inhibition of renin gene transcription, vitamin D reduces intraglomerular hypertension and

the angiotensin II–driven activation of TGF-β, podocyte injury, and mesangial cell proliferation. Active vitamin D also acts as a negative regulator of the Wnt/β-catenin and TGF-β/Smad signaling pathways, both of which are central to glomerulosclerosis and tubulointerstitial fibrosis; these renoprotective effects, documented in multiple animal models of obstructive, diabetic, and immune-mediated nephropathy, provide strong rationale for investigating vitamin D as a disease-modifying intervention in CKD (17,19,31).

Interventional trial data

Despite robust mechanistic and observational evidence, interventional RCTs have generally failed to demonstrate that vitamin D supplementation definitively slows eGFR decline. The VITAL-DKD sub-study, which followed T2DM patients allocated to vitamin D_3 (2,000 IU/day) or omega-3 fatty acids in the VITAL trial, found that the average change in eGFR from baseline to five years was −12.3 mL/min/1.73 m^2 in the vitamin D group versus −13.1 mL/min/1.73 m^2 in the placebo group, a non-significant difference of 0.9 mL/min/1.73 m^2 (95% CI −0.7 to 2.5). The absence of a significant effect in this large, well-powered trial suggests that nutritional vitamin D_3 supplementation at conventional doses does not prevent progressive kidney function loss in patients with T2DM. However, it is important to note that this trial enrolled individuals without severe vitamin D deficiency at baseline, and the effect of supplementation in patients with frank deficiency may differ (32).

The FGF23 paradox

A clinically important and unresolved issue in active vitamin D analogues to retard CKD progression is their stimulatory effect on FGF23; as noted earlier, FGF23 is elevated in most patients with CKD stages 2–4, and its elevation independently predicts both ESRD and cardiovascular events (14). Active vitamin D compounds increase FGF23 secretion, potentially attenuating their renoprotective benefit or even accelerating CKD-MBD through other pathways (33).

Cardiovascular outcomes

Observational data and biological mechanisms

Cardiovascular disease represents the primary cause of death among CKD patients, accounting for a disproportionate burden of premature death. Studies have consistently demonstrated that low vitamin D levels in CKD patients correlate with higher all-cause and cardiovascular mortality, increased risk of cardiovascular events, peripheral vascular disease, congestive heart failure, and hypertension, along with elevated left ventricular mass and increased arterial stiffness (34-39). A meta-analysis by Li et al evaluating the impact of vitamin D on cardiovascular events in patients with predialysis CKD found that treatment with calcitriol or VDR activators was linked to a significantly lower risk of cardiovascular events (RR 0.27; 95% CI 0.13–0.59) (39). A 2017 analysis of 17 RCTs and 21 observational studies found that vitamin D therapy was associated with a decreased risk of all-cause death, consistent across CKD stages, routes of administration, and vitamin D agents (38).

Left ventricular hypertrophy

Left ventricular hypertrophy is a particularly prevalent and consequential cardiovascular complication in CKD, linked to increased risk of sudden cardiac arrest, heart failure, and overall cardiovascular death. Cross-sectional data indicate that serum $1,25(OH)_2D$ levels are independently associated with LVH in CKD patients (OR 0.90, 95% CI 0.88–0.93, with an optimal cut-off value of ≤12.7 pg/dL for identifying LVH, underscoring the potential of $1,25(OH)_2D$ as a biomarker and therapeutic target (40). In elderly individuals with reduced renal function, vitamin D deficiency has been independently associated with elevated left ventricular mass and greater arterial stiffness (37). Among hemodialysis patients, treatment with calcitriol led to regression of LVH, with concurrent reductions in plasma renin activity and angiotensin II concentrations (35). However, a 2019 meta-analysis of vitamin D and heart structure in CKD found that supplementation did not significantly reduce left ventricular mass, suggesting that the observational associations may not translate into clinically meaningful structural changes with supplementation (41).

Blood pressure and vascular function

The relationship between vitamin D supplementation and blood pressure in CKD has been extensively studied but remains inconclusive. A systematic review of eight RCTs in CKD patients found no significant change in diastolic blood pressure (DBP) after consumption of vitamin D, and the authors concluded that vitamin D is not a primary antihypertensive agent (42). In the general population of hypertensive individuals with hypovitaminosis D, a 2024 meta-analysis of 14 RCTs found that vitamin D decreased systolic blood pressure (SBP), but effects on DBP were inconsistent (43).

Randomized controlled trial evidence on hard cardiovascular endpoints

The disconnection between observational associations and RCT evidence for hard cardiovascular endpoints is one of the most important findings in this field. Mann et al conducted a meta-analysis of 13 trials involving CKD patients and reported no statistically significant benefit of oral vitamin D supplementation on all-cause mortality, cardiovascular mortality, or major adverse cardiovascular events (44). An updated study of 128 RCTs evaluating the effect of vitamin D in CKD patients found that vitamin D therapy did not significantly reduce the risk of mortality or MACE (45). The most recent meta-analysis

of 11 RCTs specifically examining cardiovascular events in CKD found that vitamin D supplementation reduced the risk of adverse cardiovascular events (RR 0.39; 95% CI 0.22–0.69), though no significant differences were found in left ventricular ejection fraction, left ventricular mass index, SBP, or DBP between groups, and the authors called for further large-scale mechanistic studies (11). These discordant findings between observational and interventional data may reflect confounding by indication in observational studies, heterogeneity in trial populations, vitamin D types, doses, and durations, as well as inadequate powering of individual trials for clinical endpoints.

Conclusion

Vitamin D deficiency is universal in advanced CKD and has compelling mechanistic links to proteinuria, glomerular and tubular injury, renal fibrosis, and cardiovascular dysfunction. Active VDR activators, led by paricalcitol, have demonstrated consistent and statistically significant antiproteinuric effects in CKD patients across multiple RCTs, with a favorable safety profile at recommended doses. Nutritional vitamin D (cholecalciferol) offers a safe and practical option to correct 25(OH)D deficiency, with potential but inconsistently demonstrated benefits on proteinuria. Disease progression data from interventional trials remain inconclusive, with large-scale RCTs failing to show a definitive eGFR-preserving effect of vitamin D supplementation. Cardiovascular benefits suggested by observational studies have not been robustly replicated in RCTs, though recent meta-analyses hint at a potential reduction in adverse cardiovascular event rates. Until adequately powered long-term RCTs with hard clinical endpoints are available, the primary indication for vitamin D therapy in CKD remains correction of deficiency and management of secondary hyperparathyroidism, while antiproteinuric and cardioprotective benefits represent secondary goals of clinical interest.

Authors' contribution

Conceptualization: Farzaneh Futuhi and Behzad Azimi.
Data curation: Farzaneh Futuhi and Behzad Azimi.
Investigation: Zahra Sahraei and Behzad Azimi.
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Validation: Farzaneh Futuhi.
Visualization: Zahra Sahraei.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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